https://bit.ly/3KpVoid

Mars rover detects carbon signature that hints at past life source

Dramatically "light" carbon could also be explained by atmospheric reactions or cosmic dust

By Paul Voosen

Since 2012, NASA's Curiosity rover has trundled across Mars, drilling into rocks and running the grit through a sophisticated onboard chemistry lab, aiming to tease out evidence for life. Today, a team of rover scientists announced an intriguing signal, one that may or may not be evidence of past life, but is, at the very least, surprisingly weird. The team found that the carbon trapped in a handful of rocks probed by the rover is dramatically enriched in light isotopes of carbon. On Earth, the signal would be seen as strong evidence for ancient microbial life.

Given that this is Mars, however, the researchers are reluctant to make any grand claims, and they have worked hard to concoct alternative, nonbiological explanations involving ultraviolet (UV) light and stardust. But those alternatives are at least as far-fetched as a scenario in which subterranean microbes emitted the enriched carbon as methane gas. The team concludes the study does "inch up the plausibility" that microbes once existed on the planet—and could still today, says Christopher House, a biogeochemist at Pennsylvania State University, University Park, and lead author of the study, which was published today in the *Proceedings of the National Academy of Sciences*.

Mark Harrison, a planetary scientist at the University of California, Los Angeles, who is unaffiliated with the rover team, agrees that the carbon enrichment is a tantalizing hint at ancient life. But, "The authors are appropriately conservative," he says, noting that such signatures are debated even on Earth and that nonbiological explanations can't be ruled out.

The new study takes advantage of a time-honored insight: Life is lazy. Carbon exists in two stable isotopic forms: "light" carbon-12, which makes up the vast majority of carbon, and carbon-13, which is weighed down by an extra neutron. Because of this extra neutron, carbon-13 tends to make molecules with slightly tougher bonds. As a result, life has evolved mechanisms that favor the easier to divide carbon-12, and most organic molecules created by life are enriched in carbon-12. Methane from rice paddies, for example, is enriched in light carbon, as compared with the nonbiological methane from hydrothermal seafloor vents.

The team looked at 24 different rock samples drilled during Curiosity's journey across Gale crater, which contains the mudstones of an ancient lake. The pulverized rock was baked in an oven in the rover's belly, which converted trace amounts of carbon trapped in the rock into methane gas. The gas was then probed by a laser, which revealed the methane's isotopic makeup. The results varied widely, but at six sites, the amount of carbon-12 to carbon-13 was more than 70 parts per thousand higher than an Earth-based reference standard. "These are dramatic signals," House says. Because the strongest signals came from rocks at the top of ridges and other topographic highs in the crater, the team believes the enriched carbon was somehow deposited out of the atmosphere billions of years ago, rather than left by lake sediments.

Concentrating light carbon to such high levels might have taken multiple steps. The researchers envision deep subsurface microbes, feeding on the slightly light carbon found in martian magma, and emitting methane gas. (The martian atmosphere is deficient in light carbon, so the researchers consider it an unlikely microbial feedstock.) Then, other microbes at the surface would feed on the emitted methane, further ratcheting up the levels of light carbon, and fixing it in the fossil record when they died.

Still, the rover has seen no physical traces of ancient microbes, so

the researchers say it's also possible deep microbes might have jump-started the enrichment, with UV light driving it the rest of the way. The UV light might have broken apart the microbial methane, further enriching its light carbon while creating daughter products like formaldehyde that would eventually settle on the surface.

Or perhaps the young Solar System, including early Mars, passed through an interstellar cloud of gas and dust, which is believed to happen every 100 million years or so. The carbon in such dust is light, matching the levels seen by Curiosity, to judge by samples trapped in meteorites. The cloud might have blocked sunlight and plunged Mars into a deep freeze, causing widespread glaciation and preventing the light carbon in the rain of cosmic dust from being diluted by other carbon sources. House concedes that the scenario requires an incredible coincidence of events, and there's no evidence of glaciation at Gale crater. But he says it can't be ruled out.

More prosaically, a few studies suggest UV rays can generate the signal without help from biology at all. UV can react with carbon dioxide—which makes up 96% of the martian atmosphere—to produce carbon monoxide that is enriched in carbon-12. Yuichiro Ueno, a planetary scientist at the Tokyo Institute of Technology, says he has recently confirmed the process can occur in unpublished lab results. "The reported carbon isotope ratios are exactly what I have expected," he says.

Ueno says early Mars may have had a different atmosphere, perhaps rich in hydrogen, that reacted with the carbon monoxide to form a host of organic molecules. Those would eventually fall out of the air, depositing the signature Curiosity detected.

All these scenarios would play out in the ancient past. But Curiosity is also sniffing for carbon in today's martian air. It has detected methane, but at concentrations far too low for the rover to directly measure carbon isotope levels. (Confoundingly, sensitive instruments in orbit see no methane.) Should light carbon ever be detected in a thicker plume of methane, it would open an even more exciting possibility, House says. "Even though we're looking at a potentially ancient process, the methane today could be from the same biosphere sustained till now."

https://bit.ly/3IqnqrX

Study: Basic income would not reduce people's willingness to work

A basic income would not necessarily mean that people would work less.

by Tom Janssen, Leiden University

This is the conclusion of a series of behavioral experiments by cognitive psychologist Fenna Poletiek, social psychologist Erik de Kwaadsteniet and cognitive psychologist Bastiaan Vuyk. They also found indications that people with a basic income are more likely to find a job that suits them better.

The psychologists received a grant from the FNV union to research the behavioral effects of a basic income. They simulated the reward structure of different forms of social security in an experiment. "We got people to do a task on a computer," says De Kwaadsteniet. "In multiple rounds, which represented the months they had to work, they did a boring task in which they had to put points on a bar. The more of these they did, the more money they earned."

The psychologists researched three different conditions: no social security, a conditional benefits system and an unconditional basic income. De Kwaadsteniet: "In the condition without social security, the test participants didn't receive a basic sum. In the benefits condition they received a basic sum, which they lost as soon as they started working. In the basic income condition they received the same basic sum but didn't lose this when they started work."

The basic income did not cause a reduction in the participants' willingness to work and efforts, say the psychologists. Nor did their

salary expectations increase. "In the discussion on a basic income, it's sometimes said that people will sit around doing nothing if you give them free money," says Poletiek, who saw no indications of such a behavioral effect.

Demotivating

The conditional benefits system did prove to have a negative effect on work-seeking behavior and efforts. "As soon as you have a situation in which you lose your benefits if you start working, this is demotivating," says De Kwaadsteniet. "We saw this in nearly all the experiments."

The phenomenon in which taking on paid work leads to a reduction in benefits is also known as the benefit trap. Poletiek: "That is the disadvantage of pressurizing people to apply for jobs. You can see that this benefit trap makes people risk averse. If you are on benefits and find a job, this leads to a potentially better, but also uncertain situation in the future. You don't have this uncertainty if you keep your benefits." To avoid this risk and uncertainty, people don't look for work.

Previous studies have shown that women may work less if they receive a basic income. "In sociological studies, you see that a basic income is unfavorable to women's participation in the labor force," says Poletiek. She and De Kwaadsteniet did not see this sex difference in their own research. Poletiek: "This shows that what has been found in sociological experiments is not related to sex alone. It has nothing to do with how much women want to work. Women generally earn less than men and take on most of the caring responsibilities. That's why they are more likely to choose to swap work for caring roles if they receive a basic income."

Better match

The psychologists also found an indication that people with a basic income look for work that suits them better. "We measured whether the test participants are ambitious, whether they want to do the best they can. Are they willing to do stressful work or are they happy with a simple job as long as they earn something?" This personal attitude towards work proved to be a stronger determinant of the type of work the test participants took on in the basic income system than in the other two systems.

This is an important new finding says Poletiek. It could mean that the security of a basic income gives people the space to find the work that best suits their personal attitude, motivation and abilities. "You would then get a better match between employer and employee. That would also be an advantage to employers.

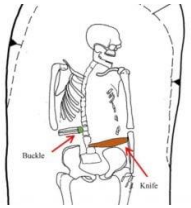
https://bit.ly/3tIXWSB

This Medieval Italian Man Replaced His Amputated Hand With a Knife

In 2018, archaeologists described a truly fascinating puzzle. It looks like this medieval Italian man went through life with a knife attached to his arm, in place of his amputated hand.

Michelle Starr

The skeleton in question was found in a Longobard necropolis in the north of Italy, dating back to around the 6th to 8th centuries CE. Hundreds of skeletons were buried there, as well as a headless horse and several greyhounds, but this particular skeleton stood out.



(Micarelli et al./Journal of Anthropological Sciences)

He was an older male, aged between 40 and 50, and his right arm had been amputated around the mid-forearm.

The researchers, led by archaeologist Ileana Micarelli of Sapienza University in Rome, determined that the hand had been removed by blunt force trauma, but exactly how or why is impossible to tell.

"One possibility is that the limb was amputated for medical reasons; perhaps the forelimb was broken due to an accidental fall or some

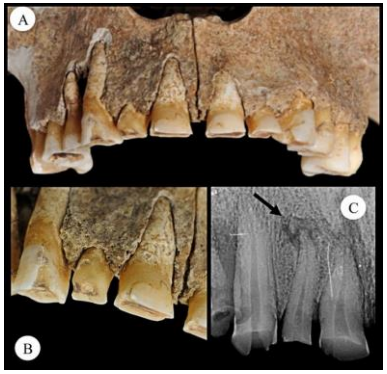
other means, resulting in an unhealable fracture," they wrote in their paper, published in the *Journal of Anthropological Sciences* in 2018.

"Still, given the warrior-specific culture of the Longobard people, a loss due to fighting is also possible."

On closer examination, the ends of the bone showed evidence of biomechanical pressure – reshaping of both bones to form a callus, and a bone spur on the ulna. These are consistent with the sort of pressure that might have been applied by a prosthesis.

Further evidence on the skeleton supports this hypothesis. The man's teeth showed extreme wear – a huge loss of enamel, and a bone lesion. He'd worn his teeth so far down on the right side of his mouth that he'd likely opened the pulp cavity, causing a bacterial infection.

What's that got to do with a prosthesis? He was probably using his teeth to tighten the straps that held it in place.



***Dental wear and the bone lesion*. (Micarelli et al.)**

His shoulder showed evidence of this too – it had developed a C-shaped ridge of bone from holding the shoulder in an unnaturally extended position to tighten the prosthesis in his mouth. The only way this ridge could have formed is if the movement was frequent.

All the other male burials with knives at the site had their arms and their weapons laid at their sides. But not this guy.

He had his right arm bent at the elbow, the arm laid across his torso. Next to it was a knife blade, the butt aligned with his amputated wrist. Also at the amputation site, archaeologists found a D-shaped buckle, and decomposed organic material – most likely leather.

This suggests a leather cap over the amputated limb, a buckle used for fastening – and a knife attached to the cap, although the purpose is unclear. However, given the advanced healing of the bone, it is clear the man lived for a long time after his hand had been amputated.

"This Longobard male shows a remarkable survival after a forelimb amputation during pre-antibiotic era. Not only did he adjust very well to his condition, he did so with the use of a culturally-derived device, along with considerable community support," the team wrote in their paper.

"The survival of this Longobard male testifies to community care, family compassion and a high value given to human life."

The team's paper was published in the *Journal of Anthropological Sciences*, where it can be read in full.

https://bit.ly/3nNKQ2K

China's population may start to shrink this year, new birth data suggest

Couples are ignoring governmental pleas and incentives to have more children

By Dennis Normile

After many decades of growth, China's population could begin to shrink this year, suggest data released yesterday by China's National Bureau of Statistics. The numbers show that in 2021, China's birth rate fell for the fifth year in a row, to a record low of 7.52 per 1000 people. Based on that number, demographers estimate the country's total fertility rate—the number of children a person will bear over their lifetime—is down to about 1.15, well below the replacement rate of 2.1 and one of the lowest in the world. Young couples are deciding against having more children, "despite all the new initiatives and propaganda to promote childbearing," says Yong Cai, a demographer at the University of North Carolina, Chapel Hill. "China's population decline will be rapid," he predicts.

The shift from growth to decline has happened startlingly fast. Projections made just a few years ago suggested China's population would expand until around 2027. Last year, when it announced

results from the 2020 census, the statistics bureau still pegged the total fertility rate at 1.3.

China's government has long promoted population control. But it has reversed course because of worries that a shrinking and aging population will strain pension systems and social services and lead to economic and geopolitical decline. The country ended its notorious one-child policy in 2016, allowing all couples to have two children. In May 2021, the limit went up to three children. Some local governments have started to offer monthly cash subsidies to couples for second and third children.

Experts say it is too little, too late. Already overworked and underpaid, and with minimal social support, few couples "put starting a family, or having another child, as their biggest priority," Cao says.

The statistics bureau also reported that China is becoming ever more urbanized, with nearly 65% of the population now living in urban areas, up 0.8 percentage points from 2020. Those who relocate to cities are typically in their reproductive prime, says Wei Guo, a demographer at Nanjing University. The crowded housing, high living costs, and exorbitant educational expenses all "reduce people's willingness to have a second child, let alone a third child," Guo says.

Yet some demographers say concerns about a looming demographic crisis are overblown. "China is certainly getting older," says Stuart Gietel-Basten, a demographer at the Hong Kong University of Science and Technology. "However, China's population is also getting healthier, better educated and skilled, and more adaptable to technology," he says. Policies to encourage lifelong training, improve productivity, and ensure healthy aging are likely to have greater impact than trying to boost the birth rate, he says.

https://bit.ly/3qK9AdX

Hormone Therapy Treatments May Increase Survival Rate in Prostate Cancer Patients

First-of-its-kind meta-analysis published in The Lancet Oncology.

Prostate cancer is the leading cause of cancer in men worldwide, and radiotherapy is one of the common forms of treatment. In a first-of-its kind meta-analysis, published today in *The Lancet Oncology*, researchers from University Hospitals (UH) and Case Western Reserve University show that there is consistent improvement in overall survival in men with intermediate- and high-risk prostate cancer with the addition of hormone therapy to radiotherapy treatments.

Throughout the past 40 years, randomized trials have been conducted on the impact of adding hormone therapy to prostate cancer treatments. While these trials individually show the benefit of hormone therapy, there are inconsistencies in timing and duration of treatment recommendations.

"Our research team set out to conduct a first-of-its-kind, comprehensive analysis by collecting individual patient data from each and every randomized trial conducted around the world, and performed a meta-analysis of the impact of various treatment intensification strategies using hormone therapy with radiation therapy for localized prostate cancer," said senior author Daniel E. Spratt, MD, Vincent K. Smith Chair in Radiation Oncology at UH Seidman Cancer Center, Professor in the Department of Radiation Oncology at Case Western Reserve School of Medicine, and Member of the Developmental Therapeutics Program at Case Comprehensive Cancer Center.

"Our goal is to better personalize therapy for prostate cancer patients, by providing the most precise and accurate estimates of the benefit of hormone therapy."

In this analysis, the team made three key discoveries:

1) Men with intermediate- and high-risk prostate cancer have an increased survival rate from the addition of hormone therapy to radiotherapy. This was seen in both younger and older men, and in men treated with lower and higher doses of radiotherapy.

2) Survival rate in men with prostate cancer improves with the prolongation of adjuvant hormone therapy to radiotherapy. This benefit was seen in both younger and older men, in men treated with lower and higher doses of radiotherapy, and in men with both intermediate- and high-risk prostate cancer. Prior to this analysis, no trial was large enough to show a clear benefit in intermediate risk disease from extending the duration of adjuvant hormone therapy.

3) The prolongation of neoadjuvant hormone therapy before radiotherapy did not benefit men in any outcome measured. This is an important finding, because some countries routinely give extended durations of hormone therapy before radiotherapy. The team showed that this method isn't advantageous over shorter durations.

"We now have estimates that show the benefit of adding and prolonging adjuvant hormone therapy for clinically relevant subsets of patients," explained Dr. Spratt. "Our team showed that treating a group of approximately ten to 15 men with hormone therapy or extended adjuvant hormone therapy, for at least 18 months, prevented one man from developing metastatic disease ten years after treatment. This is dependent on patient and tumor specific factors, but gives us a more precise estimate to work with when it comes to recommending treatment options."

The Meta-Analysis of Randomized Trials in Cancer of the Prostate (MARCAP) Consortium, is the first, comprehensive, international collaboration of randomized phase III clinical trial individual patient data. The ability to analyze data from every clinical trial group in the world, investigating the impact of hormone therapy with radiotherapy, demonstrates immense progress in the prostate oncology field.

"This work from the MARCAP consortium will bring confidence in recommending various treatment intensification strategies, and allow providers to have more accurate, shared-decision making conversations with patients about the benefits of using hormone therapy with radiotherapy for prostate cancer treatment," emphasized Dr. Spratt.

In this MARCAP analysis, 12 randomized trials were included. The research team now has more than 20 trials, and that number is continuing to grow, from groups from around the world that have agreed to share data. In the next steps for this research, this repository will be used to investigate additional clinically relevant questions regarding optimal dosing of radiotherapy, fractionation, use of pelvic nodal radiotherapy, and extending studies into the recurrent and advanced disease states.

Reference: "Androgen deprivation therapy use and duration with definitive radiotherapy for localized prostate cancer: an individual patient data meta-analysis" by Amar U Kishan, MD; Yilun Sun, PhD; Holly Hartman, PhD; Prof Thomas M Pisansky, MD; Prof Michel Bolla, MD; Anouk Neven, MSc; Allison Steigler, BMath; Prof James W Denham, FRANZCR; Prof Felix Y Feng, MD; Almudena Zapatero, MD PhD; Prof John G Armstrong, MD; Abdenour Nabid, MD; Nathalie Carrier, MSc; Prof Luis Souhami, MD; Mary T Dunne, MSc; Prof Jason A Efstathiou, MD; Prof Howard M Sandler, MD; Araceli Guerrero, MD; Prof David Joseph, MD; Prof Philippe Maingon, MD; Theo M de Reijke, PhD; Xavier Maldonado, MD; Ting Martin Ma, PhD; Tahmineh Romero, MS; Xiaoyan Wang, PhD; Matthew B Rettig, MD; Prof Robert E Reiter, MD; Nicholas G Zaorsky, MD; Prof Michael L Steinberg, MD; Nicholas G Nickols, PhD; Angela Y Jia, MD and Prof Jorge A Garcia, MD, 17 January 2022, The Lancet Oncology.
DOI: 10.1016/S1470-2045(21)00705-1 *The Prostate Cancer Program at UH Seidman Cancer Center is one of the leading clinical and research programs nationally, and serves as one of the two international data repositories for the MARCAP consortium.*

A special thanks to Dr. Jorge Garcia, Chief of Medical Oncology, UH Seidman Cancer Center; Dr. Nicholas Zaorsky, Vice Chair of Medical Education, UH Seidman Cancer Center Department of Radiation Oncology; Dr. Jonathan Shoag, UH Seidman Cancer Center, Department of Urology; Dr. Holly Hartman, Assistant Professor at Case Western Reserve University; and Dr. Yilun Sun, Director of Biostatistics at UH Seidman Cancer Center Department of Radiation Oncology, and Assistant Professor at Case Western Reserve University.

https://bit.ly/3FJZeiA

More Than Two-Thirds of Adverse COVID-19 Vaccine Events Are Due to Placebo Effect

One-third of clinical trial participants who received no vaccine reported systemic adverse advents like headache and fatigue.

The placebo effect is the well-known phenomenon of a person's physical or mental health improving after taking a treatment with no pharmacological therapeutic benefit – a sugar pill, or a syringe full of saline, for example.

While the exact biological, psychological, and genetic underpinnings of the placebo effect are not well understood, some theories point to expectations as the primary cause and others argue that non-conscious factors embedded in the patient-physician relationship automatically turn down the volume of symptoms. Sometimes placebo effects can also harm –the so-called "nocebo effect" occurs when a person experiencing unpleasant side effects after taking a treatment with no pharmacological effects. That same sugar pill causing nausea, or that syringe full of saline resulting in fatigue.

In a new meta-analysis of randomized, placebo-controlled COVID-19 vaccine trials, researchers at Beth Israel Deaconess Medical Center (BIDMC) compared the rates of adverse events reported by participants who received the vaccines to the rates of adverse events reported by those who received a placebo injection containing no vaccine. While the scientists found significantly more trial participants who received the vaccine reported adverse events, nearly a third of participants who received the placebo also reported at least one adverse event, with headache and fatigue being the most common. The team's findings are published in *JAMA Network Open*.

"Adverse events after placebo treatment are common in randomized controlled trials," said lead author Julia W. Haas, PhD, an investigator in the Program in Placebo Studies at BIDMC. "Collecting systematic evidence regarding these nocebo responses in vaccine trials is important for COVID-19 vaccination worldwide, especially because concern about side effects is reported to be a reason for vaccine hesitancy."

Haas and colleagues analyzed data from 12 clinical trials of COVID-19 vaccines. The 12 trials included adverse effects reports from 22,578 placebo recipients and 22,802 vaccine recipients. After the first injection, more than 35 percent of placebo recipients experienced systemic adverse events – symptoms affecting the entire body, such as fever – with headache and fatigue most common at 19.6 percent and 16.7 percent, respectively. Sixteen percent of placebo recipients reported at least one local event, such as pain at site of injection, redness, or swelling.

In comparison after the first injection, 46 percent of vaccine recipients experienced at least one systemic adverse event and two-thirds of them reported at least one local event.

While this group received a pharmacologically active treatment, at least some of their adverse events are attributable to the placebo – or in this case, nocebo – effect, as well given that many of these effects also occurred in the placebo group. Haas and colleagues' analysis suggested that nocebo accounted for 76 percent of all adverse events in the vaccine group and nearly a quarter of all local effects reported.

After the second dose, adverse events among the placebo group dipped to 32 percent reporting any systemic events and 12 percent reporting any local effects. In contrast, participants who received the vaccine reported more side effects, with 61 percent reporting systemic adverse events and 73 percent reporting local adverse events.

The researchers calculated that nocebo accounted for nearly 52 percent of the side effects reported after the second dose. While the

reason for this relative decline in nocebo effects cannot be confirmed, the researchers believe that the higher rate of adverse events in the vaccine group the first time may have led participants to anticipate more the second time.

“Nonspecific symptoms like headache and fatigue – which we have shown to be particularly nocebo sensitive – are listed among the most common adverse reactions following COVID-19 vaccination in many information leaflets,” said senior author Ted J. Kaptchuk, director of the Program in Placebo Studies and the Therapeutic Encounter at BIDMC and professor of medicine at Harvard Medical School. “Evidence suggests that this sort of information may cause people to misattribute common daily background sensations as arising from the vaccine or cause anxiety and worry that make people hyper alert to bodily feelings about adverse events.”

Kaptchuk and colleagues are known for a large and growing body of evidence showing that full disclosure of placebo treatment, what he calls “open label placebo,” can actually improve common chronic conditions without any nocebo effects.

While some researchers believe that informing patients about adverse effects may cause harm, Kaptchuk believes it is ethically necessary to fully inform participants about the vaccines’ potential adverse reactions.

“Medicine is based on trust,” said Kaptchuk. “Our findings lead us to suggest that informing the public about the potential for nocebo responses could help reduce worries about COVID-19 vaccination, which might decrease vaccination hesitancy.”

Reference: “Frequency of Adverse Events in the Placebo Arms of COVID-19 Vaccine Trials” 18 January 2022, JAMA Network Open.

Co-authors included Sarah Ballou, PhD, and John Kelly, PhD of BIDMC; Friederike L. Bender, MS, Marcel Wilhelm, PhD, and Winfried Rief, PhD of Philipps University Marburg; and Franklin G. Miller PhD, of Weill Cornell Medical College.

This work was supported in part by a postdoctoral fellowship by the German Academic Exchange Service (Deutscher Akademischer Austauschdienst, DAAD) to Haas.

https://wb.md/3FRiBpK

Fourth Vaccine Shot Less Effective Against Omicron, Israeli Study Says

A fourth shot of the COVID-19 vaccine boosts antibodies but doesn't provide enough protection to prevent infections from the Omicron variant, according to new research at an Israeli hospital.

Carolyn Crist

The preliminary results, released on Monday, challenge the idea of giving a second booster dose to slow the spread of the coronavirus, according to *USA Today*.

"Despite increased antibody levels, the fourth vaccine only offers a partial defense against the virus," Gili Regev-Yochay, MD, director of the hospital's infection prevention and control units, told reporters. "The vaccines, which were more effective against previous variants, offer less protection versus Omicron," she said.

In a clinical trial, 274 medical workers at Sheba Medical Center near Tel Aviv received a fourth vaccine dose in December — 154 got the Pfizer vaccine and 120 got the Moderna vaccine — after previously getting three Pfizer shots.

Both groups received a boost in antibodies that was "slightly higher" than after the third shot, Regev-Yochay said. But when compared with a control group that didn't receive the fourth dose, the extra boost didn't prevent the spread of Omicron.

"We see many infected with Omicron who received the fourth dose," Regev-Yochay said. "Granted, a bit less than in the control group, but still a lot of infections."

Some public health officials in Israel say the campaign for fourth doses is still worthwhile, according to *The Times of Israel*. The vaccine still works well against the Alpha and Delta variants, Regev-Yochay said, and a fourth shot should go to older adults and those who face higher risks for severe COVID-19.

Hours after releasing the preliminary results, Sheba Medical Center

published a statement calling for "continuing the vaccination drive for risk groups at this time, even though the vaccine doesn't provide optimal protection against getting infected with the variant." News outlets reported that the hospital was pressured into issuing the statement after Israel's Health Ministry didn't like the release of the early study results, *The Times of Israel* reported.

The second booster "returns the level of antibodies to what it was at the beginning of the third booster," Nachman Ash, MD, director of Israel's Health Ministry, told Channel 13 TV in Israel, according to The Associated Press. "That has great importance, especially among the older population," he said.

As of Sunday, more than 500,000 people in Israel had received fourth doses since the country began offering them last month to medical workers, immunocompromised patients, and people ages 60 years and older, the AP reported. At the same time, the country has faced a recent coronavirus surge that has led to record-breaking numbers of cases and rising hospitalizations.

On Tuesday, the Israeli government said it would shorten the mandatory quarantine period from 7 days to 5 days, the AP reported. "This decision will enable us to continue safeguarding public health on the one hand and to keep the economy going at this time on the other, even though it is difficult, so that we can get through this wave safely," Prime Minister Naftali Bennett said.

https://bit.ly/3rH8xLh

Something in Your Eyes May Reveal if You're at Risk of Early Death, Study Shows

A quick and pain-free scan of the human eyeball could one day help doctors identify 'fast agers', who are at greater risk of early mortality.

Carly Cassella

Getting older obviously has an impact on everybody's body, but just because two people have the same number of years under their belt doesn't mean they are physically declining at the same rate.

Looking deep into a person's eyes could be a far better way to measure their true biological age, and this could provide a glimpse into the future health of patients. A machine learning model has now been taught to predict a person's years of life simply by looking at their retina, which is the tissue at the back of the eye.

The algorithm is so accurate, it could predict the age of nearly 47,000 middle-aged and elderly adults in the United Kingdom within a bracket of 3.5 years. Just over a decade after these retinas were scanned, 1,871 individuals had died, and those who had older-looking retinas were more likely to fall in this group.

For instance, if the algorithm predicted a person's retina was a year older than their actual age, their risk of death from any cause in the next 11 years went up by 2 percent. At the same time, their risk of death from a cause other than cardiovascular disease or cancer went up by 3 percent.

The findings are purely observational, which means we still don't know what is driving this relationship at a biological level.

Nevertheless, the results support growing evidence that the retina is highly sensitive to the damages of aging. Because this visible tissue hosts both blood vessels and nerves, it could tell us important information about an individual's vascular and brain health.

Previous studies have suggested the cells at the back of the human eye can help us predict the onset of cardiovascular disease, kidney disease, and other signs of aging. But this is the first study to present the 'retinal age gap' as a strong predictor of mortality as a whole.

"The significant association between retinal age gap and non-cardiovascular/non-cancer mortality, together with the growing evidence of the link between eye and brain, may support the notion that the retina is the 'window' of neurological diseases," the authors write.

Because only 20 people in the study died due to dementia, the authors were unable to link this specific brain disorder to retinal health.

They also point out that cardiovascular-related deaths have gone down in recent years, as medicine continues to prevent what would once have been fatal events. This means that retinal health could still be an important lens into cardiovascular health, despite the fact that it was not linked to cardiovascular mortality. Previous studies, for instance, have shown photographs of the retina can help predict cardiovascular risk factors.

"This body of work supports the hypothesis that the retina plays an important role in the aging process and is sensitive to the cumulative damages of aging which increase the mortality risk," the authors conclude.

Other existing predictors of biological age, like neuroimaging, the DNA methylation clock, and the transcriptome aging clock, are not as accurate as the retinal age gap appears to be. These methods can also be costly, time-consuming and invasive.

The retina, meanwhile, can be easily scanned in less than 5 minutes. If we can learn more about how this layer of tissue is connected to the rest of the body, clinicians could have an excellent new tool on their hands.

The study was published in the *British Journal of Ophthalmology*.

https://bit.ly/33Dehh8

Scientists identify therapeutic target for Epstein-Barr virus

New potential pathway identified for developing therapeutics that target Epstein-Barr virus

A new study by researchers at The Wistar Institute, an international biomedical research leader in cancer, immunology, infectious disease, and vaccine development, has identified a new potential pathway for developing therapeutics that target Epstein-Barr virus (EBV). They discovered that the way the EBV genome folds, and thereby expresses itself and causes disease, is more complex than researchers originally thought, and they identified molecules that could be targeted to disrupt this folding.

"We identified two cellular proteins that are important to folding the EBV genome." said Italo Tempera, Ph.D., associate professor in the Gene Expression & Regulation Program at The Wistar Institute and corresponding author on the paper. "There are existing drugs that target one of these proteins. And our data suggests that if we use that drug on EBV infected cells, we have a way in which we can actually interfere with the folding. That means we can interfere in the way in which the EBV viral genome is functioning."

EBV, which affects more than 90 percent of individuals worldwide, is a dynamic virus, meaning that it can change its gene expression. If certain viral genes are expressed, the virus infects B-cells and causes them to overmultiply, which is especially problematic in individuals with suppressed immune systems, such as transplant patients.

Tempera and his colleagues wanted to understand the mechanics behind how the virus manipulates its genetic expression. To do this, they used a modified DNA sequencing technique to examine how the genome folds under different conditions.

"The virus was clever to use the same machinery that regulates the conformation of the human genome to also regulate its own gene expression," said Tempera. Specifically, the researchers found that EBV uses two proteins, CTCF and PARP1, that also play a role in the expression of the human genome.

PARP1 is already a target of the drug, olaparib (sold under the brand name Lynparza), which is used to treat patients with ovarian cancer. This new study suggests that the drug may have a use for treating EBV positive lymphomas, as well.

"Usually PARP1 is targeted in the context of DNA damage," said

Tempera. "Our paper shows that there is another role of PARP1 in the chromatin folding, so this suggests that maybe we can expand the way in which we can use this drug not only to interfere with DNA damage, but we also might interfere with DNA folding and gene expression, which is something that we are testing now in the lab."

More information: *Sarah M. Morgan et al, The three-dimensional structure of Epstein-Barr virus genome varies by latency type and is regulated by PARP1 enzymatic activity, Nature Communications (2022).* *DOI: 10.1038/s41467-021-27894-1*

https://bit.ly/3Anf2Xi

The secrets of ancient Japanese tombs revealed thanks to satellite images

Results show that kofun are oriented towards the arc of the rising sun

A research group at the Politecnico di Milano analyzed the orientation of ancient Japanese tombs—the so-called Kofun.

This study has never been carried out before, due to the very large number of monuments and the fact that access to these areas is usually forbidden. For these reasons, high-res satellite imagery was used. The results show that these tombs are oriented towards the arc of the rising sun, the Goddess Amaterasu that the Japanese emperors linked to the mythical origin of their dynasty.

Daisen Kofun, aerial view. **Credit: Ministry of Territory, Infrastructure, Transport and Tourism**

The Japanese islands are dotted with hundreds of ancient burial mounds, the largest of which are in the typical shape of a keyhole and are called Kofun. Built between the third and the seventh centuries AD, the most imposing are attributed to the semi-legendary first emperors, while the smaller ones probably belong to court officers and to members of the royal family. Among these, the so-called Daisen Kofun is one of the largest monuments ever built on Earth: it measures 486 meters in length and about 36 in height. It is traditionally attributed to Emperor Nintoku, the sixteenth emperor of Japan.

The Daisen Kofun belongs to a group of tombs recently inscribed in the UNESCO World Heritage List. There are no written sources on these tombs, and excavations are rare and limited to the smaller ones, since the largest are considered the tombs of the first semi-legendary emperors and, as such, are strictly protected by law. Protection also extends to the outside: many monuments are fenced, and it is not allowed to enter the perimeter. For these reasons, it is impossible to obtain accurate measurements of size, height and orientation. Furthermore, their number discourages any on field investigation. It is therefore natural to study them using high-resolution satellite images, which furnish simple but very powerful tools for remote sensing investigations.

This is what Norma Baratta, Arianna Picotti and Giulio Magli of the Politecnico di Milano did, with the aim of deepening the knowledge of the relationships between these fascinating monuments with the landscape and, in particular, with the sky. The team measured the orientation of more than 100 Kofuns and came to interesting conclusions. The results—just published in the scientific journal "*Remote Sensing*" —indicate a strong connection of the Kofun entrance corridors with the arc in the sky where the Sun and the Moon are visible every day of the year, and show the orientation of the hugest keyhole-shaped Kofuns to the arc of the Sun rising/shining. In particular, the Daisen Kofun is oriented towards the Sun rising at the winter solstice.

Orientation of the imperial tombs towards the Sun does not happen by chance: rather, it is in full agreement with the Japanese imperial tradition. Indeed, the mythical origin of the dynasty of the Japanese

Emperors considers them as direct descendants of the Sun Goddess Amaterasu.

More information: *Norma Camilla Baratta et al, The Orientation of the Kofun Tombs, Remote Sensing (2022). DOI: 10.3390/rs14020377 Provided by Politecnico di Milano*

https://bit.ly/3nQdQH1

Kombucha water filters can resist clogging better than commercial options

Water filters made from a kombucha culture with living bacteria and yeast are more resistant to clogging, compared to traditional membrane filters

Commercially available ultrafiltration membranes that purify water are expensive and get clogged easily by particles and microorganisms. Recently, living filtration membranes were reported as an alternative sieving material. Grown from kombucha cultures, the filters are dense, stacked sheets of bacterial cellulose. Now, researchers reporting in *ACS ES&T Water* show that these living membranes are more resistant to clogging and biofouling, making them more efficient and less expensive to use than conventional ones.

Decontaminating water so that it's safe to drink requires materials that remove impurities and disease-causing pathogens, including bacteria, parasites and viruses. Polymer-based filters with tiny holes can fulfill this need, but their lifetime is limited because their pores get plugged easily. Some contaminant microorganisms speed up this process by producing sticky substances that create a glue-like biofilm, coating the inside of the membranes and blocking water flow.

In a recent study, Katherine Zodrow and colleagues reported on living membranes made of a permeable bacterial cellulose film that they grew from a symbiotic culture of bacteria and yeast (SCOBY), which is used to ferment tea into the popular drink kombucha. These membranes can be tuned to filter different sizes of particles, and because they're alive, can heal themselves. Some of the microbes found in SCOBY belong to a family known to produce acetic acid, which can kill bacteria, including those that secrete biofilms. So, another team led by Zodrow wanted to see if living filtration membranes could resist fouling and last longer than commercial polymer membranes.

The researchers cultivated a kombucha SCOBY in a solution of sugar, black tea, distilled white vinegar and water. A thin permeable membrane of fungi and Acetobacter bacteria grew where the culture came into contact with air. Then, the team filtered water from two reservoirs and a river in Montana with both a living membrane and a commercial membrane made from two cellulose esters. While both materials clogged and filtered more slowly over time, the SCOBY-sourced membrane resisted fouling better and maintained faster filtering, especially with the dirtier and microorganism-laden water samples. Although a biofilm eventually formed in the living membrane, too, there were fewer microorganisms within that film. According to the researchers, this result could mean that the acetic acid-producing bacteria embedded within the material discouraged the growth of bacteria that contribute to biofilms. Based on these results, the team says that living membranes could be an inexpensive, biodegradable and effective way to treat water.

More information: *Carson W. Bechtel et al, Living Filtration Membranes Demonstrate Antibiofouling Properties, ACS ES&T Water (2021). DOI: 10.1021/acsestwater.1c00169*

https://bit.ly/3qTkGgO

Ice Peeks out of a Cliffside on Mars

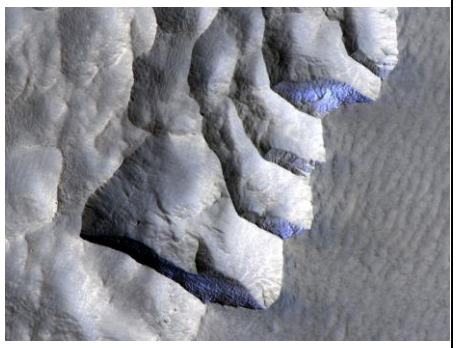
A layer of sediment obscures most of the ice, but fingers of it are visible.

by Evan Gough

The HiRISE (High-Resolution Imaging Science Experiment) camera on the Mars Reconnaissance Orbiter has captured another beauty. This time the image shows water ice peeking out from a

cliffside on Mars. A layer of sediment obscures most of the ice, but fingers of it are visible.

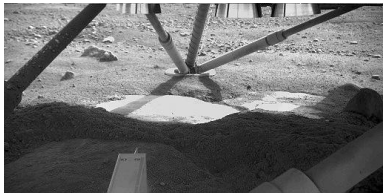
Mars likely had ancient oceans, and the remnants of all that water are hidden as ice. It's mostly buried in the planet's crust. In this image, it's under a thick layer of sediment. The image is from Mars' Milankovic Crater, a prominent impact crater that sits alone to the north of Olympus Mons, Mars' tallest volcano, and the tallest volcano in the Solar System.



Mars' ancient oceans were turned to ice when Mars lost its atmosphere between about 3.7 billion to 4.2 billion years ago. The water now exists mostly as subsurface ice.

A 2018 study found evidence of a complex of liquid saltwater lakes under the south polar region, which generated a lot of excitement. In 2019, researchers proposed that magma activity in the preceding one million years created enough heat to maintain that water in liquid form. Then in 2021, another study pointed out that the discovery of the subglacial polar lakes could be explained by other phenomena.

The existence of subglacial lakes of water on Mars will likely remain controversial for a long time. But the existence of subsurface water ice isn't controversial. We've seen it.

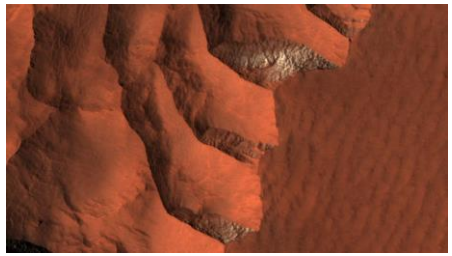


When NASA's Phoenix Lander arrived on Mars in 2008 its retro-rockets exposed the shallow subsurface. Scientists believe that the white patch is water ice. **Image Credit: By NASA/Jet Propulsion Lab-Caltech/University of Arizona/Max Planck Institute – This image or video was catalogued by Jet Propulsion Laboratory of the United States National Aeronautics and Space Administration (NASA) under Photo ID: PIA10741., Public Domain, https://commons.wikimedia.org/w/index.php?curid=4143566**

Mars' water exists as ice, locked into the planet's crust at varying depths, except for the possibility of liquid water heated by magma existing under the polar region.

Scientists think that there are at least 5 million cubic kilometres of ice underground, with even more at depths beyond the capabilities of our current remote sensing instruments. Some of that ice is visible in the HiRISE image, peeking out from under a layer of sediment.

The leading HiRISE image above is an infrared-red-blue image that highlights the presence of the ice. The RGB image below is more representative of what human eyes would see.



This image resembles more closely what the ice looks like to human eyes, but doesn't highlight the presence of the ice as well as the IR image. **Image Credit: NASA/JPL/UArizona**

We've improved our understanding of Martian water dramatically in recent years. A 2021 study showed that between 30% and 90% of Mars' original water may be frozen under the surface, with large deposits in the Arcadia Planitia region. In 2019 NASA made a map of Martian water across the planet's surface. NASA said that some of the water is only 30 cm (12 inches) deep, making it easily accessible to future explorers.

It's clear that humanity is reaching out to Mars. With our orbiters, landers, and rovers, we're piecing together the planet's history. Mars was once wet and warm and may have harboured life. Future sample-return missions might confirm the presence of microbial fossils. That would be a huge discovery, worthy of all the fanfare it would no doubt generate.

But we want to set foot on Mars, sometime, somehow. And when that happens, our explorers will know where to find water.

https://bit.ly/3r2c5Zv

The coronavirus may cause fat cells to miscommunicate, leading to diabetes

COVID-19 patients with high blood sugar had low levels of a hormone made by fat

By Tina Hesman Saey

Nola Sullivan recently marked an inauspicious anniversary. A little more than a year ago, on November 16, 2020, the 57-year-old pharmacy technician from Kellogg, Idaho, came down with COVID-19.

"I lost my taste and smell, with a very bad head cold, body aches, muscle spasm, fatigue, nausea, vomiting, diarrhea," she says. It took a month for her muscle spasms and a lingering headache to go away. She missed nearly three months of work. Her senses of smell and taste still haven't fully returned. And "I still have the fatigue. It's horrible. I'm nauseous all the time."

Sullivan has another lasting reminder of her battle with the coronavirus, too: diabetes.

When she finally returned to work at the pharmacy, "I noticed that I was so thirsty all the time. And I just thought that was part of the COVID," she says. "I was drinking gallons of water." As a pharmacy technician, though, she knew that excessive thirst can be sign of diabetes. So she decided to check her blood sugar. A person is considered diabetic when levels of glucose in their blood reach 200 milligrams of glucose per deciliter of blood. Sullivan's was over 500.

Sullivan is not alone.

People who had COVID-19 were 31 percent to 166 percent more likely to develop diabetes than people who never got the disease, researchers from the U.S. Centers for Disease Control and Prevention report in the Jan. 14 *Morbidity and Mortality Weekly Report*. And diabetes was 116 percent more likely to strike people who had infections with SARS-CoV-2, the coronavirus that causes COVID-19, than people who had infections with other respiratory viruses. The new cases of diabetes after COVID-19 includes type 1 diabetes in children younger than 18 years-old and type 2 diabetes in adults.

In an earlier study of more than 3,800 COVID-19 patients, just under half developed high blood sugar levels, including many, like Sullivan, who were not previously diabetic, cardiologist James Lo and colleagues reported November 2 in *Cell Metabolism*. About 91 percent of the intubated COVID-19 patients had high blood sugar, as did almost 73 percent of people who died of the disease, the researchers reported.

Lo's group, based at Weill Cornell Medicine in New York City, and others are now working to identify what's causing high blood sugar in COVID-19 patients and what to do about it.

Sugar spikes

In March and April of 2020 — months before Sullivan caught COVID-19 — Columbia University Medical Center in New York City was full of COVID-19 patients. There, endocrinologist Utpal Pajvani noticed that "a lot of those people — but not a majority — were coming in with very high blood sugars. For some of those people, this was brand new for them."

Lo too noticed that many of the COVID-19 patients in his hospital's intensive care unit had high blood sugar. Preexisting diabetes is a risk factor for poor outcomes from COVID-19. But, like Sullivan, many of the patients Lo and his colleagues were seeing did not have diabetes before they got ill. People sometimes develop diabetes as they age, but Lo's patients with high blood sugar were often "youngish, in their 30s and 40s," he says. And levels of glucose in their blood were incredibly high, sometimes more than twice the level that indicates diabetes.

Such sky-high levels of blood sugar were associated with a 15

times higher risk of intubation and 3.6 times higher risk of death compared with people with the disease who had normal blood sugar levels, Lo and colleagues found.

Notes Pajvani, "we don't know if the high blood sugar is causal of the bad outcome or reflective of the bad outcome." Still, he and other doctors aren't totally surprised by the connection between COVID-19 and high blood sugar, or hyperglycemia.

High blood sugar has been documented in people with acute respiratory distress syndrome, or ARDS, caused by injuries or infections with other viruses or bacteria. ARDS is a condition in which the lungs can't supply enough oxygen to the body.

COVID-19 patients with ARDS and high blood sugar spent three times longer in the hospital than people with ARDS caused by COVID-19 who have normal blood sugar levels, Lo and colleagues found. But weirdly people with hyperglycemia who had ARDS caused by COVID-19 were less likely to die than hyperglycemic people with ARDS due to other causes.

"The outlook was still bad, just not as bad in the group with ARDS and COVID, which is surprising," says Ralph DeFronzo, an endocrinologist and chief of the diabetes division at the University of Texas Health Science Center at San Antonio, who was not involved with Lo's study.

Fingering a culprit

Exactly what sends blood sugar soaring and causes diabetes in COVID-19 patients has been a mystery. Some evidence has hinted at the coronavirus infecting cells in the pancreas that make insulin, a hormone that lowers blood sugar levels by signaling cells to take in sugar and burn it for fuel. But in Lo's study, COVID-19 patients with high blood sugar still made high levels of C-peptide, a naturally occurring bit of protein that links two chains of insulin and is made alongside insulin in pancreatic cells. High C-peptide levels indicate that the patients' pancreatic cells were producing insulin.

These patients' blood sugar was still high, though. So if the pancreatic cells weren't the problem, something else must be going wrong.

That something else may be that fat cells infected with the coronavirus send the wrong message to other cells, ultimately leading to diabetes, Lo and colleagues suggest. Lo's team discovered that COVID-19 patients had low levels of adiponectin, a hormone produced by fat cells that helps other cells heed insulin's call to take in sugar. People with obesity also often make low levels of adiponectin, possibly explaining why they are at risk for poor outcomes from COVID-19 (*SN: 4/22/20*). Levels of several other hormones produced by fat cells were also out of whack, the researchers found.

The findings suggest that COVID-19 patients' high blood sugar levels result from insulin resistance — a condition in which cells ignore insulin's message to take in glucose — brought on by a dearth of fat hormones rather than by an inability to produce insulin.

The coronavirus can infect fat cells, the researchers' experiments with hamsters and with cells grown in lab dishes showed. Damage done to fat cells directly by the virus, or indirectly by inflammation directed toward fighting the virus, may interfere with fat cells' ability to make normal hormone levels and help maintain steady blood sugar levels.

Experiments by other researchers have also indicated that SARS-CoV-2, the virus that causes COVID-19, can replicate in human fat, also known as adipose tissue, says Jose Aleman, an endocrinologist at the New York University Grossman School of Medicine. That's yet another clue that fat is involved in severe disease.

For instance, autopsies revealed that the coronavirus had infected fat cells of 10 of 18 men who died of COVID-19, researchers in Germany report January 4 in *Cell Metabolism*. All 10 of the men

with coronavirus in their fat were overweight or obese. The researchers also found SARS-CoV-2 in fat cells of 5 of 12 women who died of COVID-19, but those women were not all overweight or obese.

Inspired by Lo's work, the German team uncovered evidence that coronavirus infection also affects fat cells' ability to metabolize some lipids, leading people with COVID-19 to develop high levels of triglycerides in their blood. That's yet another clue that fat isn't working properly in some COVID patients. And these changes in fat may contribute to more severe COVID-19.

Obesity is often associated with inflammation in fat and other tissues. Coronavirus infection may make that inflammation worse, tipping the scales toward messed-up hormone production and eventual diabetes, Aleman says. Lo's findings "lend credence to the idea that adipose is the reservoir for this low-grade inflammation that then gets triggered by COVID," Aleman says.

But the conclusion is not a slam dunk, Pajvani says. "This is an example of very good research done in very difficult settings." But because the study looked back a group of patients, but didn't match their characteristics and limit other variables from the beginning, the work can't definitively show the cause of COVID-related diabetes. "This gives us a great hint of the type of study to do," he says.

A lasting legacy

Whether coronavirus infections cause diabetes or simply unmask the condition in susceptible people, such as people who are overweight or obese, is not yet clear, DeFronzo says. Aleman agrees. "A lot of these patients have an underlying state of insulin resistance, likely prediabetes, but then acute illness in the form of COVID-19 tips [them] over to diabetes."

Doctors may be able to counteract high blood sugar by giving COVID-19 patients drugs called thiazolidinediones or glitazones that make cells more sensitive to insulin's action. DeFronzo says he hopes to test one of those drugs called pioglitazone in COVID-19 patients with high blood sugar. The aim is to prevent the worst outcomes from COVID-19, but patients' high blood sugar may linger.

For Sullivan, changing her diet and taking medication have helped her to control her blood sugar levels. "I've lost almost 60 pounds," she says. But "they say that the diabetes will probably be for life."

Trishla Ostwal contributed reporting to this story.

Editor's Note:

This story was updated January 13, 2022, to include a new study on the incidence of developing diabetes after a COVID-19 infection.

Citations

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https://bbc.in/3KDAaxt

Moorfields Eye Hospital gives woman, 88, bionic eye implant

An 88-year-old woman from east London has received a pioneering eye implant to help partially restore her deteriorating vision.

The surgery at Moorfields Eye Hospital involved inserting a 2mm wide microchip under her retina by surgically creating a 'trapdoor' in which the chip rests. Special glasses, containing a camera connected to a small computer attached to a waistband, make seeing possible.

"I am thrilled to be the first to have this implant," the recipient said.

The patient suffers from the most common form of dry age-related macular degeneration (AMD) and the implant offers the hope of partially restored vision for those with geographic atrophy (GA).

The 88-year-old grandmother of eight from Dagenham suffers from dry age-related macular degeneration (AMD) **Image source, Moorfields Eye Hospital**

This condition is progressive and currently has no treatment. Some 12% of those aged over 80 will be affected by dry AMD, while GA affects 6.7% of over 80s.

Once the microchip has been implanted under a patient's retina, it captures visual scenes projected by the glasses and transmits this to the computer.

Artificial intelligence (AI) algorithms process this and instruct the glasses on what to focus on. The glasses then project that image as an infra-red beam through the eye and into the chip, and convert it into an electrical signal going "into the brain, where it is interpreted as if it were natural vision".

The Dagenham dweller said AMD had stopped her from gardening, playing indoor bowls and painting with watercolours.

She added: "I am excited at the prospect of enjoying my hobbies again and I truly hope that many others will benefit from this too."

Mahi Muqit, consultant vitreoretinal surgeon at Moorfields Eye Hospital, said: "This ground-breaking device offers the hope of restoration of sight to people suffering vision loss due to dry AMD.

"The success of this operation, and the evidence gathered through this clinical study, will provide the evidence to determine the true potential of this treatment."

In November, a man from Hackney, east London, became the first person in the world to have a 3D-printed prosthetic eye at the same hospital.

https://wb.md/32nz8UO

Herpes Zoster Vaccine Can Save Your Patients' Eyesight

Herpes Zoster Vaccine Can Save Your Patients' Eyesight - The recombinant zoster vaccine (Shingrix) is 89% effective against HZO

Christopher J. Rapuano, MD

The first vaccine for shingles in the United States — Zostavax — was approved by the US Food and Drug Administration in 2006. The landmark study, published in the *The New England Journal of Medicine* in 2005, involved over 38,000 adults aged 60 years or older and found that the vaccine reduced the incidence of herpes zoster by 51%.[1] Because the FDA study only included individuals who were 60 years or older, it was only approved for that group. Plus, this vaccine was a live attenuated virus, so it was contraindicated in most immunocompromised individuals. In 2011, FDA approval was expanded to include persons aged 50 years or older.

A 50% reduction, admittedly, is not great, but as a corneal specialist and having seen firsthand the devastation that herpes zoster can do to the eye (this is called herpes zoster ophthalmicus [HZO]), I got this vaccine as soon as I was eligible and encouraged all of my relatives, friends, and patients who were eligible to do the same.

In 2017, a recombinant subunit herpes zoster vaccine (Shingrix) was FDA approved. The clinical trial leading to that FDA approval involved more than 15,000 participants aged 50 years or older, and the vaccine's effectiveness proved to be over 96% in all age groups.[2] Obviously, 96% is a lot better than 51%, plus this vaccine is not a live attenuated virus and therefore could be used in immunocompromised individuals. Because it had been many years since I received my original shingles vaccine, I got this new vaccine as soon as I could from my doctor's office (there were availability

issues for the first year or two after FDA approval) and again encouraged all of my relatives, friends, and patients who were eligible to do the same.

We all know that results in clinical trials are not always duplicated in the real world, and we also know that these trials looked at herpes zoster in general and not HZO. So, does this new shingles vaccine really prevent HZO?

Lu and colleagues used a large insurance database that included over 4.8 million individuals over the 2-year period from 2018 to 2019 to answer this question. They found that the recombinant zoster vaccine is 89% effective against HZO. Pretty damn good in real life! However, they also found that a woefully low 3.7% of eligible patients received two valid doses of the vaccine.[3] That's not totally surprising because they state that only 31% of adults aged 60 years or older had received the original zoster vaccine almost a decade after FDA approval.

As ophthalmologists, we understand how terrible HZO can be. My former partner in practice at Wills Eye Hospital, Dr Elisabeth Cohen, has stated publicly that one of the reasons she had to stop clinical practice was because of poor vision that resulted from her own case of HZO. She is now at New York University running a large multicenter trial to determine the efficacy of suppressive antiviral treatment for HZO.

What can we as eye care professionals do? We should be asking all of our patients who are 50 years or older whether they have had a shingles vaccine and encourage them all to get one! In my experience, that question is much less politically charged than asking about COVID vaccination. I'm in the process of customizing our EHR system to require the technician to ask every patient who is over 50 years old whether and when they were vaccinated for zoster. I can then easily see who is not vaccinated and encourage them to get the shingles vaccine. We *have* to do a better job!

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https://bit.ly/3ArU9KU

Special Phage Therapy Clears a Patient's Resistant Infection After 798 Days

After 700 days of antibiotic treatment, the infection of a 30-year-old bombing attack victim still raged. . . .

Conor Feehly

Tragically, the patient had suffered life-threatening injuries during the attacks at Brussels airport on 22 March 2016. Over the next three years, she faced numerous medical complications, as her fracture-related wound became infected with pan-drug-resistant bacteria, or what we know colloquially as superbugs.

Confronted with little progress, clinicians decided to turn to a combination of antibiotics and specialized bacteriophage therapy, a new treatment that harnesses specialized viruses that infect and kill bacteria. Her unique and successful case has now been described in *Nature Communications*.

Superbug infections are becoming an increasingly serious health issue, with phage therapy being amongst the most promising new tools in our arsenal.

Normally, phages infect a subset of strains of bacteria that belong to a single bacterial species, however, clinicians have been working on personalized forms of phage therapy, where phages from a prepared bank are selected by analyzing the bacterial strains isolated from the patient's bacterial infection.

When enough time and resources are available, clinicians can select 'preadapted' phage mutants that have an increased capacity for infecting the patient's specific type of bacterium, or that may have a reduced capacity to provoke bacterial resistance. The last decade has seen a surge in this type of phage therapy research.

The clinicians behind this patient's case study explain that most phage treatments developed by western countries are generalized "cocktails" which don't take into account the evolutionary battle between the bacteria and phages that often makes them so specific to each other.

"In recent randomized controlled trials, these static phage cocktails showed disappointing results, which contrast with those of an increasing number of case studies using phages as adjunctive therapy, or preadapted (or even engineered) phages that are more effective against the infecting bacteria," add the authors.

In this particular case, the patient's drug-resistant infection was due to resistant *Klebsiella pneumoniae*, a particularly nasty superbug that forms persistent biofilms which enable it to bounce back from repeated antibiotic treatments.

"Biofilms are structures elaborated by bacterial communities attached to the surface of implants or avascular tissue fragments. Within biofilms, persistent cells form a subpopulation of metabolically dormant cells that play a major role in the capacity of biofilms to survive and recover from antibiotic treatment," the authors explain.

Currently, there is still a lack of data on the overall effectiveness of phage therapy for resistant bacterial infections, as well as the potential of any adverse effects that may come to patients.

Because of this, the doctors took precautionary steps, applying the phages locally to the infected areas, rather than intravenously. Additionally, a short course of phage treatment – just six days – was chosen to minimize the chance of the patient's immune system responding negatively.

However, three months after the phage treatment, the patient's condition dramatically improved, with the bacterial infection finally beaten.

The authors believe that the combination of a personalized phage treatment, coupled with the use of a longer course of antibiotics afterwards, formed a sort of one-two punch, where phages were able to break down the defensive biofilms, allowing the antibiotics a clear path to finally eliminate the bacterial infection.

"In vitro data indicates that the phage-antibiotic combination was more effective in reducing bacterial counts for *K. pneumoniae* in mature biofilms than antibiotics or phage alone."

Thankfully, there were no observed negative outcomes associated with the use of phages for the patient. Three months after the initiation of the phage-antibiotic therapy, the woman's condition had drastically improved across the board, and her wound was finally healing properly.

Finally, 798 days post-injury, the clinicians were able to discontinue the antibiotic treatment; there was no sign of recurrent infection afterwards, and the patient has been able to slowly regain mobility. "The present case study can open a new way of thinking about phage therapy: the use of individually adjusted phage-antibiotic combinations," the authors write.

The study was published in the journal *Nature Communications*.

https://bit.ly/3tP4bEv

Terrifying Post-COVID Syndrome Makes Comeback in South Carolina Kids

Branson Diven didn't even know he'd been infected—until his organs were ravaged and he was on the brink of death.

Michael Daly Special Correspondent

Rosie Diven, a mother of three in rural South Carolina, had no idea her 16-year-old son had COVID-19 until a fearsome syndrome

nearly killed him.

Branson Diven had been vomiting and suffering a loss of appetite when Rosie brought him to an urgent care center near their home in Hartsville on Dec. 10. He did not have classic COVID symptoms such as a sore throat or a cough, and after testing negative for COVID and positive for flu, he was sent home under the assumption he would soon be better.

Six days later, Branson seemed sicker.

"I said, 'We got to go back,'" Rosie recalled.

On Dec. 16, they returned to the urgent care center. The family nurse practitioner on duty gave an instant reappraisal.

"We walk in the door and she says, 'I don't know what this is but it's not the flu,'" Rosie remembered.

They were sent to McLeod Children's Hospital in Florence, where Branson tested negative for COVID and flu but seemed to be in such bad shape that he was airlifted to MUSC Shawn Jenkins Children's Hospital in Charleston, one of the best pediatric facilities in the country.

"As soon as they said they were going to call the helicopter, I knew it was pretty serious," Rosie said.

At Shawn Jenkins, Branson again tested negative for COVID and flu, but he had antibodies from an infection of some kind. Rosie was told that Branson was suffering from MIS-C—the acronym for multisystem inflammatory syndrome in children. They explained that the condition is a delayed inflammatory response to COVID that can come as if from nowhere weeks or even months after an infection—even an asymptomatic one.

The potentially deadly disorder—which can target the major organs all at once—spiked in the early days of the pandemic, when the early variant of the coronavirus was sweeping the country. It generally was not triggered during the Delta variant that emerged last year.

The new highly contagious Omicron variant filled Shawn Jenkins and many other hospitals with a record number of pediatric COVID patients. But the doctors had hoped that Omicron would act like Delta and not trigger MIS-C.

With the arrival of Branson and another pediatric patient with MIS-C, the doctors at Shawn Jenkins figured he likely had Omicron and that it carried a threat of MIS-C. They checked an inflammation marker called ferritin in Branson. The normal level is between 40 and 200. "His was 80,000," Rosie said. The syndrome had simultaneously attacked Branson's heart, kidneys, and liver.

"They said he probably would not have woken up Friday morning if I hadn't taken him in Thursday night," Rosie told The Daily Beast. "He was going fast."

Rosie said Branson seemed "a little out of it" as he was admitted to the pediatric intensive care unit. But his spirit remained remarkably buoyant right up to when he was sedated before being intubated.

"On his deathbed, making other people laugh," Rosie marveled. "That's how he is."

Branson has no memory of his five days on the ventilator to facilitate 24-hour dialysis. Rosie and her husband, Jonathon, stayed in the room with him, sleeping on the sofa as he fought on.

Branson had not been vaccinated and Rosie was coming to understand the importance of the jab. "I definitely changed my opinion about vaccination," she told The Daily Beast.

Branson's storming immune system quieted and he was taken off the respirator in time for Christmas. His younger sisters, 14 and 15, arrived and the family spent the holiday at the hospital.

On Dec. 30, Branson was discharged with prescriptions for eight medications.

"We know the risks of the disease and we know the risks of MIS-C. So, I think the risk ratio is certainly in favor of vaccination."

— Dr. Elizabeth Mack

She reported that nobody at the hospital would tell her if the vaccine could have prevented the MIS-C. At that point, Shawn Jenkins and 23 other children's hospitals had not completed a major study to answer that question.

The results were released on Jan. 10 and summarized to the press by Dr. Elizabeth Mack, chief of pediatric critical care at Shawn Jenkins, as well as a principal investigator in the study and an author of the report. "The bottom line is MIS-C is a vaccine-preventable disease," Mack said.

Data posted by the South Carolina Children's Hospital Collaborative indicates that the one MIS-C patient who was on a ventilator as of Jan. 20 is also unvaccinated. The record total of 61 children currently hospitalized for COVID includes six who are vaccinated, 28 unvaccinated, and 26 who are under 5 and too young for the jab.

"People are worried about the risks of a vaccine," Mack noted. "What they often don't consider as a risk of the disease… We know the risks of the disease and we know the risks of MIS-C. So, I think the risk ratio is certainly in favor of vaccination."

She offered a simple calculation for those who downplay the risks children face in the pandemic. "If you're a parent of a child in the hospital, one child is a lot," she said.

Nobody knows that better than Rosie. She and her husband did not immediately convey to Branson how it could have gone. "We didn't quite come and tell him that he was close to not making it," she said.

But Branson seemed to have figured it out, learning exactly the right lesson from his brush with death. "He's very appreciative of everything," Rosie said. "Everything's amazing now."

She reports that he is doing his homework, including what she figures is his least favorite subject.

"He's doing math, believe it or not," she said.

https://bit.ly/343ORJ3

COVID-19 Vaccine Used in Much of the World No Match for Omicron Variant

Millions of people around the world have received two shots of Sinovac, a Chinese-manufactured inactive vaccine that is used in 48 countries to help reduce transmission rates of COVID-19.

However, those vaccinations alone are of no help against the widely circulating omicron variant, shows a new study by researchers at Yale and the Dominican Republic. The results are published in the journal Nature Medicine.

An analysis of blood serum from 101 individuals from the Dominican Republic showed that omicron infection produced no neutralizing antibodies among those who received the standard two-shot regimen of the Sinovac vaccine. Antibody levels against omicron rose among those who had also received a booster shot of the mRNA vaccine made by Pfizer-BioNTech.

But when researchers compared these samples with blood serum samples stored at Yale, they found that even those who had received two Sinovac shots and a booster had antibody levels that were only about the same as those who'd received two shots of the mRNA vaccines but no booster shot. In other studies, the two-shot mRNA regimen without a booster has been shown to offer only limited protection against omicron.

Also, the researchers found that individuals who had been infected by earlier strains of the SARS-Cov-2 virus saw little immune protection against omicron.

The findings will likely complicate global efforts to combat the omicron strain, which has supplanted the more dangerous but less transmissible Delta strain as the most dominant circulating virus in much of the world. An additional booster shot — and possibly two — are clearly needed in areas of the globe where the Sinovac shot has been chief source of vaccination, said Akiko Iwasaki, the

Waldemar Von Zedtwitz Professor of Immunobiology and senior author of the paper.

"Booster shots are clearly needed in this population because we know that even two doses of mRNA vaccines do not offer sufficient protection against infection with omicron," Iwasaki said.

Omicron has proven particularly problematic to combat because it possesses 36 mutations on the spike proteins on its surface, which the virus uses to enter cells, researchers say. Existing mRNA vaccines are designed to trigger antibody response when spike proteins are recognized.

Iwasaki stressed, however, that the human immune system still has other weapons it can use against COVID-19, such as T cells that can attack and kill infected cells and prevent severe disease.

"But we need antibodies to prevent infection and slow transmission of the virus," she said.

Reference: "Neutralizing antibodies against the SARS-CoV-2 Delta and Omicron variants following heterologous CoronaVac plus BNT162b2 booster vaccination" by Eddy Pérez-Then, Carolina Lucas, Valter Silva Monteiro, Marija Miric, Vivian Brache, Leila Cochon, Chantal B. F. Vogels, Amyn A. Malik, Elena De la Cruz, Aidelis Jorge, Margarita De los Santos, Patricia Leon, Mallery I. Breban, Kendall Billig, Inci Yildirim, Claire Pearson, Randy Downing, Emily Gagnon, Anthony Muyombwe, Jafar Razeq, Melissa Campbell, Albert I. Ko, Saad B. Omer, Nathan D. Grubaugh, Sten H. Vermund and Akiko Iwasaki, 20 January 2022, Nature Medicine. DOI: 10.1038/s41591-022-01705-6

Carolina Lucas and Valter Silva Monteiro, both from the Yale School of Medicine, are co-lead authors of the paper. Eddy Perez-Then, of the Health Ministry of the Dominican Republic, and Marija Miric, of Two Oceans Health in Santo Domingo, are co-lead authors.

https://bit.ly/3rE0sa2

Just a Few Common Bacteria Gobble Up Most of the Carbon in Soil

Bacterial Carbon Cycling in Soil Is Not a Shared Effort

Scientists can capture valuable demographic data about soil microbes with a tool called quantitative stable isotope probing (qSIP). This tool reveals the identity of bacteria in a community and whether they are using nutrients or are growing. In a new qSIP study, scientists found that in many soil environments just a few types of bacteria use more than half of the available carbon. Despite being home to thousands of species, only three to six groups of bacteria were responsible for most of the carbon use that occurred in several soils that were tested.

Soil contains twice as much carbon as all the vegetation on earth. To understand future climate dynamics, scientists must predict how microbial activity stores carbon in soil or releases it as carbon dioxide. By learning which bacteria in a community are responsible for important ecosystem functions, like carbon cycling, scientists can focus future research on these key bacterial groups. This research also helps to expand the broader field of microbiology.

Researchers at Northern Arizona University and Pacific Northwest National Laboratory analyzed soil samples to follow the oxygen in 18O-labeled water to see which species incorporated it into their DNA. Such uptake is a proxy for growth and can be used to model how efficiently bacteria consume soil carbon.

When the model included details on bacteria (specifically, taxonomic specificity, genome size, and growth) it more accurately predicted the measured carbon dioxide than models that looked only at the abundance of each bacterial group.

Researchers observed that just a few genera produced most of the carbon dioxide released from soils. Those bacteria included *Bradyrhizobium*, Acidobacteria *RB41*, and *Streptomyces*. These bacteria were better than less abundant species at using existing soil carbon as well as nutrients that were added to the soil. When carbon and nitrogen were added to the soil, the dominant bacteria species consolidated their control of the nutrients, gobbling up more nutrients and growing faster relative to other taxa in the soil.

The research identified thousands of unique organisms and hundreds of distinct genera, but just six groups of bacteria accounted for more than 50 percent of carbon use. The

concentration of activity was even more pronounced in the nutrient-boosted soil, where just three groups were responsible for more than half the carbon use.

This research provides insights for managing soil fertility and for better representing key bacterial processes in earth system and climate models.

Reference: "Nutrients cause consolidation of soil carbon flux to small proportion of bacterial community" by Bram W. Stone, Junhui Li, Benjamin J. Koch, Steven J. Blazewicz, Paul Dijkstra, Michaela Hayer, Kirsten S. Hofmockel, Xiao-Jun Allen Liu, Rebecca L. Mau, Ember M. Morrissey, Jennifer Pett-Ridge, Egbert Schwartz and Bruce A. Hungate, 7 June 2021, Nature Communications. DOI: 10.1038/s41467-021-23676-x

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https://bit.ly/3Iw2Eat

The 3rd Leading Global Cause of Death Is Likely Not What You Think, New Study Reveals

Antibiotic resistance is often seen as a 'future problem', but newly published data have revealed it's affecting far, far more lives than you might imagine.

Jacinta Bowler

In fact, the new estimates show that in 2019, there were 4.95 million deaths associated with bacterial antimicrobial resistance, making it the third leading cause of death worldwide.

Drugs that kill bacteria are undeniably one of humanity's greatest discoveries. Since Alexander Fleming discovered antibacterial activity in the fungi *Penicillium* all the way back in 1928, we no longer have to worry about death from rose bush scratches or gonorrhea. In the decades following, antibiotics have saved millions and millions of lives worldwide.

But bacteria have been developing resistance to antibiotics long before we started using them, as they're a naturally evolved biological weapon for warfare between microbes. Continually using the same antibiotics over and over provides bacteria with the opportunity to adapt to them even faster, leading to an increasing number of infections no longer responding to traditional (or even last-resort) antibiotics.

Unfortunately, the more bacterial species don't respond to antibiotics, the more patients will succumb to resistant infections – and researchers are sounding the alarm that we're now annually losing more people to antimicrobial resistance than to HIV/AIDS or malaria.

"These new data reveal the true scale of antimicrobial resistance worldwide, and are a clear signal that we must act now to combat the threat," says University of Washington health economist Chris Murray, who co-authored the new research.

"Previous estimates had predicted 10 million annual deaths from antimicrobial resistance by 2050, but we now know for certain that we are already far closer to that figure than we thought. We need to leverage this data to course-correct action and drive innovation if we want to stay ahead in the race against antimicrobial resistance."

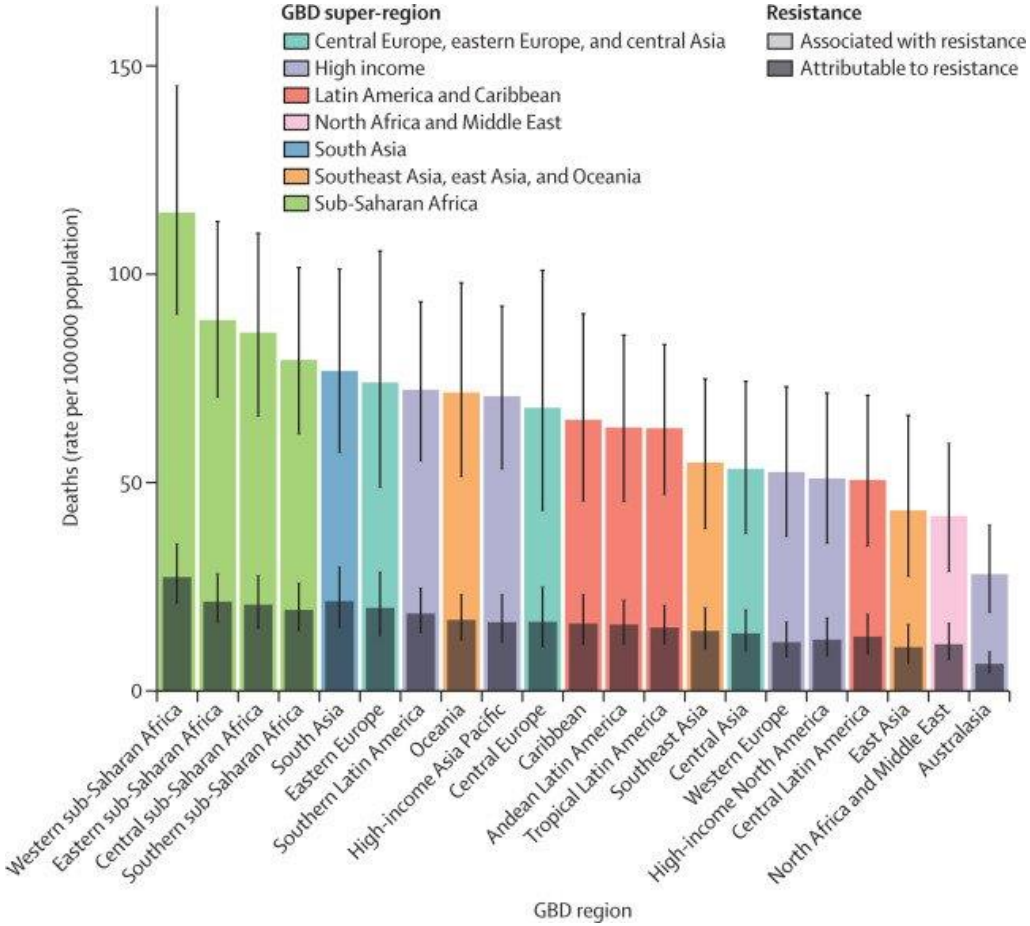
The researchers analyzed data on 23 different bacterial species (including *E. coli*, *S. pneumoniae* and *S. aureus*) and 88 microbe-drug combinations from 204 countries. This ended up covering 471 million records of infection, which they then used to create statistical models to estimate the scale of antimicrobial resistance.

The team explored two counterfactual scenarios. In the first, all drug-resistant infections were replaced with no infections, which the team explained is the number of deaths *associated* with antimicrobial resistance.

In the second scenario, they replaced all drug-resistant infections with drug-susceptible infections, leading to an estimation of deaths directly caused by antimicrobial resistance.

The team concluded that in 2019, 4.95 million deaths were associated with drug-resistant bacterial infections, of which 1.27 million deaths were directly caused by antimicrobial resistance – a

huge burden in all areas of the world, but particularly impacting low- and middle-income countries.



Rate of deaths attributable to and associated with bacterial antimicrobial resistance in 2019. **(Antimicrobial Resistance Collaborators, The Lancet, 2022)**

These calculations suggested that only stroke and heart disease caused more deaths than antimicrobial resistance that year.

The authors note that, to their knowledge, this is the first time such a global estimate has been carried out at all. Because there are gaps in data from some parts of the world, and serious difficulties in carrying out the surveillance of antimicrobial resistance, there are some limitations to their modelling. But the conclusion is clear: we have a major global health problem.

"The threat of antimicrobial resistance has long been signaled. And the steps needed to tackle antimicrobial resistance – boosting public awareness, better surveillance, improved diagnostics, more rational use of antibiotics, access to clean water and sanitation, embracing One Health, and investments in new antimicrobials and vaccines – have been consistently recommended. But action has been episodic and uneven, resulting in global inequities in antimicrobial resistance," *The Lancet* editors add in an editorial accompanying the research.

"Innovation has been extremely slow. Vaccines are available for only one of the six leading pathogens described in the study. The clinical pipeline for antibiotics is too small to tackle the increasing emergence and spread of antimicrobial resistance."

The authors of both the editorial and the original study urge leaders to move antimicrobial resistance higher up on their agendas. Without urgent action, they caution, we'll be seeing even higher levels of preventable deaths in the years to come.

The research has been published in *The Lancet*.