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Study reveals true origin of oldest evidence of animals

Two teams of scientists have resolved a longstanding controversy surrounding the origins of complex life on Earth.

The joint studies found molecular fossils extracted from 635-million-year-old rocks aren't the earliest evidence of animals, but instead common algae. The researchers from The Australian National University (ANU), Max Planck Institute and Caltech say the finding has big implications for our understanding of evolution.

"It brings the oldest evidence for animals nearly 100 million years closer to the present day," Dr Lennart van Maldegem from ANU, co-author author of one study, said. "We were able to demonstrate that certain molecules from common algae can be altered by geological processes - leading to molecules which are indistinguishable from those produced by sponge-like animals.

Professor Jochen Brocks, also based at ANU, said the mystery of when our very earliest animal ancestors emerged and became abundant in the oceans has puzzled palaeontologists for more than a century.

"Ten years ago, scientists discovered the molecular fossils of an animal steroid in rocks that were once at the bottom of an ancient sea in the Middle East," Professor Brocks said. "The big question was, how could these sponges have been so abundant, covering much of the seafloor across the world, but leave no body fossils?"

Dr Ilya Bobrovskiy, lead author of the other study, said the researchers have been able to "solve this mystery". "While it holds true sponges are the only living organism which can produce these steroids, chemical processes can mimic biology and transform common and abundant algae sterols into 'animal' sterols," he said.

"These molecules can be generated in the lab when simulating geological time and temperatures, but we also showed such processes did happen in ancient rocks."

The two complementary studies have been published in Nature Ecology and Evolution.
https://doi.org/10.1038/s41559-020-01336-5 https://doi.org/10.1038/s41559-020-01334-7

https://go.nature.com/33rnxkS

Why Oxford's positive COVID vaccine results are puzzling scientists

Preliminary data suggest that the immunization was more effective in trial participants who received a lower dose.

Ewen Callaway

A highly anticipated COVID-19 vaccine has delivered some encouraging — but head-scratching — results. The vaccine developed by the University of Oxford, UK, and pharmaceutical giant AstraZeneca was found to be, on average, 70% effective in a preliminary analysis of phase III trial data, the developers announced in a press release on 23 November.

But the analysis found a striking difference in efficacy depending on the amount of vaccine delivered to a participant. A regimen consisting of 2 full doses given a month apart seemed to be just 62% effective. But, surprisingly, participants who received a lower amount of the vaccine in the first dose and then the full amount in the second dose were 90% less likely to develop COVID-19 than were participants in the placebo arm.

Earlier this month, drug companies Pfizer and BioNTech reported that their RNA-based vaccine was around 90% effective after the trial reached its primary endpoint, and an interim analysis of an RNA vaccine by biotechnology firm Moderna showed it worked roughly as well.

Researchers caution against making head-to-head comparisons of vaccines on the basis of incomplete data. The disparity in the latest results means there will be considerable uncertainty over precisely how well the Oxford vaccine protects against COVID-19 until ongoing efficacy trials report more data, say scientists. "We're slightly in danger of rushing to compare apples and oranges," says

Daniel Altmann, an immunologist at Imperial College London. "There's a long, long way to go before these data settle down and get reported and published in full."

Viral vector

The Oxford–AstraZeneca vaccine is made from a cold-causing adenovirus that was isolated from the stool of chimpanzees and modified so that it no longer replicates in cells. When injected, the vaccine instructs human cells to produce the SARS-CoV-2 spike protein — the immune system's main target in coronaviruses. The vaccine entered phase III efficacy trials before other front runners, including Pfizer and Moderna, and trials are continuing in countries including the United States, South Africa, Japan and Russia. The 23 November analysis is based on 131 COVID-19 cases among more than 11,000 trial participants in the United Kingdom and Brazil, up to 4 November.

Overall, the developers found that the 2-dose vaccine had an efficacy of 70%, when measured 2 weeks after participants received their second dose. But that figure is an average of the 62% and 90% efficacy from the two dosing regimens. "90% is pretty good, but the 62% for the second tested regimen are not that impressive," said Florian Krammer, a virologist at Icahn School of Medicine at Mount Sinai in New York City, on Twitter.

A top priority for researchers is understanding why the vaccine seems to have performed so much better with a lower first dose. One explanation could lie in the data: the trial might not have been big enough to gauge the differences between the two regimens, in which case the differences might vanish once more cases of COVID-19 are detected, says Luk Vandenberghe, a virologist at the Massachusetts Eye and Ear institute and Harvard Medical School in Boston. The more effective 'half-dose, full dose' results were based on 2,741 trial participants, whereas the less efficacious arm included 8,895 volunteers. The press release did not specify in which group cases occurred.

On the basis of the data, Stephen Evans, a statistical epidemiologist at the London School of Hygiene & Tropical Medicine, estimates that the 'half-dose, full dose' regimen could have an efficacy as low as 66%.

Dosing theories

But, if the differences are real, researchers are eager to understand why. "I don't think it's an anomaly," says Katie Ewer, an immunologist at Oxford's Jenner Institute who is working on the vaccine. "I'm keen to get into the lab and start thinking about how we address that question." She has two leading theories for why a lower first dose might have led to better protection against COVID-19. It's possible that lower doses of vaccine do a better job at stimulating the subset of immune cells called T cells that support the production of antibodies, she says.

Another potential explanation is the immune system's response to the chimpanzee virus. The vaccine triggers a reaction not only to the SARS-CoV-2 spike protein, but also to components of the viral vector. It's possible that the full first dose blunted this reaction, says Ewer. She plans to look at antibody responses to the chimpanzee virus to help address this question.

"This is a plausible explanation," says James Wilson, a virologist at the University of Pennsylvania in Philadelphia who pioneered the use of adenoviruses for vaccines in the 1990s. By giving a half-dose first, "it is possible that AstraZeneca threaded the needle with their dosing", he adds.

Hildegund Ertl, a viral immunologist at the Wistar Institute in Philadelphia, says the results make sense in the light of some of her work on adenovirus vaccines in mice. She, too, has found that for a two-dose vaccine, a low first dose can lead to better protection than a high first dose. She thinks this is because a lower first dose leads

more quickly to the establishment of 'memory' immune cells that are triggered by a second-dose boost. Waiting longer between the two doses could achieve the same effect.

AstraZeneca hopes to gather more data on the dosing regimen. The company has so far given the vaccine to around 10,000 participants in a US arm of the efficacy trial, which was paused for more than a month starting in September, while researchers investigated a neurological condition in a UK trial participant.

The company plans to ask regulators whether it can modify the trial to include the more efficacious dosing regimen, said Mene Pangalos, vice-president of biopharmaceuticals research at AstraZeneca, which is based in Cambridge, UK, at a press briefing.

"It would be madness to use more vaccine than you needed to get less efficacy," says Ewer. "I think we will see a move towards roll-out of the 'low dose, standard dose' regime."

Hints of optimism

While Oxford and AstraZeneca make sense of their trial data and gather more, there is reason for optimism in other facets of the vaccine's performance, say scientists. No participants who received the vaccine were hospitalized or developed severe COVID-19, suggesting the vaccine might do a good job at preventing severe disease.

There were also hints that the vaccine might prevent infected people from transmitting the virus, even if they aren't showing symptoms. In the trial's UK arm, some participants routinely swabbed themselves for SARS-CoV-2 testing, even if they weren't showing symptoms. Differences in infection rates between people who received the placebo and those who got the Oxford vaccine suggest the vaccine blocks transmission, says Ewer. (The Pfizer and Moderna trials tested only people who showed symptoms.)

Even with a question mark hanging over its efficacy, the Oxford–AstraZeneca vaccine could see wider roll-out than some other COVID-19 immunizations. The vaccine is stable at refrigerator temperatures, in contrast to the Pfizer and BioNTech vaccine, which must be stored at −70 ºC until hours before vaccination.

And more of the vaccine could be available sooner, relative to other jabs. AstraZeneca estimates that it will have 200 million doses ready worldwide by the end of 2020, and capacity to produce 100 million to 200 million doses per month once production is ramped up, according to Pam Cheng, vice-president for operations and information technology at AstraZeneca.

"The battle really between all these vaccines is going to be really a logistical one," says Vandenberghe. "We will be able to use every dose that becomes available."

doi: https://doi.org/10.1038/d41586-020-03326-w

https://bit.ly/2JnxTLq

Proving viability of injection-free microneedle for single-administration of vaccines

A single-use, self-administered microneedle technology developed by UConn faculty to provide immunization against infectious diseases has recently been validated by preclinical research trials.

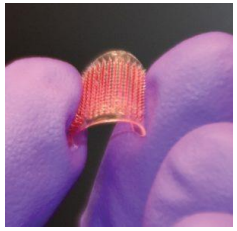
Recently published in *Nature Biomedical Engineering*, the development and preclinical testing of the microneedle patches was reported by UConn researchers in the lab of Thanh Nguyen, assistant professor in the Departments of Mechanical Engineering and Biomedical Engineering.

The concept of a single-injection vaccine, which is recognized as a preferable vaccination approach by the World Health Organization (WHO), has been investigated for many years. Previous efforts to create such a single-injection vaccine include a technology called SEAL (StampEd Assembly of Polymer Layer), developed in 2017 by Nguyen, to create single-injection vaccine microparticles which can deliver vaccines after several defined periods, simulating multiple bolus injections.

However, these microparticles require a large needle for the injection. Additionally, there is also a limited number of the particles that can be loaded into the needle, which means only a limited vaccine dose can be delivered. Ultimately, the microparticles still require traditional injections, which are painful and produce unfavorable biohazard wastes from disposed sharp syringes.

"It has been recognized for a long time that there is a need to eliminate many injections in conventional vaccination process," Thanh says. "While booster and repeated shots of vaccines are important to sustain immune-protection, these injections are associated with pain, high costs, and complicated injection schedules, causing a very low patient compliance. The issue becomes more problematic for patients in developing countries due to their limited access to health care providers. In such places, parents struggle to remember the schedule and cannot afford to repeatedly travel long distances with their children to medical centers to receive multiple booster doses of vaccines."

As detailed in *Nature Biomedical Engineering*, to overcome these problems, Nguyen's lab at UConn developed a microneedle skin patch, which only requires a single administration to perform exactly the same programmable delayed release of vaccine, as that obtained from the SEAL microparticles.



A tiny microneedle patch being held between the gloved fingers of a UConn researcher. A microneedle patch. **(Courtesy of Thanh Nguyen)**

The microneedle patch avoids any painful injections, offering a significant enhancement from the perspective of patients. Extensive research has shown microneedle skin patches are almost painless, and could even be self-administered by patients at home. The patch is small, portable, and similar to a nicotine patch, which could be easily distributed to all people over the world for self-administration in the case of a pandemic such as the COVID-19 crisis to quickly create a pan-immunity at the global scale.

The microneedles have a core-shell microstructure, in which the microneedle shells are made with biodegradable medical polymer that is FDA-approved for implants, and offers unique drug-release kinetics--which allows a preprogrammed burst release of vaccine loads over a period of a few days to more than a month from a single administration. The microneedles can be easily inserted and fully embedded inside the dermal layer, thanks to the miniscule tips and smooth geometry of the needles.

To create this vaccine microneedle patch, Khanh Tran, a PhD student in Nguyen's lab and the lead author of the published work, adapted the SEAL technology to assemble different microneedle components, including a cap, shell, and vaccine core. These components are manufactured in an additive manner, similar to the approach of 3D printing, to create arrays of core-shell microneedles over a large area.

Nguyen's team devised several new approaches to overcome many issues of the existing SEAL technology. The key novelty of their new manufacturing process is to micro-mold vaccines into the shape of the microneedle core, and insert all of the molded vaccine cores into arrays of the microneedle shells at the same time, offering a fabrication method similar to the manufacturing process of computer chips, as shown in this video: *Video Player 00:00 00:50*

"This is a tremendous advantage, compared to the previously-reported SEAL and other traditional methods to fabricate vaccine carriers, in which vaccine is often filled slowly one by one into each polymeric shell/carrier," Tran says.

In the preclinical trials, the researchers inserted microneedles loaded with a clinically available vaccine (Prevnar-13) into the skin of rats in a minimally invasive manner. The patch application caused no skin irritation during long-term implantation, and

triggered a high immune protection response against a lethal dose of infectious pneumococcal bacteria. The results from the one-time administration were similar to that obtained from multiple injections of the same vaccine over a period of approximately two months.

"We are very excited for this achievement, as for the first time, a onetime-use and injection-free skin patch can be pre-programmed to release vaccines at different times to provide a long-term and effective immune protection," Nguyen says. "The microneedle patch could facilitate the global effort for a complete vaccination process to eradicate dangerous infectious diseases and enable a quick distribution of vaccines. This could create a pan-community immune-protection at a global scale in the case of a pandemic such as the COVID-19," Nguyen says.

In this regard, Nguyen and his collaborator, Associate Professor Steve Szczepanek in the Department of Pathobiology and Veterinary Science in the College of Agriculture, Health, and Natural Resources have also received a $432,990 contract from the U.S. Department of Health and Human Services (HHS) BARDA to develop this technology.

Looking into the future, more research is needed in order to bring the microneedle patch into clinical use. While the researchers have shown the ability to use the patch for the pneumococcal vaccines, different vaccines would require different strategies for stabilization so they can be functional over a long period of implantation inside the skin.

The researchers are also working on the optimization and automation of the fabrication process, which can reduce the cost of the microneedle skin patch for clinical use. Future works on larger animal models closely mimicking human immune systems are also needed to verify the safety and efficacy of the microneedle platforms.

The reported articles include the participation of Szczepanek and Ph.D. student Tyler Gavitt from UConn Department of Pathobiology and Veterinary Science, and researchers from the Advanced Science Research Center at the Graduate Center, City University of New York, and the Department of Chemistry at Hunter College, City University of New York.

https://bit.ly/2VdV25Y

Can drinking cocoa make you smarter?

Increased consumption of flavanols can increase your mental agility

Increased consumption of flavanols - a group of molecules which occur naturally in fruit and vegetables - can increase your mental agility, according to new research at the University of Birmingham.

A team in the University's School of Sport, Exercise and Rehabilitation Sciences found that people given a cocoa drink containing high levels of flavanols were able to complete certain cognitive tasks more efficiently than when drinking a non-flavanol enriched-drink.

The study participants also underwent non-invasive brain imaging to measure blood oxygenation levels in the brain. Working with experts at the University of Illinois, the researchers showed that participants who had consumed the flavanol-rich drink produced a faster and greater increase in blood oxygenation levels in response to artificially elevated levels of CO_2 (hypercapnia).

Flavanols, a sub-group of plant flavonoids, are present in cocoa, grapes, apples, tea, berries and other foods. They are known to have a beneficial effect on cardiovascular health, but their effects on brain health are not well understood. This study, published in *Scientific Reports*, is the first time the cognitive effects of flavanols in young, healthy subjects and the link with brain blood oxygenation have been investigated.

Lead author, Dr Catarina Rendeiro, of the University of Birmingham's School of Sport, Exercise and Rehabilitation Sciences, explains: "We used cocoa in our experiment, but

flavanols are extremely common in a wide range of fruit and vegetables. By better understanding the cognitive benefits of eating these food groups, as well as the wider cardiovascular benefits, we can offer improved guidance to people about how to make the most of their dietary choices."

In the study, 18 healthy male participants aged between 18 and 40 underwent a standard procedure to challenge the brain's blood circulation that involves breathing 5% carbon dioxide - about 100 times the normal concentration in air, producing an effect called hypercapnia. Non-invasive near-infrared spectroscopy, a technique that uses light to capture changes in blood oxygenation levels, was used to track the increases in brain oxygenation in the frontal cortex in response to this carbon dioxide challenge.

Each participant underwent the test before and after drinking a cocoa drink on two occasions and on one of those occasions, the drink was enriched with flavanols. Following the carbon dioxide test, the participants were asked to complete a number of progressively complex cognitive tests.

The researchers found that the participants who had taken the flavanol-enriched drink had the highest levels of blood oxygenation in response to hypercapnia, reaching levels up to three times higher than participants drinking the non-flavanol-enriched drink. They also achieved these elevated levels 1 minute faster than participants who drank the non-enriched cocoa.

In the cognitive tests, the researchers found significant differences in the speed and accuracy with which volunteers completed the higher complexity tasks, with volunteers who had taken the flavanol-enriched drink performing the tasks 11 per cent faster on average.

"Our results showed a clear benefit for the participants taking the flavanol-enriched drink - but only when the task became sufficiently complicated," explains Dr Rendeiro. "We can link this with our results on improved blood oxygenation - if you're being challenged more, your brain needs improved blood oxygen levels to manage that challenge. It also further suggests that flavanols might be particularly beneficial during cognitively demanding tasks".

The researchers also noted a further outcome. Within the study cohort, there was a small group who did not benefit at all from the flavanol-enriched drink in terms of blood oxygenation levels, and who also did not derive any cognitive benefit. This group was shown to have existing high levels of brain oxygenation responses to start with that were not increased further by drinking the enriched cocoa. "This may indicate that some individuals, that perhaps are already very fit, have little room for further improvement" explain Dr. Rendeiro.

"The small group of participants who did not react to the flavanol gives us additional evidence to confirm the link between increased brain blood oxygenation and cognitive ability," adds Dr Rendeiro.

The research was funded by a Birmingham-Illinois Bridge Seed Grant, and by the National Institute of Ageing in the US.

Rendeiro et al (2020). *'Dietary flavanols improve cerebral cortical oxygenation and cognition in healthy adults.'* *Scientific Reports.*

https://bit.ly/2HR7N3i

Liver cancer ten times more likely in men with common genetic disorder haemochromatosis

Men who have haemochromatosis ten times more likely to develop liver cancer

Men who have the Western world's most common genetic disorder, haemochromatosis, are ten times more likely to develop liver cancer, according to a major new study.

Research led by the University of Exeter and published in the internationally renowned journal *JAMA* has led to renewed calls for routine early testing for the iron overload condition haemochromatosis, previously thought to be a lower-level health

risk. The finding could add more weight to calls for the UK National Screening Committee to recommend screening for the condition, which is currently under consultation.

The new study projected that more than seven per cent of men with two copies of the faulty haemochromatosis genes would develop liver cancer by age 75, compared to just 0.6 per cent in the general population. An estimated 175,000 men and boys of European ancestry in the UK have these faulty genes. They are particularly prevalent in Celtic bloodlines, meaning the UK and parts of North America have some of the highest rates in the world.

The research is led by the University of Exeter Medical School in the UK, in collaboration with the University of Connecticut, and Western University in Ontario, and South Warwickshire NHS Foundation Trust. Funded by the UK Medical Research Council, the study adds to the evidence to back widespread early testing for the condition. Previously, the Exeter team found that having the haemochromatosis double faulty gene quadruples the risk of liver disease and doubles the risk of arthritis and frailty in older age groups. It also causes higher risk of diabetes and chronic pain.

Reliable tests are available to identify those at risk - blood tests for measuring iron levels (serum ferritin, transferrin saturation) and genetic testing (HFE C282Y genetic blood test). Symptoms can include feeling tired all the time, muscle weakness and joint pains, meaning it is often misdiagnosed as the signs of ageing. Most of those with liver cancer develop liver damage first, often progressing to cirrhosis of the liver. Once diagnosed, the condition is easily treated by a process similar to donating blood several times a year, to lower iron levels.

The team analysed data from 2,890 men and women with two copies of the faulty gene (called HFE C282Y homozygous), from the UK Biobank, a large biomedical database of more than half a million British men and women recruited between 2006 and 2010 from across England, Scotland and Wales. People were aged 40 to 70 at the start of the study and were followed for a nine-year period. Twenty-one of the 1,294 men with the faulty genes studied have developed liver cancer thus far, of whom 14 died due to their liver cancer. Ten of these 21 men were not diagnosed with haemochromatosis by the time they had a liver cancer diagnosis.

Haemochromatosis is more serious in men, with women partially protected because they lose iron through menstruation and childbirth, although some younger women do develop the disease. The study found no increase in liver cancer risk in women with faulty haemochromatosis genes.

Dr Janice Atkins, Research Fellow at the University of Exeter and first author of the paper, said: "The haemochromatosis faulty genes are relatively common in people with European ancestries, and are causing potentially fatal diseases such as liver cancer. Unfortunately, haemochromatosis is often diagnosed too late. Earlier diagnosis could prevent so much unnecessary disease."

Professor David Melzer, who led the team, said: "Tragically, men with the haemochromatosis faulty genes have been dying of liver cancer for many years, but this was thought to be rare. The large scale of UK Biobank study allowed us to measure cancer risk accurately. We were shocked to find that more than seven per cent of men with two faulty genes are likely to develop liver cancer by age 75, particularly considering that the UK has the second highest rate of these faulty genes in the world. Fortunately most of these cancers could be prevented with early treatment. Blood donations made during routine treatment of haemochromatosis can be used for other patients, so early diagnosis would actually be a win-win for the NHS."

Dr Jeremy Shearman, a specialist in liver disease and an adviser to the charity Haemochromatosis UK, said: "Physicians and scientists have long acknowledged that iron overload is an important co-

factor fuelling the development of many serious diseases including cancer. This research is a vital step towards quantifying that risk and should raise awareness of the importance of iron in the minds of both clinicians and patients. Measurement of iron stores and recognition of the genetic risk of iron overload needs to become a routine part of health assessment and monitoring in the UK."

Professor Paul Adams Western University's Schulich School of Medicine & Dentistry, who has been studying haemochromatosis in Canada for more than four decades, said: "The UK Biobank project is a glimpse into the future of medicine where all known genes are tested and then treatable conditions are offered treatment before serious complications develop. An early diagnosis of haemochromatosis can be treated by regular blood donation in Canada."

Neil McClements, Chief Executive of Haemochromatosis UK, said: "This paper underlines the need for early diagnosis to save lives. We know from our work as the UK's only charity supporting people affected by genetic haemochromatosis that many men experience unnecessary suffering from liver cancer, caused by their genetic condition. But it's not just men who suffer - their families and loved ones do, too."

The NHS advises that it is important to talk to your GP if you have a parent or sibling with haemochromatosis, even if you don't have symptoms yourself - tests can be done to check if you're at risk of developing problems. People are also advised to talk to their GPs about haemochromatosis if they have the following persistent or worrying symptoms - particularly if you have a northern European family background. Typical symptoms include feeling very tired all the time (fatigue); weight loss; weakness and joint pain. Also, some men with haemochromatosis develop an inability to get or maintain an erection (erectile dysfunction), and some women have irregular periods or absent periods. These symptoms usually come on between ages 30 and 60.

The paper is entitled "Association of hemochromatosis HFE p.C282Y homozygosity with hepatic malignancy", by. Janice L Atkins, Luke C Pilling, Jane AH Masoli, Chia-Ling Kuo, Jeremy D Shearman, Paul C Adams, David Melzer, and is published in JAMA.

https://bit.ly/3o55xEV

Areas where the next pandemic could emerge are revealed

Up to 20% of the world's most connected cities at greatest risk

KEY FINDINGS

- ***Almost half the world's most connected cities straddle animal-human spillover hotspots***
- ***14-20 percent of these cities are in areas with poor health infrastructure, meaning infections resulting from spillovers are likely to go unreported***
- ***South and southeast Asia and Sub-Saharan Africa have the most cities at greatest risk***
- ***The new methodology builds on understanding sources of pathogen transmission at wildlife-human interfaces by locating the most connected airports adjacent to these interfaces, where infections can spread quickly globally.***

An international team of researchers has taken a holistic approach to reveal for the first time where wildlife-human interfaces intersect with areas of poor human health outcomes and highly globalised cities, which could give rise to the next pandemic unless preventative measures are taken.

Illustrative map of 'red-alert' zone. Circles represent approximate location of risk; circle size indicates level of risk. **Michael Walsh, University of Sydney**

Areas exhibiting a high degree of human pressure on wildlife also had more than 40 percent of the world's most connected cities in or

adjacent to areas of likely spillover, and 14-20 percent of the world's most connected cities at risk of such spillovers likely to go undetected because of poor health infrastructure (predominantly in South and South East Asia and Sub-Saharan Africa). As with COVID-19, the impact of such spillovers could be global.

Led by the University of Sydney and with academics spanning the United Kingdom, India and Ethiopia, the open-access paper shows the cities worldwide that are at risk. Last month, an IPBES report highlighted the role biodiversity destruction plays in pandemics and provided recommendations. This Sydney-led research pinpoints the geographical areas that require greatest attention.

The paper, "Whence the next pandemic? The intersecting global geography of the animal-human interface, poor health systems and air transit centrality reveals conduits for high-impact spillover", has published in the leading Elsevier journal, *One Health*. City lists for yellow, orange and red alert zones are available in open access.

Lead author Dr Michael Walsh, who co-leads the *One Health* Node at Sydney's Marie Bashir Institute for Infectious Diseases and Biosecurity, said that previously, much has been done to identify human-animal-environmental hotspots.

"Our new research integrates the wildlife-human interface with human health systems and globalisation to show where spillovers might go unidentified and lead to dissemination worldwide and new pandemics," said Dr Walsh, from the University of Sydney's School of Public Health, Faculty of Medicine and Health.

Dr Walsh said that although low- and middle-income countries had the most cities in zones classified at highest risk for spillover and subsequent onward global dissemination, it should be noted that the high risk in these areas was very much a consequence of diminished health systems. Moreover, while not as extensively represented in the zone of highest risk because of better health infrastructure, high-income countries still had many cities represented in the next two tiers of risk because of the extreme pressures the affluent countries exert on wildlife via unsustainable development.

Identifying Areas At Risk

The researchers took a three-staged approach:

1. ***First, identify where the sharing of space between wildlife and humans is greatest, and therefore where spillover events would be expected to be most common. The researchers refer to this as the 'yellow' and 'orange' alert zones of two- and three-way interactions between humans, domesticated animals and wildlife.***

2. Next, identify where areas of high wildlife-human interface coincide with areas of poor health system performance, which would comprise areas expected to miss ongoing chains of transmission following a spillover event ['red-alert' zone - Figure 4];

3. Finally, identify cities within or adjacent to these areas of spillover risk that are highly connected to the network of global air travel, and therefore may serve as conduits for future pandemics (city names in the alert zones can be seen by zooming up on the high-resolution maps).

"This is the first time this three-staged geography has been identified and mapped, and we want this to be able to inform the development of multi-tiered surveillance of infections in humans and animals to help prevent the next pandemic," the paper reads.

Of those cities that were in the top quartile of network centrality, approximately 43 percent were found to be within 50km of the spillover zones and therefore warrant attention (both yellow and orange alert zones). A lesser but still significant proportion of these cities were within 50km of the red alert zone at 14.2 percent (for spillover associated with mammal wildlife) and 19.6 percent (wild bird-associated spillover).

Dr Walsh said although it would be a big job to improve habitat conservation and health systems, as well as surveillance at airports

as a last line of defence, the benefit in terms of safeguarding against debilitating pandemics would outweigh the costs.

"Locally-directed efforts can apply these results to identify vulnerable points. With this new information, people can develop systems that incorporate human health infrastructure, animal husbandry, wildlife habitat conservation, and movement through transportation hubs to prevent the next pandemic," Dr Walsh said.

"Given the overwhelming risk absorbed by so many of the world's communities and the concurrent high-risk exposure of so many of our most connected cities, this is something that requires our collective prompt attention."

The authors of this research, Michael Walsh, Shailendra Sawleshwarkar, Shah Hossain and Siobhan Mor, are all associated with the University of Sydney. Additionally their various affiliations comprise The Westmead Institute for Medical Research (Australia), Manipal Academy of Higher Education (India), University of Liverpool (UK) and the International Livestock Research Institute (Addis Ababa, Ethiopia campus).

https://bit.ly/2V8I2OZ

Immunity to SARS-CoV-2 Lasts at Least Six Months, Data Show

Half a year after infection, people who had recovered from COVID-19 had robust antibodies, along with traces of the virus in their gut, which may drive long-lasting immunity.

Ashley Yeager

Immunity to the virus that causes COVID-19 lasts at least six months and might last much longer, according to a preprint posted November 5 on *bioRxiv*.

Among 87 individuals who had COVID-19, antibodies to SARS-CoV-2 dwindled after six months but were still detectable, the study's authors found. A closer look at the samples of six of those patients revealed that the antibodies that remained six months after infection were, on average, more potent in neutralizing the virus than were antibodies generated only about a month after infection. And levels of the memory immune cells that make those more-potent antibodies did not drop off with time, the researchers report.

"This is fantastic news," says immunologist Ziv Shulman of the Weizmann Institute of Science in Israel who wasn't involved in the new work. "It was unclear if we make a long-lasting immunological memory against this new coronavirus. The study shows the memory cells are there [months after infection] and able to produce high-affinity, virus-neutralizing antibodies."

The results, which have not yet been peer reviewed, suggest that individuals re-exposed to the virus have a good chance of mounting a quick and effective immune response against it, and they offer a bit of hope for making a long-lasting vaccine, experts say.

In the study, Christian Gaebler, a physician and immunologist at the Rockefeller University in New York City, and colleagues compared the levels and potency of SARS-CoV-2 antibodies in blood samples taken from 87 volunteers one month and then six roughly months after they'd been infected with the virus. The team specifically measured levels of antibodies called immunoglobulin M (IgM), immunoglobulin G (IgG), and immunoglobulin A (IgA), which are created to neutralize a pathogen. IgM is usually the first antibody to develop in response to an infection. IgG is the main type found in the blood, and IgA in the blood helps initiate an inflammatory reaction to infection.

The levels of IgM and IgG antibodies reactive to the SARS-CoV-2 spike protein's receptor binding domain (RBD) dropped sharply between the two time points, the team found, while IgA levels didn't decline as steeply. Levels of memory B cells, which generate all of these antibodies when there's a sign of reinfection, remained steady over the course of the study. The results align with a preprint posted on *medRxiv* in August that also showed memory B cells to the virus persist after a mild COVID-19 infection.

Gaebler and colleagues next identified the antibodies present both one month and six months after infection, synthesized them in the lab, and tested their reactivity to the RBD. Antibodies from six months after infection bound more tightly to the docking component of the virus than did those from shortly after infection. Those antibodies were also better at neutralizing variants of the SARS-CoV-2 virus.

Those observations indicate that the patients' bodies were activating a specific immune system program that generates long-lived memory B cells, which then produce potent antibodies against subsequent exposures to the virus, the researchers write. A lack of structures called germinal centers where this production of memory B cells takes place has been tied to severe COVID-19 infection and death.

Curious if the B cells produced the same antibodies a month after infection as six months after infection, Gaebler and colleagues compared the memory B cell receptors' genetic sequences and found significant shifts over time. This observation, combined with the improved potency of antibodies produced by these B cells, indicates the B cells and antibodies evolved in response to infection.

Gaebler says he was surprised to see the antibodies had evolved. That typically happens when a pathogen hides out somewhere in the body or specifically in cells' DNA even after symptoms of infections cease—for instance, with HIV. Saurabh Mehandru, a gastroenterologist at Mount Sinai Hospital, and colleagues had been looking for the SARS-CoV-2 virus in recovered COVID-19 patients' intestines and had identified traces of it in the gut. His group and Gaebler's decided to team up to see if those viral stowaways in the gut could be spurring memory B cells' evolution.

Mehandru's team took a close look at biopsies from 14 recovered patients infected roughly four months earlier, on average. At the time of the tissue collection, none of them had a positive PCR result for the virus, yet SARS-CoV-2 RNA was detected in the small intestine of three of the 14 patients, and biopsies from five of the patients contained SARS-CoV-2 N protein. Electron tomography on one patient's biopsy also revealed SARS-CoV-2 viral particles.

"If you have the virus persisting in the intestines, it has the potential to continue to inform the immune system," Mehandru, a coauthor of the study, tells *The Scientist*.

Shiv Pillai, an immunologist at the Ragon Institute of Massachusetts General Hospital, MIT, and Harvard who was not involved in the study, agrees, saying that the study makes a strong case for virus in the gut continuing to prime memory B cells for infection. The result also suggests that a latent gut infection may explain MIS-C, or multisystem inflammatory syndrome, a rare condition in which children who contracted SARS-CoV-2 suffer from symptoms, such vomiting, diarrhea, and severe abdominal pain, weeks after recovery. "This fits with that and says, look, there is a reservoir in the gut for the virus to stay," Pillai says.

Mehandru says it is important to emphasize that even though the team found traces of the virus in the gut, there is no evidence that SARS-CoV-2 can be transmitted via stool.

Gaebler says the team is not yet entirely sure if it is the virus in the intestine that is causing the evolution in immunity, or if the virus also persists elsewhere in the body and continues to affect the immune system from there.

How long this memory B cell immune response will last past the six-month mark is not yet clear either. Individuals who were infected with the original SARS virus in 2003 still have memory B cells for that pathogen, so the pattern could be the same for SARS-CoV-2, Gaebler says. "Usually when you see such a memory response, it is quite long lasting."

A next step, he says, is to screen the blood of individuals who receive a vaccine against the virus for the presence of memory B

cells. “The immunity data that we see from those vaccines is very encouraging, and seems to resemble the natural infection very closely, which is good news,” Gaebler says. “That might suggest that [the vaccines] also lead to the same memory response. But this would obviously be very, very important to see.”

C. Gaebler et al. “Evolution 1 of Antibody Immunity to SARS-CoV-2,” bioRxiv, doi.org/10.1101/2020.11.03.367391, 2020.

https://bit.ly/3fLuQsx

Almost like on Venus

Four-and-a-half billion years ago, Earth would have been hard to recognise.

Instead of the forests, mountains and oceans that we know today, the surface of our planet was covered entirely by magma - the molten rocky material that emerges when volcanoes erupt. This much the scientific community agrees on. What is less clear is what the atmosphere at the time was like. New international research efforts led by Paolo Sossi, senior research fellow at ETH Zurich and the NCCR PlanetS, attempt to lift some of the mysteries of Earth's primeval atmosphere. The findings were published today in the journal *Science Advances*.

Making magma in the laboratory

"Four-and-a-half billion years ago, the magma constantly exchanged gases with the overlying atmosphere," Sossi begins to explain. "The air and the magma influenced each other. So, you can learn about one from the other."

To learn about Earth's primeval atmosphere, which was very different from what it is today, the researchers therefore created their own magma in the laboratory. They did so by mixing a powder that matched the composition of Earth's molten mantle and heating it. What sounds straightforward required the latest technological advances, as Sossi points out: "The composition of our mantle-like powder made it difficult to melt - we needed very high temperatures of around 2,000° Celsius."

That required a special furnace, which was heated by a laser and within which the researchers could levitate the magma by letting streams of gas mixtures flow around it. These gas mixtures were plausible candidates for the primeval atmosphere that, as 4.5 billion years ago, influenced the magma. Thus, with each mixture of gases that flowed around the sample, the magma turned out a little different.

"The key difference we looked for was how oxidised the iron within the magma became," Sossi explains. In less accurate words: how rusty. When iron meets oxygen, it oxidises and turns into what we commonly refer to as rust. Thus, when the gas mixture that the scientists blew over their magma contained a lot of oxygen, the iron within the magma became more oxidised.

This level of iron oxidation in the cooled-down magma gave Sossi and his colleagues something that they could compare to naturally occurring rocks that make up Earth's mantle today - so-called peridotites. The iron oxidation in these rocks still has the influence of the primeval atmosphere imprinted within it. Comparing the natural peridotites and the ones from the lab therefore gave the scientists clues about which of their gas mixtures came closest to Earth's primeval atmosphere.

A new view of the emergence of life

"What we found was that, after cooling down from the magma state, the young Earth had an atmosphere that was slightly oxidising, with carbon dioxide as its main constituent, as well as nitrogen and some water," Sossi reports. The surface pressure was also much higher, almost one hundred times that of today and the atmosphere was much higher, due to the hot surface. These characteristics made it more similar to the atmosphere of today's Venus than to that of today's Earth.

This result has two main conclusions, according to Sossi and his colleagues: The first is that Earth and Venus started out with quite similar atmospheres but the latter subsequently lost its water due to the closer proximity to the sun and the associated higher temperatures. Earth, however, kept its water, primarily in the form of oceans. These absorbed much of the CO_2 from the air, thereby reducing the CO_2 levels significantly.

The second conclusion is that a popular theory on the emergence of life on Earth now seems much less likely. This so-called "Miller-Urey experiment", in which lightning strikes interact with certain gases (notably ammonia and methane) to create amino acids - the building blocks of life - would have been difficult to realise. The necessary gases were simply not sufficiently abundant.

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Engineered "stealth bomber" virus could be new weapon against metastatic cancer

Retooled adenovirus not caught by liver/innate immune system

Many cancer researchers can claim to have devised "smart bombs." What has been missing is the stealth bomber - a delivery system that can slip through the body's radar defenses.

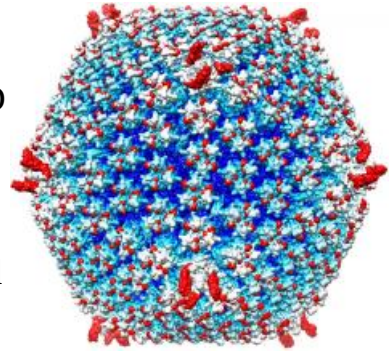
Oncolytic viruses, or viruses that preferentially kill cancer cells, have been discussed and tested for decades. An oncolytic virus against melanoma was approved by the FDA in 2015. But against metastatic cancers, they've always faced an overwhelming barrier: the human immune system, which quickly captures viruses injected into the blood and sends them to the liver, the body's garbage disposal.

Researchers at Emory and Case Western Reserve have now circumvented that barrier. They've re-engineered human adenovirus, so that the virus is not easily caught by parts of the innate immune system. This makes it possible to inject the virus into the blood, without arousing a massive inflammatory reaction.

A cryo-electron microscopy structure of the re-engineered virus and the virus's ability to eliminate disseminated tumors in mice are reported in *Science Translational Medicine*.

"The innate immune system is quite efficient at sending viruses to the liver when they are delivered intravenously," says lead author Dmitry Shayakhmetov, PhD. "For this reason, most oncolytic viruses are delivered directly into the tumor, without affecting metastases. In contrast, we think it will be possible to deliver our modified virus systemically at doses high enough to suppress tumor growth -- without triggering life-threatening systemic toxicities."

The co-first authors of the *Science Translational Medicine* paper are Emory associate scientist Svetlana Atasheva, PhD and Case Western Reserve graduate student Corey Emerson. Shayakhmetov is professor of medicine and pediatrics at Emory University School of Medicine and a member of Lowance Center for Human Immunology and Emory Vaccine Center.



Engineered adenovirus Ad5-3M with highlighted in red mutations that were introduced to target virus to tumor cells, reduce inflammation, and avoid interactions with blood factors and immune cells after systemic administration. **Credit: Phoebe Stewart**

Shayakhmetov has been working for 15 years with structural biologist Phoebe Stewart, PhD, professor in the Department of Pharmacology and a member of Cleveland Center for Membrane and Structural Biology at Case Western Reserve University. Their focus: re-engineering adenovirus, a delivery system that has been used in dozens of cancer clinical trials to stimulate host anti-tumor response.

Adenoviruses have also been central to gene therapy studies. Shayakhmetov recalls the 1999 death of Jesse Gelsinger, a

volunteer in a gene therapy clinical trial who died of cytokine storm and multi-organ failure connected with high doses of an adenovirus vector delivered into the bloodstream. He says that event inspired him to retool adenovirus, so that it would not set off a strong inflammatory reaction. He views the re-engineered adenovirus as a platform technology, which can be adapted and customized for many types of cancer, and even to individual cancer patients as a form of personalized cancer therapy.

"This is a new avenue for treatment of metastatic cancers," Shayakhmetov says. "You can arm it with genes and proteins that stimulate immunity to cancer, and you can assemble the capsid, a shell of the virus, like you're putting in Lego blocks."

Shayakhmetov started working on the modified virus technology while he was at the University of Washington and founded a company, AdCure Bio, to bring a potentially life-saving therapy to patients with metastatic disease.

In 2012, Shayakhmetov's and Stewart's labs published a cryo-EM analysis of how adenovirus interacts with one host factor in the blood, coagulation factor X, in Science.

"Sometimes even small changes in structural proteins can be catastrophic and prevent assembly of the infectious virus," Stewart says. "In this case, we modified adenovirus in three places to minimize virus interactions with specific blood factors. We found that the virus still assembles and remains functional for infecting and killing tumor cells."

It is still possible for a slower-building adaptive immune response to develop to the modified virus, similar to that observed with a vaccine. A panel of viruses could be used for sequential administration to cancer patients to extend therapeutic benefits, Shayakhmetov says.

"Our study is the first to show that we can modify the binding of natural IgM to adenovirus. We introduced mutations that prevent virus inactivation in the bloodstream and its trapping in liver macrophages, the largest pool of immune cells in our body that trap and destroy pathogens," he says. "Up to now, the prevailing view has been that any regular repeating structure, like the shell of the virus, would attract low-affinity natural IgM antibody binding, leading to its prompt inactivation and removal from the blood."

The researchers also replaced part of the adenovirus that interacts with human cellular integrins, substituting a sequence from another human protein, laminin-??? that targets the virus to tumor cells. Emerson and Stewart obtained a high resolution cryo-electron microscopy structure of the re-engineered virus (see figures).

When injected into mice, high doses of standard adenovirus triggered liver damage and death within a few days, but the modified virus did not. The modified virus could eliminate disseminated tumors from some, but not all mice engrafted with human lung cancer cells; a complete response -- lack of detectable tumors and prolongation of survival -- was observed in about thirty five percent of animals. Tumor sites in the lung were converted into scar tissue, the scientists found. Now, Shayakhmetov's lab is exploring approaches to further increase the proportion of complete responders.

In the clinic, metastatic lung cancer would be the type of cancer most appropriate to test an oncolytic virus against, Shayakhmetov says. The technology could also be harnessed for gene therapy applications.

The research reported in the paper was supported by the National Institute of Allergy and Infectious Diseases (AI107960, AI065429), David C. Lowance Endowment Fund, Children's Healthcare of Atlanta Research Trust and AdCure Bio. In addition to using resources at Case Western Reserve, cryo-EM structural and computational work was performed at the Electron Imaging Center for NanoMachines at UCLA and the Pittsburgh Supercomputing Center.

https://bit.ly/3q5NL6i

Extraction of largely-unexplored bodily fluid could be a new source of biomarkers

Interstitial fluid may provide an alternative source of biomarkers compared to blood that could be useful in diagnosing human illness.

Using an array of tiny needles that are almost too small to see, researchers have developed a minimally-invasive technique for sampling a largely-unexplored human bodily fluid that could potentially provide a new source of information for routine clinical monitoring and diagnostic testing.

Biochemical information about the body most commonly comes from analysis of blood - which represents only 6% of bodily fluids - but valuable information may also be found in other bodily fluids that are traditionally hard to get. Researchers have now developed a way to extract dermal interstitial fluid (ISF) - which circulates between cells in bodily tissues - using a simple through-the-skin technique that could provide a new approach for studying the metabolic products of cells, obtaining diagnostic biomarkers, and identifying potential toxins absorbed through the skin.

Because the dermal interstitial fluid doesn't clot like blood, the microneedle-based extraction could offer a new approach for continuous monitoring of glucose and other key health indicators.

Results of a human trial on the microneedle-based ISF sampling is reported Nov. 25 in the journal *Science Translational Medicine*. The study, conducted by researchers from the Georgia Institute of Technology and Emory University, was supported in part by the National Institutes of Health.

"Interstitial fluid originates in the blood and then leaks out of capillaries to bring nutrients to cells in the body's tissues. Because interstitial fluid is in direct communication with the cells, it should have information about the tissues themselves beyond what can be measured from testing the blood," said Mark Prausnitz, Regents' Professor and J. Erskine Love Jr. Chair in Georgia Tech's School of Chemical and Biomolecular Engineering, "This microneedle-based technique could provide a minimally-invasive and simple way to access this interstitial fluid to make it available for medical diagnostic and research applications."

ISF has been difficult to sample. Indwelling instruments for monitoring glucose in ISF already exist, and other researchers have used surgically-implanted tubing and vacuum-created blisters to extract ISF through the skin, but these techniques are not suitable for routine clinical diagnostic use.

The researchers, led by first author Pradnya Samant, used a patch containing five solid stainless-steel microneedles that were a hundredth of an inch in length. By pressing the patch at an angle into the skin of 50 human subjects, they created shallow micropores that reached only into the outer layer of skin containing ISF. The researchers then applied a suction to the area of skin containing the pores and obtained enough ISF to do three types of analysis. For comparison, they also took blood samples and obtained ISF using the older blister technique.

To accurately determine the biomarkers available in the ISF, the researcher needed to avoid getting blood mixed with the ISF. Though major blood vessels don't exist in the outer layers of skin, capillaries there can be damaged by the insertion of the microneedles. In their studies, the researchers found that if they slowly ramped up the suction after inserting the microneedles, they could obtain fluid clear of blood. The overall extraction procedure took at total of about 20 minutes for each test subject. The procedure was well tolerated by the volunteers, and the microscopic pores healed quickly within a day with minimal irritation.

The extracted fluid was analyzed at Emory University using liquid chromatography-mass spectrometry techniques to identify the

chemical species it contained. Overall, there were about 10,000 unique compounds, most of which were also found in the blood samples. However, about 12 percent of the chemical species were not found in the blood, and others were found in the ISF at higher levels than in the blood. "The skin is metabolically active, and it is full of cells that are changing the fluid," Prausnitz said. "We found that some of the compounds were unique to the ISF, or enriched there, and that is what we were hoping to find."

While not all the compounds unique to the ISF could be analyzed, the research team identified components of products that are applied to the skin - such as hand lotions - and pesticides that may enter the body through the skin. This discovery could set the stage for use of the microneedle technique for dermatological and toxicology studies.

"If you want to look at what accumulates in the skin over time, this may provide a way to obtain information about those kinds of exposures," Prausnitz said. "These are materials that may accumulate in the tissues of our body, but are not found in the bloodstream."

The researchers also determined the pharmacokinetics of caffeine and the pharmacodynamics of glucose - both small molecules - from the ISF, indicating that that dynamic biomarker information could be obtained from the technique. Those measurements suggested that ISF could provide a means for continuously monitoring of such compounds, taking advantage of the fact that the fluid does not clot.

"We were encouraged that we found a good correlation between the blood and interstitial fluid glucose, which suggests we might be able to have a continuous glucose monitoring system based on this technology," Prausnitz said. A microneedle-based system could provide a less-invasive alternative to existing implantable glucose sensors by allowing the sensing components to remain on the surface of the skin.

In future research, Prausnitz would like to reduce the time required to extract the ISF and simplify the process by eliminating the vacuum pump. Additional study of the compounds found in the fluid could also show whether they may have medical diagnostic value. "We'd like to make this microneedle-based technique available to the research community to make ISF routinely available for study," he said. "Tissue interstitial fluid could be a novel source of biomarkers that complements conventional sources. This research provides a means to study this further."

The research team also included Nicholas Raviele, and Juan Mena-Lapaix from Georgia Tech; Megan M. Niedzwiecki, Douglas I. Walker, Gary W. Miller, Vilinh Tran, Eric I. Felner, and Dean P. Jones from Emory University.

This work was supported in part by the U.S. National Institutes of Health (U2CES026560, P30ES020953, R01ES023485, P30ES019776, S10OD018006). Any opinions, findings, and conclusions or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of the funding agencies.

Mark Prausnitz is an inventor of patents licensed to companies developing microneedle-based products, is a paid advisor to companies developing microneedle-based products, and is a founder/shareholder of companies developing microneedle-based products (Micron Biomedical). This potential conflict of interest has been disclosed and is managed by Georgia Tech. Pradnya P. Samant and Prausnitz are inventors on a patent application (WO2019126735A1) submitted by Georgia Tech Research Corporation that covers ISF collection methods presented in this study.

https://bit.ly/3mg0IIx

Painting the blades of wind turbines helps birds avoid them

A Norwegian study found avian fatalities fell 70 percent after painting one blade black

Rita Ponce

Wind power is a promising renewable source of energy and wind farms are becoming increasingly more common. However, there is a concern for their impact on wildlife, in particular as collisions with them cause the deaths of thousands of bats and birds every

year. Based on previous work, a team of researchers led by Roel May from the Norwegian Institute for Nature Research set out to test whether painting one of the blades of the turbines would increase their visibility and reduce avian fatalities. They tested their prediction at a wind-power plant in the Smøla archipelago in Norway, an area designated to be Important Bird Area by Birdlife International, where researchers have collected avian fatality data since 2006.

Out of four turbines, one was painted black and the other three were left unpainted. Fatality data from searches at the base of the turbines over three-and-a-half years showed that black paint reduced the annual rotor blade fatality rate by 70 percent.

Birds of prey, such as the white-tailed eagle, benefited the most and accounted for the largest observed decline in death. The authors attribute this to the species' excellent vision.

Their data does not indicate that birds became familiar with the painted turbines. They say this is a good thing, as fatalities could increase if birds habituate to the changes. These findings still need to be replicated in other studies. However, the authors suggest that such a strategy could be more easily put in practice before building the turbines, because painting blades with the turbines already set in place was a demanding task. As wind-power plants become more common, their impact should be reduced as much as possible. Painting their blades may be one way to go.

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Physicist creates N95-type respirators using cotton candy machine

A way to produce N95-type respirator filters that is less expensive and quicker than conventional approaches

by Bob Yirka

Mahesh Bandi, a physicist with the Nonlinear and Non-equilibrium Physics Unit, OIST Graduate University, Onna, Okinawa, has found a way to produce N95-type respirator filters that is less expensive and quicker than conventional approaches. In his paper published in *Proceedings of the Royal Society A*, he describes the technique he developed and how well his filters performed.

As the pandemic has worn on, scientists have found that mask wearing can reduce the spread of COVID-19. Unfortunately, cloth masks are far from foolproof. Research has shown that to prevent infection, people need to wear an N95 respirator—a face mask that has electrocharged filters that attract and hold viruses, preventing them from passing through. Such respirators are expensive, difficult to manufacture and are in short supply. In this new effort, Bandi has found a way to make a filter as effective as those used in N95 respirators but that can be produced quickly and cheaply.

The technique involves heating ordinary plastics such as bottles or shopping bags and then putting them into an ordinary cotton candy machine (also known as a candy floss machine). The machine spins the plastic into a material that is similar to cotton candy (a mesh), which is also electrocharged by the spinning. Bandi then cuts the resulting material into small squares and then bolsters their electrostatic charge by placing them close to the vent of a common air ionizer.

Bandi tested his filters by placing several inside of surgical masks. He found the filters worked very well, but the masks were not a viable option. He then designed his own mask to allow easy insertion and removal of the filters (each mask requires three) and used a 3-D printer to produce the result. Rigorous testing (which included microscopic inspections and comparisons with N95 filters) showed the filters to be as effective at preventing inhalation of SARS-CoV-2 viruses as standard N95-type respirators.

Bandi does not say if he has plans to set up manufacturing centers for the masks—it appears he is simply publishing the idea as a way to allow others to do so.

More information: *M. M. Bandi. Electrocharged facepiece respirator fabrics using common materials, Proceedings of the Royal Society A: Mathematical, Physical and Engineering Sciences (2020). DOI: 10.1098/rspa.2020.0469*

https://bit.ly/3o7gANO

Radboud university medical center research: Most lungs recover well after COVID-19

Extensive health assessment three months after recovery from COVID-19

Lung tissue of patients who suffered severely from COVID-19 shows good recovery in most cases. This was revealed by a study carried out by the Radboud university medical center that has now been published in *Clinical Infectious Diseases*. A striking conclusion is that the group who was referred by a GP did not recover as well as patients who were admitted to the hospital's Intensive Care Unit (ICU).

The study, led by pulmonologist Bram van den Borst, included 124 patients who had recovered from acute COVID-19 infections. They visited the Radboud university medical center corona aftercare clinic. The patients were examined by CT scan, a lung functional test and more. After three months, the researchers took stock, which revealed that the patients' lung tissue is recovering well. Residual damage in the lung tissue was generally limited and is most often seen in patients who were treated in the ICU.

The most common complaints after three months are fatigue, shortness of breath and chest pains. Many people also still experience limitations in their daily life as well as a decreased quality of life. Main researcher and pulmonologist Bram van den Borst explains: "The patterns we see in these patients show similarities with recovery after acute pneumonia or acute respiratory distress syndrome (ARDS), in which fluid accumulates in the lungs. Recovery from these conditions also generally takes a long time. It is encouraging to see that lungs after COVID-19 infections exhibit this level of recovery."

Referred patients do not recover as well as admitted patients

Patients were divided into three categories for the study: a group with patients who were admitted to the ICU, a group of patients who were admitted to a nursing ward in the hospital, and finally a group with patients who could stay home but experienced persisting symptoms that eventually warranted a referral from their GP.

The study assessed how patients fared after three months and revealed that the patients who were referred to the aftercare clinic by their GP showed the worst recovery in the following period. Of course, this latter group of patients was referred because of their persisting symptoms. "However, it does seem that there is a clear subgroup of patients who initially experienced mild COVID-19 symptoms and later kept experiencing persistent long-term complaints and limitations", Bram van den Borst elaborates. "What is striking is that we barely found any anomalies in the lungs of these patients. Considering the variety and seriousness of the complaints and the plausible size of this subgroup, there is an urgent need for further research into explanations and treatment options."

Aftercare clinic for patients with persisting symptoms

Radboud university medical center established the corona aftercare clinic at the Dekkerswald location as a reaction to an observed increase in the signals that a substantial number of COVID-19 patients was experiencing long-term complaints, ranging from coughing, fatigue and shortness of breath to anxiety and physical limitations. At the aftercare clinic, an extensive analysis is performed involving multiple disciplines. Based on this analysis, the care requirements of the patients and the subsequent steps are determined. Patients who were admitted at Radboud university medical center with COVID-19 will receive an invitation from the

corona aftercare clinic. People who went through COVID-19 from home and are still experiencing symptoms can get a referral from their GP to visit the aftercare clinic as well.

https://nyti.ms/3q6EWt7

This Rat Covers Itself With Poison That Can Take Out an Elephant

The African crested rat gnaws on poisonous tree branches, then grooms its noxious spittle into its fur.

By Katherine J. Wu

For a rodent that resembles the love child of a skunk and a steel wool brush, the African crested rat carries itself with a surprising amount of swagger. The rats "very much have the personality of something that knows it's poisonous," says Sara Weinstein, a biologist at the University of Utah and the Smithsonian Conservation Biology Institute who studies them.

The African crested rat. **Credit...Stephanie Higgins**

In sharp contrast to most of their skittish rodent kin, Lophiomys imhausi lumber about with the languidness of porcupines. When cornered, they fluff up the fur along their backs into a tip-frosted mohawk, revealing rows of black-and-white bands that run like racing stripes down their flanks — and, at their center, a thicket of specialized brown hairs with a honeycomb-like texture.

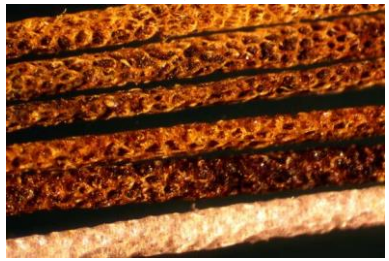
Those spongy hairs contain a poison powerful enough to bring an elephant to its knees, and are central to Dr. Weinstein's recent research, which confirmed ideas about how this rat makes itself so deadly.

Give them a chance and African crested rats will take nibbles from the branch of a poison arrow tree. It's not for nutrition. Instead, they will chew chunks of the plants and spit them back out into their fur, anointing themselves with a form of chemical armor that most likely protects them from predators like hyenas and wild dogs. The ritual transforms the rats into the world's only known toxic rodents, and ranks them among the few mammals that borrow poisons from plants.

Dr. Weinstein's research, which was published last week in the Journal of Mammalogy, is not the first to document the crested rats' bizarre behavior. But the new paper adds weight to an idea described nearly a decade ago, and offers an early glimpse into the animals' social lives.

First documented in the scientific literature in 1867, the rarely-glimpsed African crested rat "has captured so much interest for so long," said Kwasi Wrensford, a behavioral ecologist at the University of California, Berkeley who wasn't involved in the study. "We're now just starting to unpack what makes this animal tick."

People in East Africa have long known about the crested rat's poisonous punch, which has felled many an overcurious dog. (Those that survive their encounters tend to give the rats a wide berth.) In 2011, a team of researchers described the heart-stopping toxins that the rats milked from Acokanthera schimperi, a tree traditionally harvested by hunters who would use its juices to lace their arrows.



But only one crested rat, held in captivity, was observed engaging in these slathering shenanigans in the 2011 paper, raising the possibility that the behavior had been a fluke.

A microscope view of the hairs of the African crested rat, showing the honeycomb-like structure that allows them to hold the poison. **Credit...Sara B. Weinstein**

For their new paper, Dr. Weinstein and her team snared 25 rodents and filmed them in the lab. When offered cuttings of Acokanthera,

some of the animals chomped on the bark then groomed it into their stripes. Scientists still aren't sure how often the rats anoint, or even how they tolerate the toxins themselves, especially if some of it ends up going down their gullets. (Like all other rodents, they are incapable of vomiting.)

For all their toxic toughness, though, the rats seem to enjoy surprisingly heartwarming private lives. The researchers found evidence that some of the male and female rats might go steady, or even jointly care for their young, while in captivity.

"Monogamy is very rare in mammals," said Ricardo Mallarino, an evolutionary biologist at Princeton who wasn't involved in the study. If it applies to these rats, "that could be very exciting." But more research will be needed to confirm the rats' familial fidelity, he said.

Lophiomys data is apparently precious to simians other than humans as well. While doing field work in Kenya, Dr. Weinstein was horrified when a gang of monkeys broke into her lab and absconded with some of the team's crested rat fecal samples. In the chase that ensued, some of the packets of poop ripped open, scattering scat all about.

"The monkeys, I think, were equally disappointed," Dr. Weinstein said. "That's not what they were hoping was in there."

https://bbc.in/2VeaBdF

Oxford/AstraZeneca Covid vaccine 'dose error' explained

On Monday, the world heard how the UK's Covid vaccine - from AstraZeneca and Oxford University - was highly effective in advanced trials.

By Michelle Roberts Health editor, BBC News online

It gave hope of another new jab to fight the pandemic that should be cheaper and easier to distribute than the Pfizer/BioNTech and Moderna mRNA vaccines that announced similarly impressive results just days before. But after the jubilation, some negative press has followed. On Thursday, multiple news outlets in the UK and US reported that there were questions over the data. They weren't about safety, but rather how effective the jab is.

The questions centre around efficacy levels. Three were reported from the trial - an overall efficacy of 70%, a lower one of 62% and a high of 90%.

That's because different doses of the vaccine were mistakenly used in the trial. Some volunteers were given shots half the planned strength, in error. Yet that "wrong" dose turned out to be a winner.

What does that mean?

Some of the shots were weaker than they were designed to be, containing much less of the ingredient that is meant to give a person immunity. The jab is actually two shots, with the second given a month after the first as a booster. While most of the volunteers in the trial got the correct dose for both of their two shots, some didn't.

Regulators were told about the error early on and they agreed that the trial could continue and more volunteers could be immunised.

The error had no effect on vaccine safety.

What were the results?

About 3,000 participants were given the half dose and then a full dose four weeks later, and this regime appeared to provide the most protection or efficacy in the trial - around 90%.

In the larger group of nearly 9,000 volunteers, who were given two full doses also four weeks apart, efficacy was 62%.

AstraZeneca reported these percentages and also said that its vaccine was, on average, 70% effective at preventing Covid-19 illness. The figures left some experts scratching their head.

Prof David Salisbury, immunisation expert and associate fellow of the global health program at the Chatham House think tank, said: "You've taken two studies for which different doses were used and

come up with a composite that doesn't represent either of the doses. I think many people are having trouble with that."

AstraZeneca stressed that the data are preliminary, rather than full and final - which is true for the reported Pfizer and Moderna jab results too. It is science by press release.

When they can, all of the companies will publish full results in medical journals for public scrutiny. And they are submitting full data to regulators to apply for emergency approval so that countries can start using these three different vaccines to immunise whole populations.

Does it change anything?

The US regulator, called the FDA, have said any Covid vaccine needs to be at least 50% effective to be useful in fighting the pandemic. Even if you take the lowest figure of effectiveness for the AstraZeneca jab, it still passes that benchmark.

The efficacy analysis was based on 131 cases of Covid-19 that occurred in the study participants:

- ***101 of these cases happened in people who received dummy injections (either a saline jab or a meningitis vaccine).***
- ***The other 30 were in people who received the real jab - three who got the half-strength initial dose and 27 who had the two full doses.***

The Oxford researchers are investigating why the weaker dose followed by a full one appeared to work better than two full ones.

media captionLaura Foster explains why the Oxford vaccine matters

One idea is that a low then high dose shot may be a better mimic of a coronavirus infection and lead to a better immune response.

But it is possible that the volunteers who got the half doses are somewhat different to those who got two big shots.

Moncef Slaoui, the scientific head of the US's Operation Warp Speed - the programme to supply America with vaccines - told US reporters that the half-dose group only included people younger than 55.

Since age is the biggest risk factor for getting seriously ill with Covid-19, a vaccine that protects the elderly is extremely important.

However, results from an earlier phase two study of the Oxford vaccine, published in The Lancet medical journal, showed the vaccine produced a strong response in all age groups.

An AstraZeneca spokesman said: "As we communicated earlier this week, there is strong merit in continuing to further investigate the half-dose/ full dose regimen.

"We are further evaluating the data and will work with regulators on the best approach for further evaluation. This would add to data from existing trials which are currently being prepared for regulatory submission."

What do other experts say?

Although the dosing was different, the rest of the study didn't change from the original plan.

Prof Peter Openshaw, an expert at Imperial College London, says the take home message should be that we have three very promising Covid vaccines that could soon become available to help save lives.

"We have to wait for the full data and to see how the regulators view the results.

"All we have to go on is a limited data release. The protection from the Oxford AstraZeneca vaccine may be less than that from the mRNA vaccines, but we need to wait and see.

"It is remarkable that each of the trials that are now reporting shows protection, which we did not know was going to be possible."

He added: "We have been wanting vaccines for many diseases for a long time and they haven't arrived - HIV, TB and malaria being good examples. "The results so far seem to show that it can be done for Covid-19, and that's very good news indeed."

https://bit.ly/2HSd2zI

Fossil Reveals Weird, Toothed 'Toucan' That Lived Alongside The Dinosaurs

The discovery of a creature described as resembling a "buck-toothed toucan" that lived some 68 million years ago has upended assumptions about diversity in the birds that lived alongside dinosaurs.

Sara Hussein, AFP

Illustration of Falcatakely forsterae alongside dinosaurs. **Mark Witton**

At less than nine centimetres (3.5 inches) long, the delicate skull of the bird scientists have dubbed *Falcatakely forsterae* might be easily overlooked.

In fact, it almost was, sitting in a backlog of excavated fossils for years before CT scanning suggested the specimen deserved more attention.

It turns out that its tall, scythe-like beak, while resembling the toucan, is something never before seen in the fossil record.

Birds in the Mesozoic era - between 250 million and 65 million years ago - had "relatively unspecialised snouts", Patrick O'Connor, lead author of a study on the new creature, told AFP.

"Falcatakely just changed the game completely, documenting a long, high beak unlike anything known in the Mesozoic," added O'Connor, professor of anatomy and neuroscience at Ohio University.

The skull, described in a study published Wednesday in the journal *Nature*, offered other surprises. While Falcatakely would have had a face quite familiar to us from such modern birds as toucans and hornbills, the bones that made up its face bear little resemblance to those modern creatures.

"Despite an overall face shape similar to modern birds like toucans, the underlying skeleton is much more similar to non-avian theropod dinosaurs like Deinonychus and Velociraptor," O'Connor said.

That "turns what we know about Mesozoic bird anatomy upside-down."

'An almost comical profile'

Revealing these features was no easy task. The fossil was originally collected in 2010 in northwestern Madagascar. When researchers finally turned their attention to it seven years later, they faced a problem: the skull and beak were far too fragile to extract for examination.

So the team used a form of high-resolution imaging and digital modelling to "virtually dissect" the bones. They then used 3D printers to rebuild the skull and compare it with other known species.

Artist reconstruction of Falcatakely forsterae. **Mark Witton**

What they found was an almost touchingly improbable animal, according to Daniel Field, of Cambridge University's department of earth sciences, who reviewed the study for *Nature*.

It is not just the unexpected bill, but the fact that the beak in the fossil is tipped with a single preserved tooth, possibly one of many the bird would have had. "These features give the skull of Falcatakely an almost comical profile - imagine a creature resembling a tiny, buck-toothed toucan," Field wrote.

None of the approximately 200 bird species known from the period "has a skull resembling anything like Falcatakely", he added.

For O'Connor, the discovery is evidence of the potentially enormous gaps that remain in our knowledge of the birds that lived alongside dinosaurs. "There is a span exceeding 50 million years

where we know next to nothing about avian evolutionary history," he said.

Finding intact fossils of birds from the period is comparatively rare because their lightweight skeletons were generally too delicate to be well preserved.

The research team, which has been working in the area of Madagascar where Falcatakely was found since the mid-1990s, is continuing excavations, and O'Connor is excited about what else might be discovered.

He also hopes to explore just why Falcatakely had the beak it did.

"Did it relate to processing food? Acquiring prey? Was it used as a signal by other members of the species? There are many questions left," O'Connor said.

https://bit.ly/36kwNtc

A Day-by-Day Breakdown of Coronavirus Symptoms Shows How The Disease Progresses

As doctors observe a growing number of coronavirus patients, they have identified a few patterns in how typical symptoms progress.

Aria Bendix, Business Insider

As many as 40 percent of coronavirus cases are asymptomatic, according to the Centres for Disease Control and Prevention. And 20 percent of symptomatic cases become severe or critical.

Among patients who develop symptoms, a fever and cough are usually the first to arrive. They're often followed by a sore throat, headache, muscle aches and pains, nausea, or diarrhoea (though in severe cases, gastrointestinal issues can appear earlier in the course of an infection). Patients with severe infections tend to develop difficulty breathing - one of the virus' hallmark symptoms - around five days after symptoms start.

But symptoms generally don't appear right after a person has been infected. The virus' median incubation period is about four to five days, according to the Centres for Disease Control and Prevention.

During that time, an infected person likely won't yet know they're sick, but evidence shows they could transmit the virus during the presymptomatic phase.

A day-by-day breakdown

After observing thousands of patients during China's outbreak earlier this year, hospitals there identified a pattern of symptoms among COVID-19 patients:

- **Day 1:** ***Symptoms start off mild. Patients usually experience a fever, followed by a cough. A minority may have had diarrhoea or nausea one or two days before this, which could be a sign of a more severe infection.***
- **Day 3:** ***This is how long it took, on average, before patients in Wenzhou were admitted to the hospital after their symptoms started. A study of more than 550 hospitals across China also found that hospitalized patients developed pneumonia on the third day of their illness.***
- **Day 5:** ***In severe cases, symptoms could start to worsen. Patients may have difficulty breathing, especially if they are older or have a preexisting health condition.***
- **Day 7:** ***This is how long it took, on average, for some patients in Wuhan to be admitted to the hospital after their symptoms started. Other Wuhan patients developed shortness of breath on this day.***
- **Day 8:** ***By this point, patients with severe cases will have most likely developed shortness of breath, pneumonia, or acute respiratory distress syndrome (ARDS), an illness that may require intubation. ARDS is often fatal.***
- **Day 9:** ***Some Wuhan patients developed sepsis, an infection caused by an aggressive immune response, on this day.***
- **Days 10-11:** ***If patients have worsening symptoms, this is the time in the disease's progression when they're likely to be admitted to the***

ICU. These patients probably have more abdominal pain and appetite loss than patients with milder cases.

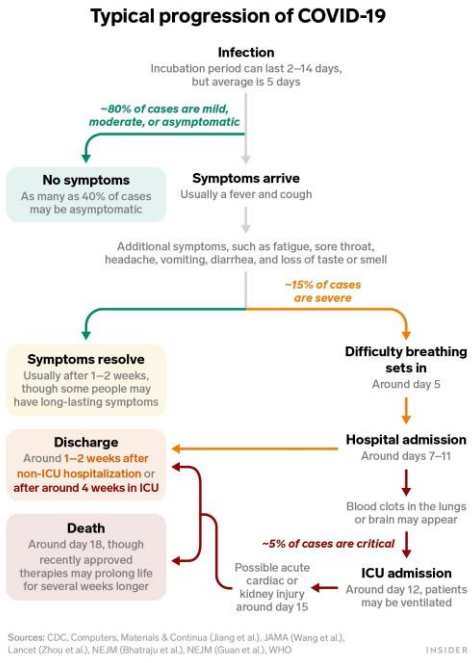
- **Day 12:** ***In some cases, patients don't develop ARDS until nearly two weeks after their illness started. One Wuhan study found that it took 12 days, on average, before patients were admitted to the ICU. Recovered patients may see their fevers resolve after 12 days.***
- **Day 16:** ***Patients may see their coughs resolve on this day, according to a Wuhan study.***
- **Day 17-21:** ***On average, people in Wuhan either recovered from the virus and were discharged from the hospital or passed away after 2.5 to 3 weeks.***
- **Day 19:** ***Patients may see their shortness of breath resolve on this day, according to a Wuhan study.***
- **Day 27:** ***Some patients stay in the hospital for longer. The average stay for Wenzhou patients was 27 days.***

Just because patients leave the hospital, though, doesn't mean their symptoms are fully gone.

Some coronavirus patients report having symptoms for months, including chest pain, shortness of breath, nausea, heart palpitations, and loss of taste and smell.

People who got sick and were never hospitalized can have lingering symptoms, too.

A July report from CDC researchers found that among nearly 300 symptomatic patients, 35 percent had not returned to their usual state of health two to three weeks after testing positive.



Shayanne Gal/Insider

Patients who felt better after a few weeks said their symptoms typically resolved four to eight days after getting tested. Loss of taste and smell usually took the longest to get back to normal, they said: around eight days, on average.

COVID-19 may be a vascular disease more than a respiratory one

Though the coronavirus attacks the lungs first, it can infect the heart, kidneys, liver, brain, and intestines as well. Some research has suggested that COVID-19 is a vascular disease instead of a respiratory one, meaning it can travel through the blood vessels. This is the reason for additional complications like heart damage or stroke.

Scientists have a few theories about why some coronavirus patients take a rapid turn for the worse. One is that immune systems overreact by producing a "cytokine storm" - a release of chemical signals that instruct the body to attack its own cells.

Dr. Panagis Galiatsatos, a pulmonary physician at Johns Hopkins Bayview Medical Centre, compared that process to an earthquake - generally, it's the falling buildings that kill someone, not the quake itself. "Your infection is a rattling of your immune system," he said. "If your immune system is just not well structured, it's just going to collapse."

The most concerning symptom: shortness of breath

Once symptoms appear, some early signs should be treated with more caution than others.

"I would of course always ask about shortness of breath before anything, because that's somebody who has to be immediately helped," Megan Coffee, an infectious-disease clinician who analysed the Wenzhou data, told Business Insider.

Patients who develop ARDS may need to be put on a ventilator in ICU. Coffee estimated that one in four hospitalized COVID-19 patients wind up on the ICU track. Those who are ultimately

discharged, she added, should expect another month of rest, rehabilitation, and recovery.

But viewing coronavirus infections based on averages can hide the fact that the disease often doesn't progress in a linear fashion.

"Courses can step by step worsen progressively. They can wax and wane, doing well one day, worse the next," Coffee said.

"An 80-year-old man with medical issues can do quite well. Sometimes a 40-year-old woman with no medical issues doesn't."

This story was originally published February 21, 2020. It has been updated over time with additional research findings.

https://bit.ly/36j9f7O

'Sistine Chapel of the ancients' rock art discovered in remote Amazon forest

Tens of thousands of ice age paintings across a cliff face shed light on people and animals from 12,500 years ago

Dalya Alberge

One of the world's largest collections of prehistoric rock art has been discovered in the Amazonian rainforest.

Hailed as "the Sistine Chapel of the ancients", archaeologists have found tens of thousands of paintings of animals and humans created up to 12,500 years ago across cliff faces that stretch across nearly eight miles in Colombia.

***The paintings are being filmed for a major Channel 4 series to be screened in December, Jungle Mystery: Lost Kingdoms of the Amazon*. Photograph: Ella Al-Shamahi**

Their date is based partly on their depictions of now-extinct ice age animals, such as the mastodon, a prehistoric relative of the elephant that hasn't roamed South America for at least 12,000 years. There are also images of the palaeolama, an extinct camelid, as well as giant sloths and ice age horses.

These animals were all seen and painted by some of the very first humans ever to reach the Amazon. Their pictures give a glimpse into a lost, ancient civilisation. Such is the sheer scale of paintings that they will take generations to study.

The discovery was made last year, but has been kept secret until now as it was filmed for a major Channel 4 series to be screened in December: *Jungle Mystery: Lost Kingdoms of the Amazon*.

The site is in the Serranía de la Lindosa where, along with the Chiribiquete national park, other rock art had been found. The documentary's presenter, Ella Al-Shamahi, an archaeologist and explorer, told the *Observer*: "The new site is so new, they haven't even given it a name yet." She spoke of the excitement of seeing "breathtaking" images that were created thousands of years ago.

The discovery was made by a British-Colombian team, funded by the European Research Council. Its leader is José Iriarte, professor of archaeology at Exeter University and a leading expert on the Amazon and pre-Columbian history.

He said: "When you're there, your emotions flow … We're talking about several tens of thousands of paintings. It's going to take generations to record them … Every turn you do, it's a new wall of paintings. "We started seeing animals that are now extinct. The pictures are so natural and so well made that we have few doubts that you're looking at a horse, for example. The ice-age horse had a wild, heavy face. It's so detailed, we can even see the horse hair. It's fascinating." The images include fish, turtles, lizards and birds, as well as people dancing and holding hands, among other scenes. One figure wears a mask resembling a bird with a beak.

The site is so remote that, after a two-hour drive from San José del Guaviare, a team of archaeologists and film-makers trekked on foot for around four hours.

They somehow avoided the region's most dangerous inhabitants. "Caimans are everywhere, and we did keep our wits about us with

snakes," Al-Shamahi said, recalling an enormous bushmaster – "the deadliest snake in the Americas with an 80% mortality rate" – that blocked their jungle path. They had been delayed getting back, and it was already pitch black. They had no choice but to walk past it, knowing that, if they were attacked, there was little chance of getting to a hospital. "You're in the middle of nowhere," she said. But it was "100%" worth it to see the paintings, she added.

Many of the painting are very high up, some so high they can only be reached by drones. **Photograph: Marie-Claire Thomas/Wild Blue Media**

As the documentary notes, Colombia is a land torn apart after 50 years of civil war that raged between Farc guerrillas and the Colombian government, now with an uneasy truce in place. The territory where the paintings have been discovered was completely off limits until recently and still involves careful negotiation to enter safely. Al-Shamahi said: "When we entered Farc territory, it was exactly as a few of us have been screaming about for a long time. Exploration is not over. Scientific discovery is not over but the big discoveries now are going to be found in places that are disputed or hostile."

The paintings vary in size. There are numerous handprints and many of the images are on that scale, be they geometric shapes, animals or humans. Others are much larger.

Al-Shamahi was struck by how high up many of them are: "I'm 5ft 10in and I would be breaking my neck looking up. How were they scaling those walls?" Some of the paintings are so high they can only be viewed with drones.

Iriarte believes that the answer lies in depictions of wooden towers among the paintings, including figures appearing to bungee jump from them. He added: "These paintings have a reddish terracotta colour. We also found pieces of ochre that they scraped to make them." Speculating on whether the paintings had a sacred or other purpose, he said: "It's interesting to see that many of these large animals appear surrounded by small men with their arms raised, almost worshipping these animals."

Observing that the imagery includes trees and hallucinogenic plants, he added: "For Amazonian people, non-humans like animals and plants have souls, and they communicate and engage with people in cooperative or hostile ways through the rituals and shamanic practices that we see depicted in the rock art."

Al-Shamahi added: "One of the most fascinating things was seeing ice age megafauna because that's a marker of time. I don't think people realise that the Amazon has shifted in the way it looks. It hasn't always been this rainforest. When you look at a horse or mastodon in these paintings, of course they weren't going to live in a forest. They're too big. Not only are they giving clues about when they were painted by some of the earliest people – that in itself is just mind-boggling – but they are also giving clues about what this very spot might have looked like: more savannah-like."

Iriarte suspects that there are many more paintings to be found: "We're just scratching the surface." The team will be back as soon as Covid-19 allows.

Jungle Mystery: Lost Kingdoms of the Amazon starts at 6.30pm on Channel 4 on 5 December. The rock art discovery is in episode 2, on 12 December