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Suspicions grow that nanoparticles in Pfizer's COVID-19 vaccine trigger rare allergic reactions

May be due to a compound in the packaging of the messenger RNA (mRNA) that forms the vaccine's main ingredient

By Jop de VriezeDec. 21, 2020 , 5:10 PM

Severe allergy-like reactions in at least eight people who received the COVID-19 vaccine produced by Pfizer and BioNTech over the past 2 weeks may be due to a compound in the packaging of the messenger RNA (mRNA) that forms the vaccine's main ingredient, scientists say. A similar mRNA vaccine developed by Moderna, which was authorized for emergency use in the United States on Friday, also contains the compound, polyethylene glycol (PEG).

PEG has never been used before in an approved vaccine, but it is found in many drugs that have occasionally triggered anaphylaxis—a potentially life-threatening reaction that can cause rashes, a plummeting blood pressure, shortness of breath, and a fast heartbeat. Some allergists and immunologists believe a small number of people previously exposed to PEG may have high levels of antibodies against PEG, putting them at risk of an anaphylactic reaction to the vaccine.

Others are skeptical of the link. Still, the U.S. National Institute of Allergy and Infectious Diseases (NIAID) was concerned enough to convene several meetings last week to discuss the allergic reactions with representatives of Pfizer and Moderna, independent scientists and physicians, and the Food and Drug Administration (FDA).

NIAID is also setting up a study in collaboration with FDA to analyze the response to the vaccine in people who have high levels of anti-PEG antibodies or have experienced severe allergic responses to drugs or vaccines before. "Until we know there is truly a PEG story, we need to be very careful in talking about that as a done deal," says Alkis Togias, branch chief of allergy, asthma, and airway biology at NIAID.

Pfizer, too, says it is "actively seeking follow-up." A statement emailed to *Science* noted it already recommends that "appropriate medical treatment and supervision should always be readily available" in case a vaccinee develops anaphylaxis.

Anaphylactic reactions can occur with any vaccine, but are usually extremely rare—about one per 1 million doses. As of 19 December, the United States had seen six cases of anaphylaxis among 272,001 people who received the COVID-19 vaccine, according to a recent presentation by Thomas Clark of the U.S. Centers for Disease Control and Prevention (CDC); the United Kingdom has recorded two. Because the Pfizer and Moderna mRNA vaccines use a new platform, the reactions call for careful scrutiny, says Elizabeth Phillips, a drug hypersensitivity researcher at Vanderbilt University Medical Center who attended an NIAID meeting on 16 December. "This is new."

News reports about the allergic reactions have already created anxiety. "Patients with severe allergies in the US are getting nervous about the possibility that they may not be able to get vaccinated, at least with those two vaccines," Togias wrote in an invitation to meeting participants. "Allergies in general are so common in the population that this could create a resistance against the vaccines in the population," adds Janos Szebeni, an immunologist at Semmelweis University in Budapest, Hungary, who has long studied hypersensitivity reactions to PEG and who also attended the 16 December gathering.

Scientists who believe PEG may be the culprit stress that vaccination should continue. "We need to get vaccinated," Phillips says. "We need to try and curtail this pandemic." But more data are urgently needed, she adds: "These next couple of weeks in the U.S. are going to be extremely important for defining what to do next."

Toothpaste and shampoo

Pfizer's and Moderna's clinical trials of the vaccines, which involved tens of thousands of people, did not find serious adverse events caused by the vaccine. But both studies excluded people with a history of allergies to components of the COVID-19 vaccines; Pfizer also excluded those who previously had a severe adverse reaction from any vaccine. People with previous allergic reactions to food or drugs were not excluded, but may have been underrepresented.

The two vaccines both contain mRNA wrapped in lipid nanoparticles (LNPs) that help carry it to human cells but also act as an adjuvant, a vaccine ingredient that bolsters the immune response. The LNPs are "PEGylated"—chemically attached to PEG molecules that cover the outside of the particles and increase their stability and life span.

PEGs are also used in everyday products such as toothpaste and shampoo as thickeners, solvents, softeners, and moisture carriers, and they've been used as a laxative for decades. An increasing number of biopharmaceuticals include PEGylated compounds as well.

PEGs were long thought to be biologically inert, but a growing body of evidence suggests they are not. As much as 72% of people have at least some antibodies against PEGs, according to a 2016 study led by Samuel Lai, a pharmaco-engineer at the University of North Carolina, Chapel Hill, presumably as a result of exposure to cosmetics and pharmaceuticals. About 7% have a level that may be high enough to predispose them to anaphylactic reactions, he found. Other studies have also found antibodies against PEG, but at lower levels.

"Some companies have dropped PEGylated products from their pipeline as a result," Lai says. But he notes that the safety record of many PEGylated drugs has persuaded others that "concerns about anti-PEG antibodies are overstated."

Szebeni says the mechanism behind PEG-conjugated anaphylaxis is relatively unknown because it does not involve immunoglobulin E (IgE), the antibody type that causes classical allergic reactions. (That's why he prefers to call them "anaphylactoid" reactions.) Instead, PEG triggers two other classes of antibodies, immunoglobulin M (IgM) and immunoglobulin G (IgG), involved in a branch of the body's innate immunity called the complement system, which Szebeni has spent decades studying in a pig model he developed.

In 1999, while working at the Walter Reed Army Institute of Research, Szebeni described a new type of drug-induced reaction he dubbed complement activation-related pseudoallergy (CARPA), a nonspecific immune response to nanoparticle-based medicines, often PEGylated, that are mistakenly recognized by the immune system as viruses.

Szebeni believes CARPA explains the severe anaphylactoid reactions some PEGylated drugs are occasionally known to cause, including cancer blockbuster Doxil. A team assembled by Bruce Sullenger, a surgeon at Duke University, experienced similar issues with an experimental anticoagulant containing PEGylated RNA. The team had to halt a phase III trial in 2014 after about 0.6% of 1600 people who received the drug had severe allergic responses and one participant died. "That stopped the trial," Sullenger says. The team found that every participant with an anaphylaxis had high levels of anti-PEG IgG. But some with no adverse reaction had high levels as well, Sullenger adds. "So, it is not sufficient to just have these antibodies."

Until we know there is truly a PEG [polyethylene glycol] story, we need to be very careful in talking about that as a done deal.

Alkis Togias, National Institute of Allergy and Infectious Diseases

At the NIAID meeting, several attendees stressed that PEGylated nanoparticles may cause problems through a mechanism other than CARPA. Just last month, Phillips and scientists at FDA and other institutions published a paper showing patients who suffered an anaphylactic reaction to PEGylated drugs did have IgE antibodies to PEG after all, suggesting those may be involved, rather than IgG and IgM.

Other scientists, meanwhile, are not convinced PEG is involved at all. "There is a lot of exaggeration when it comes to the risk of PEGs and CARPA," says Moein Moghimi, a nanomedicine researcher at Newcastle University who suspects a more conventional mechanism is causing the reactions. "You are technically delivering an adjuvant at the injection site to excite the local immune system. It happens that some people get too much excitement, because they have a relatively high number of local immune cells."

Others note the amount of PEG in the mRNA vaccines is orders of magnitude lower than in most PEGylated drugs. And whereas those drugs are often given intravenously, the two COVID-19 vaccines are injected into a muscle, which leads to a delayed exposure and a much lower level of PEG in the blood, where most anti-PEG antibodies are.

Nevertheless, the companies were aware of the risk. In a stock market prospectus filed on 6 December 2018, Moderna acknowledged the possibility of "reactions to the PEG from some lipids or PEG otherwise associated with the LNP." And in a September paper, BioNTech researchers proposed an alternative to PEG for therapeutic mRNA delivery, noting: "The PEGylation of nanoparticles can also have substantial disadvantages concerning activity and safety.'"

Katalin Karikó, a senior vice president at BioNTech who co-invented the mRNA technology underlying both vaccines, says she discussed with Szebeni whether PEG in the vaccine could be an issue. (The two know each other well; both are Hungarian and in the 1980s, Karikó taught Szebeni how to make liposomes in her lab.) They agreed that given the low amount of lipid and the intramuscular administration, the risk was negligible.

Karikó emphasizes that based on what we know so far, the risk is still low. "All vaccines carry some risk. But the benefit of the vaccine outweighs the risk," she says.

Szebeni agrees, but says he hopes that's also true in the long run. He notes that both mRNA vaccines require two shots, and he worries anti-PEG antibodies triggered by the first shot could increase the risk of an allergic reaction to the second or to PEGylated drugs.

Stay for 30 minutes.

To understand the risk, Phillips says, it's crucial to unravel the mechanisms underlying the immune reactions and find out how often they are likely to occur. The known U.S. cases are currently under study, but key clues may have vanished: Anaphylactic reactions produce biomarkers that only remain in the blood for a few hours. At the NIAID meeting, participants discussed ways to ensure that blood samples from future cases are taken immediately and tested for those markers.

If PEG does turn out to be the culprit, the question is, what can be done? Screening millions of people for anti-PEG antibodies before they are vaccinated is not feasible. Instead, CDC guidelines recommend not giving the Pfizer or Moderna vaccines to anyone with a history of severe allergic reaction to any component of the vaccine. For people who have had a severe reaction to another vaccine or injectable medication, the risks and benefits of vaccination should be carefully weighed, CDC says. And people who might be at high risk of an anaphylactic reaction should stay at

the vaccination site for 30 minutes after their shot so they can be treated if necessary.

“At least [anaphylaxis] is something that happens quickly,” Philips says. “So, it’s something that you can be very much alerted to, prepared to recognize early and be prepared to treat early.”

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The Achilles' heel of cancer stem cells

Protein that regulates stem cell genes found in cancer stem cells

Since colonoscopies were introduced in Germany for early cancer detection, the number of diagnoses of advanced cancer every year has decreased, as precancerous lesions can now be detected and immediately removed as part of the examination. As a result, the death rate from colon cancer has also gone down - by 26 percent in women and 21 percent in men. Nevertheless, it remains the fourth deadliest cancer in the Western world - just behind lung, prostate and breast cancer. This is because the slow-growing tumors only become noticeable in the advanced stages of the disease and are therefore often diagnosed too late. Survival rate for advanced colorectal cancer is just five percent.

"Treatment options are very limited - not least because the cancer can return even after successful chemotherapy," explains Johanna Grinat, the study's lead author and a doctoral student in the Signal Transduction in Development and Cancer Lab. "The recurrent cancer is often more aggressive than the original tumor, which is thought to be caused by cancer stem cells. So we took a closer look at these cells."

Molecular switch found in cancer stem cells

The researchers led by Professor Walter Birchmeier identified Mll1, a protein that regulates stem cell genes in mice and in human colon cancer cells. In mice, the team was able to genetically trigger the formation of intestinal tumors. However, if the mice lacked the gene for Mll1, no tumors were able to be induced. And this seems to be the case in humans as well: Human colon cancer cell cultures that the scientists enriched with cancer stem cells lost some of their stem cell properties and behaved less aggressively when Mll1 was blocked. Together with Professor Eduard Batlle and bioinformaticians at the IRB in Barcelona, the MDC group used clinical data to show that colon cancer patients whose tumors have a large amount of this protein have a worse prognosis than patients with tumors that contain little Mll1.

Mll1 is an enzyme that sits on the DNA and controls the expression of certain genes "epigenetically," as the researchers say. "It primarily does this in cancer stem cells, where the Wnt signaling pathway is strongly activated," Grinat explains. "This means that, by deactivating it, we can specifically treat cancer stem cells."

The Wnt signaling pathway regulates the self-renewal and division of stem cells. If mutations occur that trigger a more active Wnt signaling cascade, the affected stem cells become more resistant than healthy stem cells. They then multiply uncontrollably and form tumors. Although chemotherapy slows down the cell division, it can also increase the selection pressure on cancer stem cells: "They become resistant to the treatment and form new tumors that, due to the mutation, grow more rapidly and are even more aggressive," says Dr. Julian Heuberger. This is why it is so important, he explains, to understand the regulatory mechanisms of cancer stem cells in particular. The postdoctoral researcher is also lead author and head of the study and now works in the Division of Hepatology and Gastroenterology in the Medical Department of Charité - Universitätsmedizin Berlin. "With Mll1," he adds, "we have found a molecular switch that primarily controls the self-renewal and division of cancer stem cells in colon cancer"

Hope and more effective therapies

Genetically "knocking out" a gene, as the scientists did with mice, is not possible in humans. In mice, the formation of cancer stem

cells can be followed over time and there are always enough stem cells available for experiments. However, MII1 could be blocked with a chemical drug. Small molecules have already been developed for this research, for example, the inhibitors MI-2 and MM-401, which bind to essential Mll1 complexes and thereby inactivate its function. "Understanding the way these molecules work will enable us to develop and test these and even more clinically effective Mll1 inhibitors," says Birchmeier, who is the study's last author.

Healthy stem cells in the intestine are apparently not blocked in the process. "We were able to use another system in mice, salivary gland cancer cells, to show that Mll1 only affects cancer cells and not healthy stem cells," says Birchmeier. This also provides hope for the treatment of other types of cancer, as animal models have shown that head and neck tumors have the same Achilles' heel. "On the basis of our mouse studies, clinical trials are currently being conducted at the University Hospital of Düsseldorf to evaluate the use of Mll1 inhibitors in the treatment of head and neck tumors."

If they are successful, patients with colon cancer could be treated in the future with both chemotherapy and Mll1 inhibitors, i.e., therapeutics that specifically impede cancer stem cells. This increases the chances of a successful treatment - even with advanced colon cancer.

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Ancient European Hunters Carved Human Bones Into Weapons

Scientists suggest 10,000-year-old barbed points washed up on Dutch beaches were made for cultural reasons

As the Ice Age waned, melting glaciers drowned the territory of Doggerland, the ground that once connected Britain and mainland Europe. For more than 8,000 years, distinctive weapons—slender, saw-toothed bone points—made by the land's last inhabitants rested at the bottom of the North Sea. That was until 2oth-century engineers, with mechanical dredgers, began scooping up the seafloor and using the sediments to fortify the shores of the Netherlands. The ongoing work has also, accidentally, brought artifacts and fossils from the depths to the Dutch beaches.

Fossil-hunter hobbyists collected these finds, amassing nearly 1,000 of the jagged bone weapons, known to archaeologists as Mesolithic barbed points. Not only known from the North Sea, barbed points have been found at sites from Ireland to Russia, dating between 8,000 to 11,000 years ago, when the last foragers inhabited Europe before farmers arrived. Mesolithic people likely fastened the points to longer shafts to make arrows, spears and harpoons, key for their hunting and fishing livelihoods. But scholars mostly ignored the barbed points dotting Dutch beaches because they weren't recovered from systematic digs of proper archaeological sites, like the barbed points found in the U.K. and continental Europe.

Now a team, led by Leiden University archaeologists, has analyzed some of the washed-up weapons, performing molecular measurements to determine which species the barbed points were made from. The scientists mainly wanted to test if this kind of analysis, which depends on proteins surviving in bone, was even possible for artifacts buried underwater for millennia. Not only did the method work, it delivered shocking results: While most of the roughly 10,000-year-old points were made of red deer bone two were fashioned from human skeletons.

"As an expert in this field, I really wasn't expecting that. It's really cool," says Newcastle University archaeologist Benjamin Elliott, who was not involved in the research. Never before have archaeologists found unambiguous evidence that ancient Europeans carefully crafted human bones into deadly weapons.

The study scientists puzzled over why Mesolithic people used red deer and human skeletons for their weapons. "What's going on with

these points?" says Virginie Sinet-Mathiot, an anthropologist at the Max Planck Institute in Leipzig, Germany, who worked on the project. "What does it mean?"

Practical or economic concerns seemed unlikely explanations: Other raw materials like antler would have been more readily available and durable. Rather, the researchers concluded that ancient hunters chose these particular bones for symbolic reasons, related to their social or spiritual beliefs.

"This was not an economic decision," says archaeologist Joannes Dekker, lead author of the study, forthcoming in the *Journal of Archaeological Science: Reports*. The economic move would have been for ancient hunter-gatherers to produce strong points, quickly from animal parts leftover from meals. In that case, researchers would expect to find points made from antler as well as bones of aurochs, other deer species and Eurasian elk. These creatures roamed Mesolithic Doggerland, and experiments by modern archaeologists have shown their bones make excellent projectile weapons.

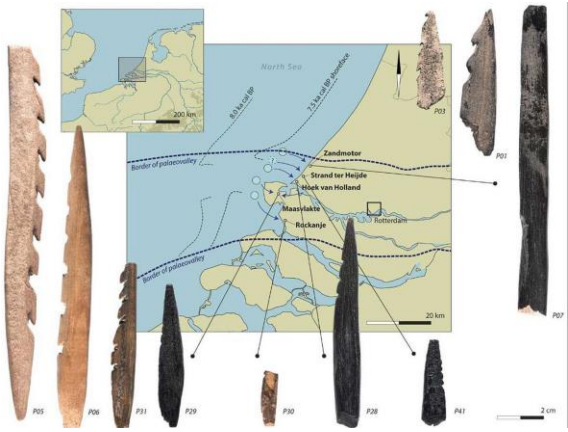
The fact that the scientists found predominately red deer and human bones suggests, "There must have been some other reason, a cultural reason, why it was important to use these species," says Dekker, a Masters student at Leiden University in the Netherlands.

The specific motivations driving this Doggerland fad, though, remain a mystery. "You can measure modern bone to see its properties as a projectile point," says Dekker. "You can't measure the thoughts in the head of a Mesolithic hunter-gatherer."

Still, knowing Mesolithic people used human bones this way is a major discovery. "The human stuff is a complete shock," says Elliott.

According to him, earlier researchers had floated the idea that human bone comprised some especially long barbed points found in Ireland. Those speculations were based on the fact that there weren't many large mammals, besides humans, on the island back when the artifacts were made. But until recently, no technology existed to test those claims.

Generally, archaeologists can eyeball a bone, and based on its size and contours, know the body part and animal type from which it came. But that's nearly impossible for barbed points because the identifying features have been whittled and worn away through manufacture, use and burial.



This graphic shows the barbed points analyzed in the study, the beaches they were found on, and the probable dredging location of the original sediments in the North Sea. **(Dekker et al. in press JAS: Reports, original file provided by Dekker)**

Over the past decade, a new technology has been developed that solves this problem. The method, Zooarchaeology by Mass Spectrometry or ZooMS, detects the molecular building blocks of collagen, the main protein in bone. Because these collagen components differ slightly between animal types, measuring them can indicate the species of a bone—even for skeletal bits or sculpted artifacts that can't be identified by visual features.

During ZooMS, scientists chemically dissolve a dash of powdered bone to extract collagen molecules, which are run through a measurement instrument. The method has proven handy for distinguishing between bones of similar-looking creatures like sheep and goat, or rat and mouse. And for Stone Age sites, the process has been used to scan thousands of matchstick-sized skeletal pieces to find rare Neanderthal, Denisovan and *Homo*

sapiens specimens among heaps of animal bones. Since its introduction in 2009, ZooMS has been successfully used on remains from dozens of sites worldwide, dating from the Stone Age to modern times.

But scientists questioned whether the method would work on Mesolithic Doggerland points; millennia under the sea may have destroyed the collagen proteins. “The challenge here was would we be able to extract collagen and to perform species identifications from material that had been submerged in water for such a long time,” says Sinet-Mathiot, who works to innovate ZooMS protocols through her research.

In 2018, Dekker decided to try, in a small project for his bachelor’s thesis in archaeology at Leiden University. Dekker got permission from a dozen collectors to scrap or chip a bit of bone from their barbed points. He brought the samples to the Max Plank Institute in Leipzig, Germany and worked with Sinet-Mathiot to run the ZooMS analysis. Collaborators at the University of Groningen measured radiocarbon dates, confirming the artifacts were Mesolithic age.

For scholars of European prehistory, the new results are tantalizing, but present more questions than answers. Because the study only tested ten points, washed ashore, scientists don’t know how often, and under what circumstances, people armed themselves with human bones. “It's super interesting that they found two humans in there, out of ten analyzed in total,” says Theis Zetner Trolle Jensen, a postdoctoral researcher at the University of Copenhagen, who was not involved in the study. “But it might very well be that they found the needle in the haystack.”

Earlier this year Jensen and colleagues published a much larger ZooMS study, which determined the animal types comprising 120 Mesolithic barbed points recovered from peat bogs of Denmark and Sweden. They found bones from red deer, moose, bovine and a few brown bear—but not one from *Homo sapiens*. And, they concluded the Mesolithic crafters chose bone types with preferable mechanical properties. The hunters picked their mediums for practical reasons, not cultural considerations.

The differing results raise the possibility that only inhabitants of Doggerland turned human bones into deadly points during the Mesolithic. “It might be that there are strange people there… people that did different things,” Jensen says.

He and other scholars hope these questions will be clarified through more ZooMS work of barbed points. Although the new study analyzed a small number of artifacts, it showed the scientific value of artifacts washed onto Dutch shores.

“Ideally we’d love [the artifacts] to come from securely excavated contexts,” says Elliott. But Doggerland sites lie beneath the North Sea, so out-of-context beach finds offer invaluable, accessible evidence. “We can’t be snobby about it,” he says. “We have to really embrace it and try to get as much information and understanding from those artifacts as we possibly can.”

Everyday more fossils and artifacts appear on Dutch beaches, enticing a growing number of collector hobbyists. The Facebook group for this community now includes some 600 members, according to its moderator Erwin van der Lee of Rotterdam. “The competition is also very large,” he says.

Rick van Bragt, a university student in The Hague, has found about 10,000 ancient items since he began searching nearly ten years ago. Van Bragt and van der Lee entered their barbed points in the ZooMS study. While van der Lee’s artifact failed to produce results, van Bragt’s point was identified as red deer from 8,000 years ago. Both collectors were fascinated by the news that human bone formed two of the points.

Beyond bone points, the tides washing over Dutch beaches drop shark teeth, flint tools made by Neanderthals, fossils from long-

extinct mammoths and other treasures. Spotting the finds takes practice though, and most beachgoers are unaware of what's there. In the summer, "there's a lot of people on the beach and they just step on everything," says Van Bragt. "They don't see it."

Editor's Note, December 21, 2020: This article mistakenly stated 21st-century engineers dredged the seafloor; it was 20th century engineers that started the work.

http://bit.ly/2WMgsaQ

Prostate cancer regulator plays role in COVID-19, providing a promising treatment lead

Clinical trials underway are testing whether drugs that target the androgen receptor -- successful in controlling prostate cancer -- could also work against the coronavirus

Ann Arbor, Michigan By taking a lesson from prostate cancer, researchers now have a promising lead on a treatment for COVID-19.

Two proteins, ACE2 and TMPRSS2, help the coronavirus gain entry and replicate within cells. TMPRSS2 is well-known to Arul Chinnaiyan, M.D., Ph.D. His lab discovered that TMPRSS2 fuses with the ETS gene to drive more than half of all prostate cancers. They also knew that TMPRSS2 was regulated by the androgen receptor.

So when cancer research shut down in the spring, Chinnaiyan's lab turned its attention to the coronavirus. With a grant from the National Cancer Institute, the team used its existing knowledge and resources to determine how TMPRSS2 was regulated in the lungs.

They found that, just like in prostate cancer, TMPRSS2 is regulated by the androgen receptor in the lungs. And notably, blocking the androgen receptor led to lower expression of TMPRSS2 as well as ACE2, which led to decreased coronavirus infection in mice and cellular models. Results are published in *PNAS*.

"What's especially appealing about this is that anti-androgen treatments are already FDA-approved. This opens the door to look at these drugs, which we know work in prostate cancer, as potential COVID-19 treatments," says Chinnaiyan, director of the Michigan Center for Translational Pathology.

Using cell lines infected with SARS-CoV-2, the virus that causes COVID-19, researchers found that inhibitors of androgen receptor, including enzalutamide, apalutamide and darolutamide, inhibited the coronavirus infection.

They also tested a class of drugs designed to inhibit or degrade BET proteins. BET protein activity is essential for androgen signaling and these drugs are being looked at for prostate cancer. In cell lines infected with coronavirus, the BET inhibitors decreased androgen signaling and inhibited viral infection.

The findings also provide some explanation for observations that COVID-19 affects men more than women. Researchers looked at human lung tissue and found higher androgen receptor signaling in men than women. They also found androgen signaling was highest in men over 70 and in smokers.

"This explains why elderly men who are smokers are more vulnerable to COVID-19 infection. High androgen receptor signaling allows the virus to gain entry and replicate more easily. This may explain why the disease is often particularly severe in older men," Chinnaiyan says.

Several clinical trials are underway testing androgen receptor inhibitors as a treatment for COVID-19, and additional trials are being developed to look at BET inhibitors.

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Food trade with South Asia revealed by Near East food remains

Exotic Asian spices such as turmeric and fruits like the banana had already reached the Mediterranean more than 3000 years ago, much earlier than previously thought.

by Ludwig Maximilian University of Munich

A team of researchers working alongside archaeologist Philipp Stockhammer at Ludwig-Maximilians-Universität in Munich (LMU) has shown that even in the Bronze Age, long-distance trade in food was already connecting distant societies.

Imagine this scene from a market in the city of Megiddo in the Levant 3700 years ago: The market traders are hawking not only wheat, millet or dates, which grow throughout the region, but also carafes of sesame oil and bowls of a bright yellow spice that has recently appeared among their wares. This is how Philipp Stockhammer imagines the bustle of the Bronze Age market in the eastern Mediterranean.

Working with an international team to analyze food residues in tooth tartar, the LMU archaeologist has found evidence that people in the Levant were already eating turmeric, bananas and even soy in the Bronze and Early Iron Ages. "Exotic spices, fruits and oils from Asia had thus reached the Mediterranean several centuries, in some cases even millennia, earlier than had been previously thought," says Stockhammer. "This is the earliest direct evidence to date of turmeric, banana and soy outside of South and East Asia."

It is also direct evidence that as early as the second millennium BCE there was already a flourishing long-distance trade in exotic fruits, spices and oils, which is believed to have connected South Asia and the Levant via Mesopotamia or Egypt. While substantial trade across these regions is amply documented later on, tracing the roots of this nascent globalization has proved to be a stubborn problem. The findings of this study confirm that long-distance trade in culinary goods has connected these distant societies since at least the Bronze Age. People obviously had a great interest in exotic foods from very early on.

For their analyses, Stockhammer's international team examined 16 individuals from the Megiddo and Tel Erani excavations, which are located in present-day Israel. The region in the southern Levant served as an important bridge between the Mediterranean, Asia and Egypt in the 2nd millennium BCE. The aim of the research was to investigate the cuisines of Bronze Age Levantine populations by analyzing traces of food remnants, including ancient proteins and plant microfossils, that have remained preserved in human dental calculus over thousands of years.

The human mouth is full of bacteria, which continually petrify and form calculus. Tiny food particles become entrapped and preserved in the growing calculus, and it is these minute remnants that can now be accessed for scientific research thanks to cutting-edge methods. For the purposes of their analysis, the researchers took samples from a variety of individuals at the Bronze Age site of Megiddo and the Early Iron Age site of Tel Erani. They analyzed which food proteins and plant residues were preserved in the calculus on their teeth. "This enables us to find traces of what a person ate," says Stockhammer. "Anyone who does not practice good dental hygiene will still be telling us archaeologists what they have been eating thousands of years from now."

Palaeoproteomics is the name of this growing new field of research. The method could develop into a standard procedure in archaeology, or so the researchers hope. "Our high-resolution study of ancient proteins and plant residues from human dental calculus is the first of its kind to study the cuisines of the ancient Near East," says Christina Warinner, a molecular archaeologist at Harvard University and the Max Planck Institute for the Science of Human

History and co-senior author of the article. "Our research demonstrates the great potential of these methods to detect foods that otherwise leave few archaeological traces. Dental calculus is such a valuable source of information about the lives of ancient peoples."

"Our approach breaks new scientific ground," explains LMU biochemist and lead author Ashley Scott. That is because assigning individual protein remnants to specific foodstuffs is no small task. Beyond the painstaking work of identification, the protein itself must also survive for thousands of years. "Interestingly, we find that allergy-associated proteins appear to be the most stable in human calculus", says Scott, a finding she believes may be due to the known thermostability of many allergens. For instance, the researchers were able to detect wheat via wheat gluten proteins, says Stockhammer. The team was then able to independently confirm the presence of wheat using a type of plant microfossil known as phytoliths. Phytoliths were also used to identify millet and date palm in the Levant during the Bronze and Iron Ages, but phytoliths are not abundant or even present in many foods, which is why the new protein findings are so groundbreaking—paleoproteomics enables the identification of foods that have left few other traces, such as sesame. Sesame proteins were identified in dental calculus from both Megiddo and Tel Erani. "This suggests that sesame had become a staple food in the Levant by the 2nd millennium BCE," says Stockhammer.

Two additional protein findings are particularly remarkable, explains Stockhammer. In one individual's dental calculus from Megiddo, turmeric and soy proteins were found, while in another individual from Tel Erani banana proteins were identified. All three foods are likely to have reached the Levant via South Asia. Bananas were originally domesticated in Southeast Asia, where they had been used since the 5th millennium BCE, and they arrived in West Africa 4000 years later, but little is known about their intervening trade or use. "Our analyses thus provide crucial information on the spread of the banana around the world. No archaeological or written evidence had previously suggested such an early spread into the Mediterranean region," says Stockhammer, although the sudden appearance of banana in West Africa just a few centuries later has hinted that such a trade might have existed. "I find it spectacular that food was exchanged over long distances at such an early point in history."

Stockhammer notes that they cannot rule out the possibility, of course, that one of the individuals spent part of their life in South Asia and consumed the corresponding food only while they were there. Even if the extent to which spices, oils and fruits were imported is not yet known, there is much to indicate that trade was indeed taking place, since there is also other evidence of exotic spices in the Eastern Mediterranean—Pharaoh Ramses II was buried with peppercorns from India in 1213 BCE. They were found in his nose.

The results of the study have been published in the journal *PNAS*.

The work is part of Stockhammer's project "FoodTransforms—Transformations of Food in the Eastern Mediterranean Late Bronze Age," which is funded by the European Research Council. The international team that produced the study encompasses scientists from LMU Munich, Harvard University and the Max Planck Institute for the Science of Human History in Jena. The fundamental question behind his project—and thus the starting point for the current study—was to clarify whether the early globalization of trade networks in the Bronze Age also concerned food. "In fact, we can now grasp the impact of globalization during the second millennium BCE on East Mediterranean cuisine," says Stockhammer. "Mediterranean cuisine was characterized by intercultural exchange from an early stage."

More information: *Ashley Scott el al., "Exotic foods reveal contact between South Asia and the Near East during the second millennium BCE," PNAS (2020).* *www.pnas.org/cgi/doi/10.1073/pnas.2014956117*

http://bit.ly/34EesGb

COVID immunity lasts up to 8 months, new data reveals

Real hope for longevity of COVID vaccinations

Australian researchers have revealed - for the first time - that people who have been infected with the COVID-19 virus have immune memory to protect against reinfection for at least eight months.

The research is the strongest evidence for the likelihood that vaccines against the virus, SARS-CoV-2, will work for long periods. Previously, many studies have shown that the first wave of antibodies to coronavirus wane after the first few months, raising concerns that people may lose immunity quickly. This new work allays these concerns.

The study is the result of a multi-centre collaboration led by Associate Professor Menno van Zelm, from the Monash University Department of Immunology and Pathology, with the Alfred Research Alliance between Monash University, The Alfred hospital and the Burnet Institute, and published today in the prestigious journal, *Science Immunology*. The publication reveals the discovery that specific cells within the immune system called memory B cells, "remembers" infection by the virus, and if challenged again, through re-exposure to the virus, triggers a protective immune response through rapid production of protective antibodies.

The researchers recruited a cohort of 25 COVID-19 patients and took 36 blood samples from them from Day 4 post infection to Day 242 post infection.

As with other studies - looking only at the antibody response - the researchers found that antibodies against the virus started to drop off after 20 days post infection.

However - importantly - all patients continued to have memory B cells that recognised one of two components of the SARS-CoV-2 virus, the spike and nucleocapsid proteins. These virus-specific memory B cells were stably present as far as eight months after infection.

According to Associate Professor van Zelm, the results give hope to the efficacy of any vaccine against the virus and also explains why there have been so few examples of genuine reinfection across the millions of those who have tested positive for the virus globally.

"These results are important because they show, definitively, that patients infected with the COVID-19 virus do in fact retain immunity against the virus and the disease," he said.

"This has been a black cloud hanging over the potential protection that could be provided by any COVID-19 vaccine and gives real hope that, once a vaccine or vaccines are developed, they will provide long-term protection."

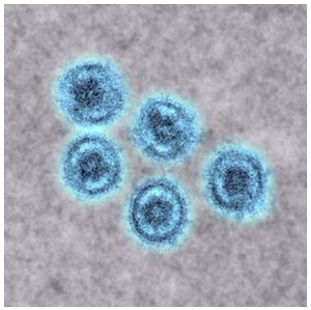
http://bit.ly/38Pivkn

Reston ebolavirus spreads efficiently in pigs

Should be considered a livestock pathogen with potential to affect other mammals, including people

Reston ebolavirus (RESTV) should be considered a livestock pathogen with potential to affect other mammals, including people, according to National Institutes of Health scientists. The caution comes from a study published in *Proceedings of the National Academy of Sciences* in which the scientists found that experimental piglets infected with RESTV developed severe respiratory disease and shed the virus from the upper respiratory tract. RESTV can infect humans but is not known to cause disease. Now the scientists express concern that pigs could serve as an "interim or amplifying host for ebolaviruses."

"The emergence of RESTV in pigs is a wake-up call as transmission into humans through direct contact with pigs or the food chain is a possibility," they state in their study report. Scientists from NIH's National Institute of Allergy and Infectious Diseases (NIAID) conducted the work at Rocky Mountain Laboratories in Hamilton, Montana.



This colorized transmission electron micrograph shows a slice of Reston virus particles (blue) in the lung of an infected pig. **Credit: NIAID**

Scientists first identified RESTV in 1989 in research monkeys shipped from the Philippines to Reston, Virginia. The virus also gained attention in 2008 when an outbreak swept through pigs in the Philippines. That outbreak led to the first association of pig-to-human RESTV transmission, prompting the World Health Organization to issue a global alert in February 2009. RESTV sequences also have been identified in pigs in China, and the scientists suggest officials monitor pigs for disease throughout the Philippines and Southeast Asia.

The NIAID scientists conducted their study to answer two key questions: could they cause disease in young pigs—mimicking natural infection with RESTV isolated from the 2008 swine outbreak—and if so, would those pigs shed virus through their respiratory tract? Their work confirmed that in fact the pigs developed severe pneumonia with virus shedding from the upper respiratory tract. They also determined that the age of the piglets at the time of infection—they used animals between three and seven weeks old—did not change the course of disease. Their work involved Yorkshire cross-bred pigs, which frequently are used in commercial pig production systems. RESTV has not been found in commercial pigs in the United States.

Continued studies in this project will examine whether co-infection with other swine viruses affects the ability of RESTV to cause severe disease in pigs and whether pigs have a broad role in hosting ebolaviruses.

More information: *E Haddock et al. Reston virus causes severe respiratory disease in young domestic pigs. PNAS DOI: 10.1073/pnas.2015657118 (2020).*

http://bit.ly/37Lt8oK

Even after long-term exposure, bionic touch does not remap the brain

A new study of people with amputations who used a bionic hand for over one year highlights future challenges for developing realistic prosthetic devices

Advances in neuroscience and engineering have generated great hope for Luke Skywalker-like prosthetics: robotic devices that are almost indistinguishable from a human limb. Key to solving this challenge is designing devices that not only can be operated with a user's own neural activity, but can also accurately and precisely receive and relay sensory information to the user.

A new study by neuroscientists at the University of Chicago and Chalmers University of Technology, published on December 22 in the journal *Cell Reports*, highlights just how difficult this may prove to be. In a cohort of three subjects whose amputated limbs had been replaced with neuromusculoskeletal prosthetic limbs, the investigators found that even after a full year of using the devices, the participant's subjective sensation never shifted to match the location of the touch sensors on their prosthetic devices.

The stability of the touch sensations highlights the limits in the ability of the nervous system to adapt to different sensory input.

Three participants with above-elbow amputations were equipped with high-tech neuroprosthetic devices that were affixed directly to their humerus bone. The users could control the prosthetic device thanks to signals received from electrodes implanted in the residual

arm muscles, and received sensory feedback via another set of implanted electrodes. A sensor located on the prosthetic thumb triggered stimulation of the nerve, which in turn elicited a touch sensation.

However, because the organization of the nerve is essentially arbitrary, surgeons can't be sure whether their placement of the electrodes will generate a sensation in the correct location on the thumb. In the study, the prosthetic users did not report feeling the sensation on the thumb, but rather in other hand locations, such as their middle finger or the palm.

Participants then wore the prosthesis for upwards of 12 hours a day, every day, using it to manipulate objects during their daily routine for over a year.

"One problem with current neural electrodes is that you can't tell during the implantation surgery which part of the nerve corresponds to what sensation, so the electrodes don't always land in exactly the location in the nerve that would match the location of the sensors in the prosthetic hand," said lead author and developer of the neuromusculoskeletal prostheses, Max Ortiz Catalan, PhD, an associate professor of bionics at Chalmers University of Technology and Director of the Center for Bionics and Pain Research in Gothenburg, Sweden.

"We hoped that because the patients were grabbing objects and feeling the sensation somewhere else in the hand, all day and every day for several months, the brain would resolve the mismatch by shifting the perceived sensation to the thumb," he continued.

Despite being able to observe their hand while interacting with objects, none of the users ever reported that they felt the sensation on their thumb, but rather that the sensation persisted in the same area where it was originally felt.

"Every day, for a year, these subjects saw their prosthetic thumb touching things and felt it in a different location - sometimes close to the thumb, but not on it - and the sensation never budged. Not even a smidge," said senior author Sliman Bensmaia, PhD, the James and Karen Frank Family Professor of Organismal Biology and Anatomy at UChicago.

These results challenge prevailing dogma regarding brain plasticity following limb loss. Many have believed that the brain has a high capacity to reorganize itself after losing sensory input, co-opting existing, unused brain tissue for other purposes.

"There's been this idea that the nervous system is really plastic, so if you see a mismatch between what you see and what you feel, it's a great opportunity for neural remapping," said Bensmaia. "For example, if you sew two fingers together and look at how that's represented in the brain, they seem to have merged."

"But I think that this idea has been vastly overstated. It's less like you're reorganizing a room and more like you're just hearing echoes bouncing around an empty chamber," he continued. "You might get some overlapping sensation from adjacent limbs, but it's just because the area of the brain that used to respond to sensation is empty, and activating the neurons around it leads to an echo through the emptiness."

This study highlights the importance of knowing exactly where to place electrodes when implanting sensory arrays for patients using these types of neuroprosthetic devices, as it appears unlikely that the brain is capable of making substantial adjustments in how it perceives that sensory input. "This means that you really have to get it right," said Bensmaia. "There are no do-overs here."

The study, "Chronic use of a sensitized bionic hand does not remap the sense of touch," was supported by the Promobilia Foundation, the IngaBritt and Arne Lundbergs Foundation, VINNOVA, the Swedish Research Council (Vetenskapsrådet), the European Research Council and NINDS grant NS095251. Additional authors include Enzo Mastinu of the Center for Bionics and Pain Research and Chalmers University of Technology in Sweden and Charles Greenspon of the University of Chicago.

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

Doctors heard music when checking a man's pulse. Here's why.

The music was playing loud and clear, as if someone had turned on a radio.

By Rachael Rettner - Senior Writer

When doctors checked the man's pulse, they couldn't believe their ears — they heard music playing, loud and clear, as if someone had turned on a radio. The 65-year-old man arrived at the hospital after he experienced a fall and dislocated his hip, according to a report of the case, published Saturday (Dec. 19) in The New England Journal of Medicine. Previously, the man had undergone hip-replacement surgery on both hips, the report said.

As the man lay in his hospital bed, doctors checked the pulse in his feet using a Doppler (ultrasound) device.

But then something bizarre happened: In addition to the thump thump of the man's heart, they heard music through the device's speaker. (In a video accompanying the report, an upbeat tune with someone singing, possibly in Spanish, can be heard filling the room. The app Shazam identifies the song as "Gracias Por Tu Amor" by Banda El Recodo De Cruz Lizárraga.) The music played only when the Doppler was placed on the man's feet. It didn't happen when hospital staff used the device on themselves.

The authors suspect the Doppler may have picked up a radio signal that was being received by the patient's prosthetic hips, the report said. It's also possible this signal was being received by other equipment in the room, such as the patient's hospital bed.

The authors reported their findings to their hospital's engineering department, and no faulty equipment was found.

Eight months later, the patient was doing well and had not experienced any more falls, and had not transmitted any other phantom music, the report said.

https://bit.ly/38Ba9MU

First Mariana Islanders Came from Philippines, New Study Shows

Moreover, they are closely related to ancient humans from Vanuatu and Tonga

In new research, researchers from the Max Planck Institute for Evolutionary Anthropology, Australian National University and the University of Guam analyzed ancient DNA from two humans who lived on Guam 2,200 years ago and found that their ancestry is linked to the Philippines. Moreover, they are closely related to ancient humans from Vanuatu and Tonga, suggesting that the early Mariana Islanders may have been involved in the colonization of Polynesia.

Humans reached the Mariana Islands in the western Pacific by 3,500 years ago, contemporaneous with or even earlier than the initial peopling of Polynesia. They crossed more than 2,000 km (1,243 miles) of open ocean to get there, whereas voyages of similar length did not occur anywhere else until more than 2,000 years later. There is debate over where people came from to get to the Marianas, with various lines of evidence pointing to the Philippines, Indonesia, New Guinea, or the Bismarck Archipelago.

“We know more about the settlement of Polynesia than we do about the settlement of the Mariana Islands,” said Dr. Irina Pugach, a researcher in the Department of Evolutionary Genetics at the Max Planck Institute for Evolutionary Anthropology.

Dr. Pugach and her colleagues from Germany, Australia and Guam wanted to find out where people came from to get to the Marianas and how the ancestors of the present Mariana Islanders, the Chamorro, might be related to Polynesians.

To address these questions, the researchers obtained ancient DNA from two skeletons from the Ritidian Beach Cave site in northern Guam, dating to around 2,200 years ago.

"We found that the ancestry of these ancient skeletons is linked to the Philippines," Dr. Pugach said.

"These findings strengthen the picture that has emerged from linguistic and archaeological studies, pointing to an Island Southeast Asia origin for the first settlers of the Marianas," said co-author Dr. Mike Carson, an archaeologist in the Micronesian Area Research Center at the University of Guam.

"We also find a close link between the ancient Guam skeletons and early Lapita individuals from Vanuatu and Tonga in the Western Pacific region," Dr. Pugach said. "This suggests that the Marianas and Polynesia may have been colonized from the same source population, and raises the possibility that the Marianas played a role in the eventual settlement of Polynesia."

While the new results provide interesting new insights, they are based on only two skeletons that date from around 1,400 years after the first human settlement in Guam. "The peopling of Guam and the settlement of such remote archipelagos in Oceania needs further investigation," said senior author Dr. Mark Stoneking, a researcher in the Department of Evolutionary Genetics at the Max Planck Institute for Evolutionary Anthropology.

The results appear in the P*roceedings of the National Academy of Science*.

Irina Pugach et al. 2021. Ancient DNA from Guam and the peopling of the Pacific. PNAS 118 (1): e2022112118; doi: 10.1073/pnas.2022112118

http://bit.ly/2JrcHEW

New research highlights the importance of the thymus in successful pregnancies

Findings reveal important changes that occur in the thymus to prevent miscarriages and gestational diabetes

How the immune system adapts to pregnancies has puzzled scientists for decades. Now, findings from an international group of researchers, led by researchers at Karolinska Institutet in Sweden, reveal important changes that occur in the thymus to prevent miscarriages and gestational diabetes. The results are published in the journal *Nature*.

The thymus is a central organ of the immune system where specialised immune cells called T lymphocytes mature. These cells, commonly referred to as T cells, then migrate into the blood stream and tissues to help combat pathogens and cancer. An important T cell subset, known as a regulatory T cell or Treg, is also produced in the thymus. The main function of a Treg is to help regulate other immune cells.

In the study, the researchers have found that during pregnancy, the female sex hormones instruct the thymus to produce Tregs specialised in dealing with physiological changes during pregnancy. The study--which involved researchers at Karolinska Institutet, IMBA - the Institute of Molecular Biotechnology of the Austrian Academy of Sciences in Vienna and the University of British Columbia in Vancouver--further reveals that RANK, a receptor expressed in the thymus epithelia, is the key molecule behind this mechanism.

"We knew RANK was expressed in the thymus, but its role in pregnancy was unknown", says first and co-corresponding author Dr. Magdalena Paolino, assistant professor and team leader at the Department of Medicine, Solna, Karolinska Institutet.

To get a better understanding, the authors studied mice where RANK had been deleted from the thymus.

"The absence of RANK prevented the production of Tregs in the thymus during pregnancy. This resulted in less Tregs in the placentas, leading to miscarriages," continues Magdalena Paolino.

The study further shows that in normal pregnancies, the produced Tregs also migrate to the mother's fat tissue to prevent inflammation and help control glucose levels in the body. Pregnant mice lacking RANK had high levels of glucose and insulin in their

blood and many other indicators of gestational diabetes, including fetal macrosomia.

"Similar to babies of women with gestational diabetes, the newborn pups were much heavier than average," explains Magdalena Paolino.

In addition, the deficiency of Tregs during pregnancy was proven to result in long-lasting transgenerational effects on the offspring, which remained prone to diabetes and overweight throughout their life spans. Giving the RANK deficient mice thymus-derived Tregs that had been isolated from normal pregnancies, reversed all issues including fetal loss and maternal glucose levels and the body weights of the pups.

The researchers also analysed women with gestational diabetes, revealing a reduced number of Tregs in their placentas, much similar to the study on mice.

"This research changes our view of the thymus, as an active and dynamic organ required to safeguard pregnancies," Magdalena Paolino says. "It also provides new molecular insight for gestational diabetes, a disease that affects many women and which we still know little about. It emphasises the importance of clinics detecting and managing glucose metabolism in pregnant women to avert its long-term effects."

Co-corresponding author Dr. Josef Penninger notes that how rewiring of the thymus contributes to a healthy pregnancy was one of the remaining mysteries of immunology - until now.

"Our work over many years has now not only solved this puzzle - pregnancy hormones rewire the thymus via RANK - but uncovered a new paradigmatic function: the thymus not only changes the immune system of the mother to allow the fetus, but it also controls metabolic health of the mother," Josef Penninger says.

The study was possible thanks to a close collaboration between the laboratory of Magdalena Paolino at Karolinska Institutet and the laboratories of Josef Penninger at IMBA and UBC. Researchers from the CeMM Institute and the Medical University of Vienna, as well as from the University of Birmingham and Oxford in the U.K. also participated.

The researchers were supported by grants from Karolinska Institutet, the Ragnar Soderberg Foundation, the Swedish Research Council, the Swiss National Foundation, The Wellcome Trust, MRC, CRUK, Austrian Science Fund, European Training Network, IMBA, a Canada150 Chair, the T. von Zastrow foundation and the European Research Council.

***Publication:** "RANK links thymic Tregs to fetal loss and gestational diabetes in pregnancy", Magdalena Paolino, Rubina Koglgruber, Shane J. F. Cronin, Iris Uribesalgo, Esther Rauscher, Juergen Harreiter, Michael Schuster, Dagmar Bancher-Todesca, Blanka Pranjic, Maria Novatchkova, Andrea White, Verena Sigl, Sabine Dekan, Juan P. Fededa, Thomas Penz, Christoph Bock, Lukas Kenner, Georg A. Holländer, Graham Anderson, Alexandra Kautzky-Willer, and Josef M. Penninger, Nature, online December 23, 2020, DOI: 10.1038/s41586-020-03071-0*

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What does 'do not resuscitate' mean? Varying interpretations may affect patient care, reports American Journal of Nursing

Nurses report significant variations in the way DNR orders are perceived or acted on in clinical practice

When patients have a do-not-resuscitate (DNR) order, it means they have chosen not to receive cardiopulmonary resuscitation (CPR). But hospital nurses report significant variations in the way DNR orders are perceived or acted on in clinical practice, reports a survey study in the January issue of the *American Journal of Nursing (AJN)*. The journal is published in the Lippincott portfolio by Wolters Kluwer.

"While the definition of DNR might seem straightforward, its interpretation in clinical practice can be complicated," according to the new research, led by Patricia A. Kelly, DNP, APRN, AGN-BC, AOCN, of Texas Health Presbyterian Hospital of Dallas, and Kathy A. Baker, PhD, APRN, ACNS-BC, FCNS, FAAN, of Harris College of Nursing and Health Sciences at Texas Christian University.

Differing perceptions of DNR orders may lead to unintended

consequences

Do-not-resuscitate orders have been a part of healthcare for more than 40 years. Published guidelines define DNR in terms of deciding to withhold CPR only, however, studies have shown healthcare providers and patients may be confused about the meaning and implications of DNR orders. An American Nurses Association position statement (PDF link) emphasizes that "patients with do-not-resuscitate orders must not be abandoned, nor should these orders lead to any diminishment in quality of care."

Based on her experiences, clinical nurse Karen Hodges, BSN, RN, OCN wondered, "How do nurses understand and act on DNR orders?" In response, Drs. Kelly, Baker, and colleagues performed a survey and interviews with 35 hospital nurses involved in caring for patients with DNR orders.

Analyzing the responses, the researchers identified one major theme: "Varying interpretations of DNR orders among nurses were common, resulting in unintended consequences." Within this overarching theme, there were three key subthemes:

- ***While the nurses provided clear definitions of DNR, they gave varying interpretations of the specifics of care. For example, while nurses agreed that DNR meant no CPR, some interpreted it as meaning no other aggressive lifesaving measures.***
- ***The nurses reported situations where healthcare team members disagreed about how DNR orders affected clinical care and responsibilities. One nurse pointed out that having a DNR doesn't mean the person is a hospice patient: "It doesn't mean that you're not going to do everything that you would for anybody else."***
- ***The nurses encountered family conflicts and confusion about DNR orders, particularly when the patient's condition changed, and patients and family members sometimes disagreed about DNR status.***

These differing perceptions have the potential to affect care in many ways, including varying responses when the patient's condition deteriorates, tensions among team members, and differences in role expectations. "Lack of clarity and agreement about what DNR means in practice has a far-reaching impact," Dr. Kelly and colleagues write. "It's critical for nurses to understand that DNR orders do not substitute for plans of care."

Maureen Shawn Kennedy, MA, RN, FAAN, editor in chief of *AJN*, notes that the study is important because, "Everyone - nurses, physicians, and families - needs to be on the same page in understanding the level of care a patient will receive."

Dr. Kelly, Baker, and coauthors believe that nurses play a key role in making sure that patients, families, and healthcare providers have a clear understanding of what DNR orders mean - and what they don't mean. "In every setting, nurses have opportunities to clarify such misinterpretations through practice, education, advocacy and policy, and research," the researchers conclude. "After 40 years as one of the most widely recognized medical abbreviations, DNR should mean 'do not resuscitate,' not an acronym that may diminish care."

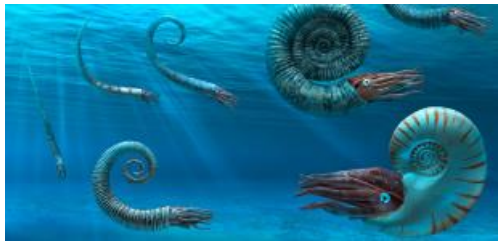
Click here to read "Nurses' Perspectives on Caring for Patients with Do-Not-Resuscitate Orders." *DOI: 10.1097/01.NAJ.0000731652.86224.11*

http://bit.ly/38y97kQ

Where Have All the Ammonites Gone?

They went extinct 66 million years ago. But the more interesting question is why?

by Riley Black



Ammonites are long gone. The last of their coil-shelled, many-tentacled kind disappeared 66 million years ago in one of the worst mass extinctions of all time.

Ammonites existed for hundreds of millions of years, persisting through three mass extinctions before succumbing to the one that took out the non-avian dinosaurs. **Photo by Masato Hattori/Science Photo Library**

The nearly 10-kilometer-wide asteroid that struck the Earth and drew the curtain on the Cretaceous wiped them out, just as it did the flying pterosaurs and non-avian dinosaurs.

And yet, there were survivors. While more than 70 percent of known species went extinct during the disaster, many others survived. The puzzle facing paleontologists now: why did the prolific and long-lived ammonites perish while other marine life—including their distant cousins, the nautilus and squid—persist? After all, ammonites had previously survived three other mass extinctions.

Looking at what made the end of the Cretaceous so catastrophic provides some clues. The previous mass extinctions the cephalopods had managed to weather were gradual perturbations of Earth's systems, like intense volcanic activity that played out over hundreds of thousands of years. But when the asteroid whapped into the planet at the end of the Cretaceous, the effects were unprecedented. Within the first day, the Earth's atmosphere heated to oven-like temperatures. Soon after, debris from the impact, and soot from widespread forest fires sparked by the ejecta, started to blot out the sun. Photosynthesis stopped for years, causing a near total collapse of the ecosystem.

Life in the ocean suffered. Most ocean ecosystems rely on photosynthesizers, but the extended night wiped out countless of these prolific autotrophs, nearly reverting the ocean to a bacterial state not seen for a billion years. Whatever survived had to eat other organisms to make it through the dark. That may have proved a problem for ammonites, which routinely fed on their own offspring. The asteroid's impact also released carbon into the atmosphere, turning the ocean acidic—a condition that would have made it harder for baby planktonic ammonites to form shells. If they perished, any surviving ammonite adults would have been deprived of this critical food source, says Amane Tajika, a paleontologist at the American Museum of Natural History in New York.

Before their sudden end, ammonites were flourishing. By the end of the Cretaceous many ammonites had specialized to particular niches—occupying varied depths within the seas—and required comparatively more energy to grow. Ammonites might have been used to ocean resources supporting their needs to rapidly grow shells, and so suffered when those resources became scarce. Their cousin the nautilus instead took the slow-growing, generalist route.

And, as often happens during extinctions, bad luck may have had a hand in the ammonites' demise.

"Modern squid and their relatives have obscene boom-bust cycles on seasonal, annual, and decadal timescales," says Kathleen Ritterbush, a paleontologist at the University of Utah. Despite data recorded by scientists and the fishing industry, no one knows what causes these fluxes. "We can't say what they're going to do next Tuesday."

It's possible that ammonites also followed such volatile cycles. If the asteroid struck during an ammonite bust, "you could tank the smallest ammonite population on their worst day," Ritterbush says.

Even if paleontologists were able to strap on scuba gear and dive into the Late Cretaceous ocean, finding the reason why ammonites disappeared would still be difficult. Doing it 66 million years after the fact is infinitely more challenging. But the story isn't just important for understanding a loss.What transpired at the end of the Cretaceous set the foundation of our modern ocean. The end of the ammonites marks the beginning of the ocean as we know it.

http://bit.ly/3o5zFk9

Sex Differences in Death After Stroke

Women were 39% more likely to die by 1 year after a first stroke.

New Rochelle, NY - The sex difference was due to advanced age and more severe strokes in women, according to a new study in the *Journal of Women's Health*. Click here to read the article now.

Among women and men with a first-ever stroke, women were approximately 7 years older. In addition, 9.3% fewer women could walk independently on admission to the hospital, suggestive of a more severe stroke.

"Among those deceased by any cause, men had more deaths due to cancer (12% vs women 6%) and ischemic heart disease (8% vs women 6%) while women had more deaths attributed to stroke (50% vs men 41%) or other cardiovascular disease (16% vs men 13%), state Dominique Cadilhac, PhD, School of Clinical Sciences at Monash Health, and coauthors.

"Cadilhac and colleagues showed that women had a 65% greater risk of death associated with stroke. Not only were women more likely to be older at first stroke and to have greater stroke severity, but they were also less likely to be treated with aspirin for secondary stroke prevention," says *Journal of Women's Health* Editor-in-Chief Susan G. Kornstein, MD, Executive Director of the Virginia Commonwealth University Institute for Women's Health, Richmond, VA.

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Pharmaceuticals roundup 2020: Performance under pressure

Alongside the race for Covid-19 treatments and vaccines, the industry has maintained momentum

By Sarah Houlton

2020's headlines have been dominated by coronavirus since the first reports of a mysterious virus causing pneumonia in Wuhan, China, in January. The pharmaceuticals sector's response was huge. While the pharma landscape has been somewhat unusual this year, at least some business has carried on.

The need for effective and innovative ways to treat disease is something that even a global pandemic will not blunt

Of course, a lot of the focus on clinical trials this year has been Covid-19-related, but trials continue elsewhere, despite the challenges and delays the pandemic has caused. However, there has been disruption. According to Evaluate Pharma's World preview 2020, outlook to 2026 report, 'Hundreds of clinical trials have been mothballed and trial readouts delayed; smaller developers in particular are exposed here, as they rely on fresh data for financial injections and partnering agreements.'

While many biotechs may be feeling the pinch, some of the pandemic fallout may prove positive in the longer term. Part of the temporary flexibility the US Food and Drug Administration introduced in an attempt to keep cancer clinical trials on track could be made permanent, and clinical research may be accelerated as a result.

New drug approvals continue apace and, in particular, the arsenal of cell and gene therapy products is growing. Kite's chimeric antigen receptor T-cell (CAR-T) therapy Tecartus (brexucabtagene autoleucel) was approved to treat mantle cell lymphoma, and Orchard Therapeutics' Libmeldy stem cell gene therapy was recommended by the European Medicines Agency (EMA) for the rare genetic condition metachromatic leukodystrophy. The EMA also conditionally authorised Zolgensma (onasemnogene abeparvovec) from AveXis, a gene therapy to treat children with another rare condition, spinal muscular atrophy.

Several cell- and gene-therapies were approved this year, mostly for rare diseases, such as Zolgensma for spinal muscular atrophy

Other highlights include a triple combination drug, Kaftrio (elexacaftor, tezacaftor and ivacaftor) from Vertex, for cystic fibrosis. Two long-acting antiretroviral medicines for HIV: Rekambys (rilpivirine) from Janssen and Vocabria (cabotegravir) from ViiV. If used together, injections every month or two can replace daily tablets for HIV patients who have reached undetectable virus levels in their blood. A vaccine from Janssen to

prevent Ebola was also approved in Europe.

Alzheimer's disease remains a hot topic, with yet more hopes being dashed on the altar of failed trials and regulatory knock-backs. Biogen's aducanamab is in the final stages of the regulatory process in the US, and while the final decision is not due until March 2021, in November members of an FDA advisory committee cast doubt on the clinical data. There was also disappointment for Eli Lilly and Roche, whose antibodies solanezumab and gantenerumab both failed to halt cognitive decline in a phase 3 trial in early onset Alzheimer's.

Merger desert

There was a near-total absence of M&A activity until the mid-December announcement of AstraZeneca's $39 billion acquisition of Boston, US-based rare disease specialist Alexion. Mylan's merger with Pfizer's generics business under the new name Viatris (initiated in mid-2019) finally completed in November, after regulatory delays caused by the pandemic. Shionogi acquired Tetra Therapeutics in May, having already increased its equity investment in the US biotech to 50% a couple of months earlier.

While M&A activity has been minimal, there has been a lot more action on the manufacturing front, with several large investments in plants and facilities. Pfizer, for example, is investing €300 million (£270 million) in a new facility at its Ringaskiddy, Ireland, site to make clinical trials supplies. While Samsung Biologics has opened an R&D centre in San Francisco, US, allowing it to carry out contract development services closer to its clients.

The growing focus on cell and gene therapies has, unsurprisingly, led to a lot of manufacturing investment there. Novartis, which already has cell therapy products on the market, has boosted its capacity for CAR-T therapy Kymriah (tisagenlecleucel) after a deal in Japan. Takeda opened a cell therapy facility in Boston to make clinical trial supplies. Thermo Fisher is investing $180 million (£135 million) in a facility in Plainville, US, that will double the company's commercial viral vector capacity for the gene therapy and vaccine markets.

85% of companies are actively recruiting AI specialists, and 60% are already using AI in their clinical operations

Merck KGaA, meanwhile, is spending €250 million on a manufacturing and R&D facility in Switzerland. It's also investing €59 million in a facility to manufacture highly potent active pharmaceutical ingredients in Madison, US, with continuous flow manufacturing technology for making antibody–drug conjugates.

Sanofi is investing nearly $700 million in a new vaccine research and production facility in France, while a $470 million injectable products facility in North Carolina, US, is on the cards at Eli Lilly. UCB is spending €300 million on a manufacturing site for monoclonal antibodies in Belgium, and South Korea's Celltrion will invest at least $500 million over five years on a biological drugs plant in Wuhan, China.

Chinese outsourcing giant WuXi continues to expand its foreign footprint, with a new $60 million manufacturing hub in Worcester, US. It is also acquiring a drug product manufacturing facility in Leverkusen, Germany, from Bayer.

There was a degree of portfolio shuffling, particularly of products whose patents have expired. Takeda sold 18 products to Brazil's Hypera Pharma for $825 million, for example, while AstraZeneca (AZ) sold several ageing hypertension drugs to UK-headquartered Atnahs for $350 million, and some European rights to cholesterol lowering agent Crestor (rosuvastatin) to Grünenthal.

The list of new research deals was far more extensive. For example, AZ and Daiichi Sankyo are collaborating to develop an antibody–drug conjugate to treat cancer. AZ is also working with Silence Therapeutics on small interfering RNA (siRNA) therapeutics in a number of areas. Biohaven, meanwhile, is to develop a number of

calcitonin gene-related peptide receptor antagonists discovered by Sosei–Heptares. Takeda and Carmine Therapeutics are collaborating on gene therapies for rare diseases, and Jiangsu Hansoh is partnering with artificial intelligence (AI) specialist Atomwise to discover new treatments for various diseases, including cancer.

Covid-19 has wiped nearly $8 billion off forecasts of biopharma sales in the year, with 60% of that decrease being borne by the biggest 15 companies

The interest in AI and machine learning tools continues elsewhere, too. According to a survey by the Drug Information Association and the Tufts Center for the Study of Drug Development, 85% of companies are actively recruiting AI specialists, and 60% are already using AI in their clinical operations.

The year has seen start-ups and biotechs attract significant investment. The UK BioIndustry Association and Clarivate said that in the three months from June 2020, UK biotechs raised more than £1 billion in equity finance, making it the highest quarter on record, and bringing the total for the first nine months of the year to £1.9 billion.

Opioid withdrawal?

There are finally signs that the US's opioid epidemic may be on the decline. An analysis of data in the US National Survey on Drug Use and Health by scientists at the Rush University Medical Center in Chicago indicates that the number of people reporting using opioids without their doctor's consent fell by 26% between 2007 and 2018.

FDA continues its battle against unlicensed online sellers of opioids, having sent warning letters to the owners of 17 websites in the US, China, Iceland, India, New Zealand and Pakistan for selling the drugs online without prescription to US consumers.

More of the ongoing lawsuits have also been settled. Endo and Par settled for $8.75 million in Oklahoma, which has been spearheading state legislation. Mallinckrodt agreed a $1.6 billion deal covering 47 states and territories. But these were dwarfed by the $8.3 billion Purdue agreed to pay the federal government, although it is still facing a multitude of state cases. Indivior paid $600 million in July, and former chief executive Shaun Thaxter pleaded guilty to US federal charges of misrepresentation a day after stepping down from the company at the end of June, with a reported payoff of £2.3 million. In October, he was given a six-month jail sentence. This is on top of the $1.4 billion settlement reached by Indivior's former parent company, Reckitt Benckiser, in December 2019.

Shoring up supplies

Concern about the reliance on foreign sources for pharmaceuticals has been a common theme. Both Europe and the US are looking at the composition of their pharma supply chains, and whether more manufacturing should be done domestically.

Fake and counterfeit medicines continue to pose threats to patients, and a joint operation in January between the FDA, other US federal agencies and the Indian government intercepted about 500 shipments of illicit treatments entering the country through an international mail facility across three days in January. About 50 different products were found, including cancer and HIV drugs, and a lot of opioids. Many of them had been shipped via third countries to conceal their true origins.

The US FDA and Indian authorities have collaborated to intercept hundreds of shipments of counterfeit drugs

Drugs contaminated with tiny quantities of carcinogenic nitrosamines remain an issue. For example, in January the Indian manufacturer Granules recalled more than 23 million ranitidine tablets in the US because of contamination with *N*-nitrosodimethylamine. In Europe, the EMA recommended suspending sales of all ranitidine products because of the impurity

in April, while in July it introduced a set of measures designed to ensure the contaminant remains at acceptably low levels. In September, the FDA issued guidance to help manufacturers detect and prevent these impurities in finished drug products, particularly by collaborating with the manufacturers of the APIs.

Another weight loss drug has is being withdrawn from the market, with Eisai voluntarily withdrawing Belviq (lorcaserin). It was only allowed onto the market after a large five-year trial in 12,000 patients showed it did not have the cardiovascular side effects that dogged other weight loss drugs. However, subsequent FDA analysis of data from this trial showed an increased incidence of cancer that outweighs the benefits of treatment.

Sales and forecasts

Humira (adalimumab) has remained at the top of the best-seller list since 2012, and is likely to stay there for another couple of years, with sales totalling nearly $20 billion last year. But growing biosimilar competition is expected to see it surrender its long-standing place at the top of the list. Merck & Co's Keytruda (pembrolizumab) immunotherapy is set to overtake it in 2024, with sales projected to top $24 billion by 2026, according to EvaluatePharma. It is already approved for 20 cancer indications, and this list will continue to grow.

However, Covid-19 has wiped nearly $8 billion off forecasts of biopharma sales in the year, with 60% of that decrease being borne by the biggest 15 companies. Yet despite the challenges and short-term losses relating to the pandemic, Evaluate was still predicting 3.7% growth for 2020 in its July report, stating: 'The need for effective and innovative ways to treat disease is something that even a global pandemic will not blunt.'

Of course the end to pandemic restrictions will almost certainly come in the form of a vaccine. A huge amount of work and investment has been put into the effort, with vaccines being developed at unprecedented speed. Pfizer was the first to produce sufficient safety and efficacy data to convince regulators to consider emergency approval, closely followed by Moderna; both of these rely on mRNA, a new type of vaccine technology that the pandemic has accelerated into the clinic. Close behind is the product from AstraZeneca and the University of Oxford, UK, which works in a very different way. Many more are in the pipeline at various companies and institutions around the world.

Manufacturing will be an issue, and distribution even more so – particularly for the mRNA products that need to be stored at low or ultra-low temperatures. But thanks to the huge efforts of the pharma industry, there is finally a glimmer of light at the end of the pandemic tunnel.

http://bit.ly/2KHBOUp

Tsunami May Have Seeded a Fungal Outbreak in Pacific Northwest

A bold hypothesis could account for the perplexing presence of multiple fungi

By Jennifer Frazer

The great Alaska earthquake lasted four minutes and 38 seconds when it struck on March 27, 1964. The outbreak it may have seeded wouldn't strike for another 35 years.

In 2013, I wrote in *Scientific American* about a subtropical fungus called *Cryptococcus gattii* that appeared unexpectedly in 1999 in the lungs of hundreds of humans, pets and porpoises in the Pacific Northwest. Although rare, it could be picked up from something as simple as a walk in the woods and prove fatal in otherwise healthy individuals.

One of the most surprising and puzzling twists of the *C. gattii* story was that what appeared to be one outbreak was actually at least two and maybe three. Two unrelated strains of *C. gattii* appeared around 1999 on Vancouver Island, while a third emerged six years later in

Oregon's Willamette Valley. Today we know the three are so different they may be separate species. At the time, experts were puzzled about the origins of all.

Many ideas were floated, including chance introduction by wind, ocean, animals, eucalyptus trees, tires, crates or tennis shoes. Most scientists agreed that the fungi seemed to have made their way to the Pacific Northwest many decades prior, and some subsequent disturbance—perhaps climate change—generated a burst of infections.

Now David Engelthaler and Arturo Casadevall, infectious disease scientists at the Translational Genomics Research Institute in Flagstaff and Johns Hopkins University (I interviewed Casadevall for my 2013 story), have suggested a surprising hypothesis: that the fungi not only hitchhiked on ships from South America to the Pacific Northwest, but then surfed a tsunami to reach land. If so, why would infections not strike mammals for another 35 years?

Describing their hypothesis in the journal *mBio* last year, the pair stitch together a circumstantial case. DNA analyses of all three fungi suggest a burst of evolution when they arrived in the Pacific Northwest around 70 to 90 years ago, hinting at a common origin.

One candidate for that origin, Engelthaler and Casadevall suggest, is the 1914 opening of the Panama Canal. Empty cargo ships pump water into their hull as stabilizing ballast. The water—and any hitchhiking life—is often dumped in the next port. *Cryptococcus* species survive in seawater, and *C. gattii* can survive for at least a year. The burst of shipping through the new canal may have brought *C. gattii* repeatedly from a place like Brazil to the waters off Seattle, Portland and Vancouver.

If so, the fungus still needed to make it on to land. The 1964 earthquake—which generated a tsunami so large it killed people on beaches as far south as California—seems like it could have done the job, they say.

Natural disasters are well-documented vectors. A burst of fungal lung infections followed the 2011 Joplin, Mo., tornado, as I documented here. The 1994 Northridge earthquake in California sparked a mini-outbreak of Valley fever, another inhaled fungal disease. People roughed up by tsunami waves may go on to suffer invasive skin and lung infections, a condition called "tsunami lung," and such waterborne infections from ocean flooding occurred after both the 2004 Indian Ocean tsunami and the 2011 Japanese tsunami. A survivor of the 2004 tsunami even suffered a skin infection from *C. gattii.*

But could a natural disaster introduce a pathogen to a new place, resulting in the outbreak of a new disease decades later?

Several lines of evidence suggest so, the pair argue. The forests and soils most heavily contaminated with *C. gattii* in the Pacific Northwest are those most affected by the tsunami: low-lying and close to the ocean. One exception—the area around Port Alberni in interior Vancouver Island—was nonetheless hard hit by the tsunami. A surge of water traveled down an inlet where it reached 26 feet high and washed away 55 homes. Today the fungus is found abundantly there, even though the town is relatively far from the coast.

The genetic data also reveal a second burst of evolution midcentury followed by another period of stability. After decades at sea, newly marooned fungi may have been forced to evolve quickly to survive in a place not only vastly different from the ocean but also dissimilar to their original home. Wild amoebas—amorphous single-celled microbes—prey on *C. gattii.* Learning to outsmart their new North American predators may have taken several decades. It may also have inadvertently trained the fungi to evade the amoeba-like immune cells called macrophages that travel our bodies doing essentially the same thing. This learning period could

explain the decades-long delay between the tsunami and outbreak, Engelthaler and Casadevall suggest.

The earliest known case of Pacific Northwest *C. gattii* occurred in 1971 in Seattle. Nothing else is known about this case, but the tsunami hypothesis would help explain this outlier, since the fungi would have already been ashore for several years. Other scattered infections may have occurred between 1971 and 1999 and simply escaped detection, as the *Cryptococcus* can go dormant in hosts.

Finally, and perhaps most importantly, this hypothesis would help account for both the potpourri of apparently unrelated *C. gattii* in the Pacific Northwest and their varied emergence times. If several strains had established themselves in the ocean as a result of years of shipping, the tsunami could have washed them ashore simultaneously across hundreds of miles of coast. The corollary, of course, is that there could be still more "surprises" in store for us, ones perhaps even more efficient at attacking mammals. Further environmental testing both in the Pacific Northwest and in ports and nearby land unaffected by tsunamis could help support or refute their hypothesis and would be relatively easy to do, they suggest.

The *mBio* paper was published in October 2019, but it has implications for subsequent events. Engelthaler and Casadevall propose the Pacific Northwest *C. gattii* outbreak may be a "black swan": an unpredictable event of extreme consequence. Indeed, it may be that many or even most outbreaks defy prediction.

The 2014 outbreak of Ebola in West Africa was probably inevitable given the conditions, many scientists believe, but the actual cause was the chance meeting of a group of sick migratory bats with children playing in a hollow tree. No one predicted that a flu pandemic would start in Mexico, but that happened in 2009. Similarly unexpected and unpredicted were the appearance of HIV, the SARS-CoV-1 and MERS coronaviruses, the Nipa and Hendra viruses and the monkeypox virus in the United States; the suddenly severe prenatal effects of Zika virus and the recent polio-like attacks in children suspected to be caused by a previously benign enterovirus D68 were also unforeseen, as was the appearance of *C. Gattii* in the temperate zone. Our present predicament is probably the biggest swan since the 1918 flu pandemic, which itself may have originated unexpectedly in Kansas.

Huge amounts of money, computing power and investigation resources have been thrown at the problem of predicting outbreaks of new disease. Those efforts failed us spectacularly this year. Financial philosopher Nassim Taleb, who coined the term black swan, argues that the proper response to such events is not to try to predict them; it's to prepare for them. Although, in my view, it's worthwhile to plumb their origins so we can try to avert future disasters (outlawing and aggressively prosecuting the sale of wildlife and reducing deforestation seem like obvious and humane choices), governments should just assume pandemics and outbreaks are inevitable and take appropriate action.

It's not as though we don't have precedent for expensive, defensive investments. In California, city planners and engineers know giant earthquakes will strike, but they don't worry too much about the particulars. After all, even after a century or more of studying Golden State seismology and geology, the destructive 1994 Northridge earthquake occurred on a fault that didn't even appear on seismic maps. Instead, they simply build accordingly.

https://go.nature.com/2L1zNCq

Pain-sensing neurons mobilize blood stem cells from bone marrow

Pain-sensing nerve cells can mobilize blood stem cells in mice, with a component of chilli peppers being one stimulus. The finding holds the promise of improving procedures for stem-cell transplantation.

Anastasia N. Tikhonova & Iannis Aifantis

The cardinal feature of blood stem cells is their ability to regenerate the body's entire blood and immune systems. The process is known as haematopoiesis, and the cells are better known as haematopoietic stem cells (HSCs). In developing embryos, HSCs shuffle around distinct anatomical sites, with blood circulation enabling their trafficking. After birth, these cells reside in specialized niches in the bone marrow that support their quiescence and self-renewal[1]. Throughout life, HSCs are released from the bone marrow to replenish blood cells in a circadian pattern that is under the control of involuntary nerves[2]. Pain-sensing nerves also make connections with the bone marrow, but can these neurons mobilize HSCs, too? Writing in *Nature*, Gao *et al.*[3] address this question and identify a surprising role for chilli peppers.

This work is of potential clinical as well as biological importance. For people who have blood cancers such as aggressive leukaemia, lymphomas and multiple myeloma, an essential part of treatment, following high-dose chemotherapy, is autologous stem-cell transplantation (ASCT)[4] — replacing damaged HSCs with healthy ones. To avoid the possibility of complications, ASCT uses an individual's own stem cells, which are collected from the blood before chemotherapy, then re-infused intravenously afterwards to regenerate damaged bone marrow.

This procedure requires a way to prompt healthy HSCs to leave their bone-marrow niche and enter the bloodstream to be collected. Since the 1990s, a secreted factor known as granulocyte-colony-stimulating factor (G-CSF) has been the most commonly used molecular prompt. The introduction of another prompt came in 2003 in the form of plerixafor, a small molecule that stops HSCs from remaining glued to the bone-marrow scaffold[4]. Since then, advances have included different routes of administration and combining G-CSF with plerixafor. But in a fraction of people, HSCs still do not mobilize sufficiently, with clinical risk factors including age, genetics and the type of cancer (up to 25% of people with lymphoma show poor mobilization), as well as repeated rounds of chemotherapy[5]. So, there is an urgent need to understand the molecular mechanisms of HSC mobilization[4].

Enter Gao and colleagues. The authors began with an immunofluorescent imaging survey of the bone marrow's nerve fibres in mice, revealing most to be 'nociceptive' nerves. These nociceptors are sensory neurons that protect organisms from danger by eliciting pain in response to injury. Nociceptors can be found in any area of the body that senses noxious stimuli[6]. These neurons have been best investigated in barrier tissues such as the skin and gut. The biological role of nociceptors in non-barrier tissues, such as the bone marrow, remains poorly studied with the exception of pain perception.

To examine a possible role of nociceptors in maintaining haematopoiesis, Gao *et al.* used pharmacological and genetic strategies to eliminate these neurons. This had no effect on the maintenance of HSCs in the bone marrow. It did lead to a marked reduction of G-CSF-induced mobilization of HSCs to the bloodstream, which suggests that this class of neuron affects HSC adhesion or migration.

Calcitonin-gene-related peptide (CGRP) is a major neurotransmitter molecule secreted by nociceptor neurons[6]. Gao *et al.* found that administering CGRP greatly improved HSC mobilization following treatment with G-CSF, plerixafor, or both. They also observed that CGRP affects HSCs directly (rather than acting indirectly through the bone marrow), inducing the formation of a dimeric receptor comprising the CALCRL and RAMP1 proteins on the HSC surface (Fig. 1). Genetically engineering mice to lack either of these in bone-marrow HSCs resulted in defective HSC mobilization.

In the clinic, continuous rounds of chemotherapy often lead to a decrease in HSC mobilization — a deficit that Gao *et al.*

recapitulated by treating mice with five weekly cycles of the chemotherapy drug cisplatin. Remarkably, administering CGRP restored HSC mobilization in these animals. This is a potentially crucial finding that could greatly improve protocols for HSC collection in 'poor mobilizer' individuals.

Certain types of spicy food can trigger nociceptor activation, leading Gao *et al.* to wonder whether consuming spicy food might cause HSC mobilization. To test this idea, the authors fed mice a diet rich in capsaicin — an active component of chilli peppers.

This spicy fare increased the levels of CGRP in the extracellular fluid of the bone marrow, and increased the CGRP-induced mobilization of HSCs. The effect disappeared when nociceptors were blocked pharmacologically, indicating that these neurons mediated the effect of the capsaicin-rich diet.

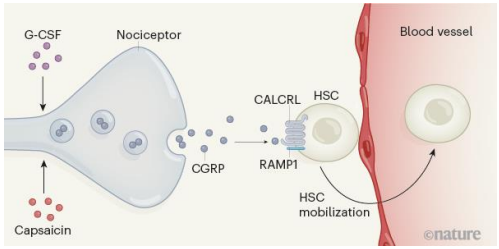

Figure 1 | Pain-sensing nerve cells regulate the mobilization of haematopoietic stem cells. *Gao and colleagues[3] report that most nerves in the bone marrow are neurons called nociceptors. They find that stimulation of these nerves by the protein granulocyte-colony-stimulating factor (G-CSF), or by a component of chilli peppers called capsaicin (it is not known whether stimulation was direct or indirect), leads the cells to release the neurotransmitter molecule calcitonin-gene-related peptide (CGRP). In turn, CGRP binds directly to blood stem cells called haematopoietic stem cells (HSCs) through a receptor dimer comprising the CALCRL and RAMP1 proteins. This stimulates the HSCs to move from the bone marrow into blood vessels.*

This paper adds intriguing pieces to our picture of the connections between the nervous system, bone marrow and blood-cell development. Early studies using photomicrographs of neurons in the bone marrow showed that it is innervated by nerve fibres[7]. During the past decade, surgical, pharmacological and genetic denervation models have established the nervous system's role in regulating the HSC niche[8]. But these studies mainly focused on sympathetic nerve fibres (those involved in involuntary actions of the body), showing that they help to maintain the functional integrity of the niche[9]. Here, Gao *et al.* have found that the adhesion of HSCs to their bone-marrow niche and their ability to mobilize to the peripheral blood is controlled by nociceptive neurons acting directly on HSCs through secretion of the neurotransmitter CGRP.

Surprisingly, the authors did not detect neuron-induced changes in the cell-surface levels of CXCR4, CD44 and VLA4 — molecules known to be expressed on HSCs and associated with their trafficking. Future studies, then, will need to delineate the precise mechanisms that mediate HSC mobilization following CALCRL–RAMP1 stimulation. It is also not known whether G-CSF affects nociceptors directly or indirectly through other cell types in the marrow. Such questions can be addressed using cell-type-specific gene targeting in animals. Moreover, findings that might be relevant to humans would need to be validated in clinical trials, because human biology is often not perfectly reflected in mice.

Finally, we should also consider stress responses in the bone marrow and their effects on neurons: for example, leukaemia induces nerve damage in the marrow[10], so it will be valuable to study the effects of blood cancers and ageing specifically on bone-marrow nociceptors. These issues notwithstanding, a robust molecular understanding of the neural regulation of haematopoiesis is now beginning to emerge.

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http://bit.ly/3mVEOtk

The Most Common Pain Relief Drug in The World Has Been Linked to Risk-Taking Behaviour

The most commonly taken analgesic worldwide could be doing a lot more than simply taking the edge off your headache

Peter Dockrill

One of the most consumed drugs in the US – and the most commonly taken analgesic worldwide – could be doing a lot more than simply taking the edge off your headache, recent evidence suggests.

Acetaminophen, also known as paracetamol and sold widely under the brand names Tylenol and Panadol, also increases risk-taking, according to a September 2020 study that measured changes in people's behaviour when under the influence of the common over-the-counter medication.

"Acetaminophen seems to make people feel less negative emotion when they consider risky activities – they just don't feel as scared," said neuroscientist Baldwin Way from The Ohio State University in September 2020.

"With nearly 25 percent of the population in the US taking acetaminophen each week, reduced risk perceptions and increased risk-taking could have important effects on society."

The findings add to a recent body of research suggesting that acetaminophen's effects on pain reduction also extend to various psychological processes, lowering people's receptivity to hurt feelings, experiencing reduced empathy, and even blunting cognitive functions.

In a similar way, the recent research suggests people's affective ability to perceive and evaluate risks can be impaired when they take acetaminophen. While the effects might be slight, they're definitely worth noting, given acetaminophen is the most common drug ingredient in America, found in over 600 different kinds of over-the-counter and prescription medicines.

In a series of experiments involving over 500 university students as participants, Way and his team measured how a single 1,000 mg dose of acetaminophen (the recommended maximum adult single dosage) randomly assigned to participants affected their risk-taking behaviour, compared against placebos randomly given to a control group.

In each of the experiments, participants had to pump up an uninflated balloon on a computer screen, with each single pump earning imaginary money. Their instructions were to earn as much imaginary money as possible by pumping the balloon as much as possible, but to make sure not to pop the balloon, in which case they would lose the money.

The results showed that the students who took acetaminophen engaged in significantly more risk-taking during the exercise, relative to the more cautious and conservative placebo group. On the whole, those on acetaminophen pumped (and burst) their balloons more than the controls.

"If you're risk-averse, you may pump a few times and then decide to cash out because you don't want the balloon to burst and lose your money," Way said.

"But for those who are on acetaminophen, as the balloon gets bigger, we believe they have less anxiety and less negative emotion about how big the balloon is getting and the possibility of it bursting."

In addition to the balloon simulation, participants also filled out surveys during two of the experiments, rating the level of risk they perceived in various hypothetical scenarios, such as betting a day's income on a sporting event, bungee jumping off a tall bridge, or driving a car without a seatbelt.

In one of the surveys, acetaminophen consumption did appear to reduce perceived risk compared to the control group, although in another similar survey, the same effect wasn't observed.

Overall, however, based on an average of results across the various tests, the team concludes that there is a significant relationship between taking acetaminophen and choosing more risk, even if the observed effect can be slight.

That said, they acknowledge the drug's apparent effects on risk-taking behaviour could also be interpreted via other kinds of psychological processes, such as reduced anxiety, perhaps.

"It may be that as the balloon increases in size, those on placebo feel increasing amounts of anxiety about a potential burst," the researchers explain. "When the anxiety becomes too much, they end the trial. Acetaminophen may reduce this anxiety, thus leading to greater risk taking."

Exploring such psychological alternative explanations for this phenomenon – as well as investigating the biological mechanisms responsible for acetaminophen's effects on people's choices in situations like this – should be addressed in future research, the team said.

While they're at it, scientists no doubt will also have future opportunities to further investigate the role and efficacy of acetaminophen in pain relief more broadly, after studies in recent years found that in many medical scenarios, the drug can be ineffective at pain relief, and sometimes is no better than a placebo, in addition to inviting other kinds of health problems.

Despite the seriousness of those findings, acetaminophen nonetheless remains one of the most used medications in the world, considered an essential medicine by the World Health Organisation, and recommended by the CDC as the primary drug you should probably take to ease symptoms if you think you might have coronavirus.

In light of what we're finding out about acetaminophen, we might want to rethink some of that advice, Way said.

"Perhaps someone with mild COVID-19 symptoms may not think it is as risky to leave their house and meet with people if they're taking acetaminophen," Way said.

"We really need more research on the effects of acetaminophen and other over-the-counter drugs on the choices and risks we take."

The findings are reported in *Social Cognitive and Affective Neuroscience*.

http://bit.ly/2McJsqq

New drug offers hope for thousands with cystic fibrosis

There were fears for patients with the lung disease as Covid-19 emerged but new treatments have shown remarkable benefits

Robin McKie

It threatened to be a calamitous year for those affected by Britain's most widespread inherited illness, cystic fibrosis. The disease attacks patients' lungs, leaving them dangerously susceptible to airborne infections. The appearance of Covid-19 – which can cause deadly lung disease and pneumonia in healthy individuals – triggered serious alarm among doctors, carers and patients.

"We were really worried that this previously unknown virus could be particularly bad news for people with cystic fibrosis," said Keith

Brownlee, a director at the Cystic Fibrosis Trust. "We thought this could be very dangerous."

Yet 2020 has not turned out to be the disastrous year for cystic fibrosis patients that had been anticipated. They have proved to be largely resilient to the threat of Covid-19 infections while the release of a new class of treatments for the condition has made remarkable improvements to the lives of many of the 10,600 people in Britain who have the disease.

"I started taking one of the new drugs – called Kaftrio – earlier this year," Michael Winehouse, a cystic fibrosis patient, told the *Observer*. "Within a day I felt better. Since then, my lung function has increased, my weight has returned to normal, I am better able to fight off infection, my energy levels have rocketed and I have less need of antibiotic treatments."

Cystic fibrosis is caused by a mutant gene that interferes with the body's ability to move chloride molecules. Individuals who carry a single copy of this gene are unaffected but those who inherit two copies – one from their father, one from their mother – are affected. Their cells cannot produce healthy digestive juices, sweat or mucus. Lungs clog up and become infected.

"Together these genes mean that the functioning of chloride channels in the lungs is disrupted," added Brownlee. "The crucial point about the new drug is that it can restore some of that functioning. Everything stems from that."

Winehouse, a charity fundraiser from Epping, agreed. "It has had a wonderful impact on my life," he added.

Given the grim prognosis for cystic fibrosis patients that was being forecast at the beginning of the Covid-19 pandemic, this has certainly been a remarkable transformation in fortunes for many patients.

"The other factor that has worked in our favour is that we already knew how to isolate ourselves effectively," added Winehouse. "We are very susceptible to infections. If there is a family party being held, I have to check if anyone who is going to be there has a cold or a cough. If they do, I cannot attend. We have spent our lives becoming trained in the arts of shielding ourselves."

In the past, people with cystic fibrosis would die in childhood. The development of antibiotics has helped to keep them alive, but even today few live beyond their 40s and only survive by going through long daily physiotherapy sessions, the consumption of dozens of vitamin and digestive enzyme tablets, and the constant use of antibiotics and asthma inhalers.

"I am 34 and was beginning to look at the next decade with some apprehension," said Winehouse. "Now the drug has changed that, I can look to the future with a bit more confidence."

Not every patient responds to the new drug, which is still being rolled out by doctors, and some are still ineligible to get it.

"At the moment, patients under the age of 12 cannot get the drug but we are confident that will change very soon. It has actually been a fantastic year in some respects for patients," added Brownlee.

http://bit.ly/34Oc7bw

Mysterious asteroid the size of a dwarf planet is lurking in our solar system

Where did this strange meteorite come from?

By Rafi Letzter - Staff Writer

There's a giant asteroid somewhere out in the solar system, and it hurled a big rock at Earth.

The evidence for this mystery space rock comes from a diamond-studded meteor that exploded over Sudan in 2008.

NASA had spotted the 9-ton (8,200 kilograms), 13-foot (4 meters) meteor heading toward the planet well before impact, and researchers showed up in the Sudanese desert to collect an unusually rich haul of remains. Now, a new study of one of those meteorites suggests that the meteor may have broken off of a giant

asteroid — one more or less the size of the dwarf planet Ceres, the largest object in the asteroid belt.

Like about 4.6% of meteorites on Earth, this one — known as Almahata Sitta (AhS) — is made of a material known as carbonaceous chondrite. These black rocks contain organic compounds as well as a variety of minerals and water.

The mineral makeup of these space rocks offers clues about the "parent asteroid" that birthed a given meteor, researchers said in a statement.

"Some of these meteorites are dominated by minerals providing evidence for exposure to water at low temperatures and pressures," study co-author Vicky Hamilton, a planetary geologist at the Southwest Research Institute in Boulder, Colorado, said in the statement. "The composition of other meteorites points to heating in the absence of water."

The team analyzed a teensy 0.0018-ounce (50 milligrams) sample of AhS under a microscope and found it had a unique mineral makeup. The meteorite harbored an unusual suite of minerals that form at "intermediate" temperatures and pressures (higher than what you'd find in a typical asteroid, but lower than the inside of a planet). One mineral in particular, amphibole also requires prolonged exposure to water to develop.

Amphibole is common enough on Earth, but it's only appeared once before in trace amounts in a meteorite known as Allende — the largest carbonaceous chondrite ever found, which fell in Chihuahua, Mexico, in 1969

The high amphibole content of AhS suggests the fragment broke off a parent asteroid that's never left meteorites on Earth before.

And samples brought back from the asteroids Ryugu and Bennu by Japan's Hayabusa2 and NASA's OSIRIS-REx probes, respectively, will likely reveal more space rock minerals that rarely turn up in meteorites, the researchers wrote in their study.

Maybe some types of carbonaceous chondrite just don't survive the plunge through the atmosphere as well, Hamilton said, and that's kept scientists from studying a flavor of chondrite that might be more common in space. "We think that there are more carbonaceous chondrite materials in the solar system than are represented by our collections of meteorites," she said.

The paper was published Dec. 21 in the journal Nature Astronomy.

http://bit.ly/37TqRb9

Dig of Pompeii Fast-food Place Reveals Tastes

A fast-food eatery at Pompeii has been excavated, helping to reveal dishes that were popular for the citizens of the ancient Roman city who were partial to eating out.

ROME - Pompeii Archaeological Park's longtime chief, Massimo Osanna, said Saturday that while about 80 such fast-foods spots have been found at Pompeii, it is the first time such a hot-food-drink eatery - known as a thermopolium - was completely unearthed.

A fresco on an ancient counter depicting a nymph riding a horse uncovered during excavations in Pompeii, Italy, is seen in this handout picture released Dec. 26, 2020.

A segment of the fast-food counter was partially dug up in 2019 during work to shore up Pompeii's oft-crumbling ruins. Since then, archaeologists kept digging, revealing a multisided counter, with typical wide holes inserted into its top. The countertop held deep vessels for hot foods, not unlike soup containers nestled into modern-day salad bars.

Plant and animal specialists are still analyzing remains from the site, with its counter frescoed with a figure of an undersea nymph astride a horse. Images of two upside-down mallards and a rooster, whose

plumage was painted with the typical vivid color known as Pompeiian red, also brightened the eatery and likely served to advertise the menu.

Another fresco depicted a dog on a leash, perhaps not unlike modern reminders to leash pets. Vulgar graffiti were inscribed on the painting's frame.

Valeria Amoretti, a Pompeii staff anthropologist, said "initial analyses confirm how the painted images represent, at least in part, the foods and beverages effectively sold inside." Her statement noted that duck bone fragment was found in one of the containers, along with remains from goats, pigs, fish and snails. At the bottom of a wine container were traces of ground fava beans, which in ancient times were added to wine for flavor and to lighten its color, Amoretti said.

"We know what they were eating that day," said Osanna, referring to the day of Pompeii's destruction in 79 A.D. The food remains indicated "what's popular with the common folk," Osanna told Rai state TV, noting that street-food places weren't frequented by the Roman elite.

One surprise find was the complete skeleton of a dog. The discovery intrigued the excavators, since it wasn't a "large, muscular dog like that painted on the counter but of an extremely small example" of an adult dog, whose height at shoulder level was 20 to 25 centimeters, Amoretti said. It's rather rare, Amoretti said, to find remains from ancient times of such small dogs, discoveries that "attest to selective breeding in the Roman epoch to obtain this result."

Also unearthed were a bronze ladle, nine amphorae, which were popular food containers in Roman times, a couple of flasks and a ceramic oil container.

Successful restaurateurs know that a good location can be crucial, and the operator of this ancient fast-food eatery seemed to have found a good spot. Osanna noted that right outside was a small square with a fountain, with another thermopolium in the vicinity.

Pompeii was destroyed by the volcanic eruption of Mount Vesuvius, which is near present-day Naples. Much of the ancient city still lies unexcavated. The site is one of Italy's most popular tourist attractions. Human remains were also discovered in the excavation of the eatery.

A fresco depicting two ducks and a rooster on an ancient counter discovered during excavations in Pompeii, Italy, is seen in this handout picture released Dec. 26, 2020.

Those bones were apparently disturbed in the 17th century during clandestine excavations by thieves looking for valuables, Pompeii authorities said. Some of the bones belonged to a man, who, when the Vesuvius volcano erupted, appeared to have been lying on a bed or a cot, since nails and pieces of wood were found under his body, authorities said. Other human remains were found inside one of the counter's vessels, possibly placed there by those excavators centuries ago.

http://bit.ly/3hookcn

AstraZeneca's vaccine is expected to work on new COVID-19 strains, says CEO

AstraZeneca CEO Pascal Soriot says his company's COVID-19 vaccine "should remain effective" against mutated virus strains, reports The Sunday Times.

Kevin Shalvey

AstraZeneca's coronavirus vaccine is expected to be effective against mutating COVID-19 strains, including those discovered in the UK and South Africa.

"So far, we think the vaccine should remain effective," CEO Pascal Soriot told The Sunday Times. "But we can't be sure, so we're going to test that," he told the newspaper.

As vaccine vials made their way around the world last week, news also spread of mutated coronavirus variants.

The first variant, discovered in the UK, had 23 documented changes. It could be about 70% more transmissible and had already infected about 40,000 people in the UK by midweek, per Reuters. The second variant was first found in South Africa but made its way to the UK last week, according to health officials.

"This new variant is highly concerning because it is yet more transmissible and it appears to have mutated further than the new variant that has been discovered in the UK," said Matt Hancock, British health secretary, on Wednesday.

As the strains spread, other countries closed their doors to UK visitors.

The new strain was discovered in Japan on Friday, brought by travelers from the UK, according to Reuters. About seven people, including five who had traveled from the UK to Japan, tested positive, The Associated Press reported on Sunday.

On Monday, Japan plans a sweeping ban on foreigners entering the country, in part because of the new strains, according to The Associated Press.

In saying AstraZeneca's vaccine will protect against strains of the coronavirus, Soriot echoed Ugur Sahin, CEO of BioNTech. There was a "relatively high" possibility that the Pfizer-BioNTech vaccine would work against variants, Sahin said last week.

The UK government signed deals for 100 million doses of the AstraZeneca vaccine, which was developed in partnership with Oxford University. That vaccine is the largest single order from the government, which has signed deals for 357 million doses of various vaccines.

As of Christmas Eve, about 617,000 people in the UK had received doses of Pfizer's vaccine, according to official statistics.

The UK government is now reviewing vaccines from AstraZeneca and Moderna.

"The NHS across the UK is working incredibly hard to scale up the vaccination program as fast as they can to make sure everyone on the priority list can get their vaccine easily," said Nadhim Zahawi, the minister overseeing vaccine deployment, in a statement.

http://bit.ly/3aL1pq7

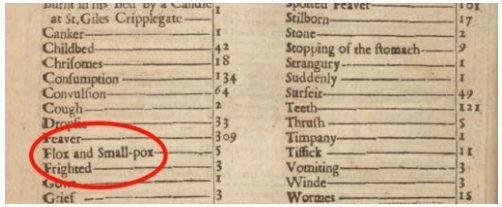
Centuries-Long Timeline of Smallpox Records Shows How a Fatal Disease Is Eliminated

Amidst a global pandemic, researchers are looking back in time at the only human disease we've ever successfully eradicated.

Carly Cassella

Even today, four decades after smallpox stopped circulating in the public, the disease is still regarded as one of history's greatest killers, taking more lives for more centuries than any other single infectious disease, even plague and cholera.

In the 18th century, 400,000 Europeans died each year from smallpox. In London alone, more than 321,000 people died from the disease post 1664.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1665 burial records for London. **(London: E. Cotes, 1665)**

A third of those who survived were left blind, and many more were disfigured by scars.

"The current COVID-19 pandemic has caused a surge of interest in the study of infectious disease transmission and how public health interventions could change the course of the pandemic," says David Earn, who models infectious disease transmission at the McMaster University in Ontario.

"Our goal was to describe and make publicly available the weekly time series of smallpox mortality in London and to identify historical events that might have influenced smallpox dynamics over the centuries."

For nearly 300 years, between 1664 and 1930, officials in London kept careful records of smallpox deaths. Digitising more than 13,000 of these weekly reports, researchers have created a major timeline of smallpox mortality and prevention, tracking the virus' movements in London and the ways in which it was influenced by seasons, public health policies and historical events.

Over time, the results clearly show that better control of the virus led to fewer smallpox deaths.

Outbreaks appeared sporadically in earlier records, settling into regular tides of infection by 1770 as a crude form of smallpox inoculation called variolation gained popularity.

Only in 1810, coinciding with the introduction of the far safer practice of vaccination, does the data show a dramatic reduction in the amplitude of epidemics, though outbreaks were more frequent and the data are noisier."

A particularly large epidemic in 1830s London, which ultimately spread to Europe, was actually the impetus for England's first Vaccination Act in 1840, giving free shots to anyone who wanted them and banning more dangerous practices like variolation. Only then did vaccination levels increase, with fatalities taking a downward plummet.

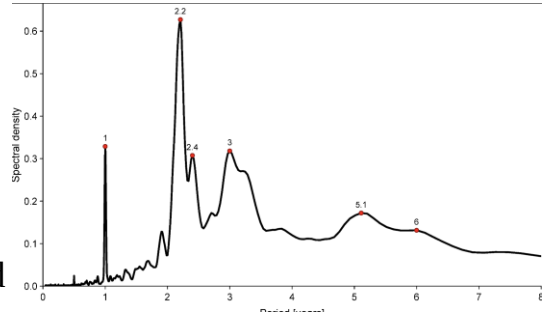
Other impacts like the seasonal structure of epidemics and the seasonal timing of outbreaks were more challenging to untangle, and the authors admit their data will need more investigation.

That said, the timeline is, to their knowledge, the longest weekly series of infectious disease mortality ever put together. As such, it helps illustrate how a virus can go from being "a terrifying and unavoidable danger" - killing roughly one out of every three people infected - to an extremely unusual cause of death.

From killer to rarity

In the years leading up to the last smallpox death in London, circa 1934, only a handful of deaths were reported from the virus.

"It is clear that the introduction of smallpox control measures - [inoculation] and later vaccination - made eradication possible," says Olga Krylova, who worked on the project while studying mathematics and statistics at McMaster.



Weekly smallpox mortality time series for London, England, 1664–1930.
(Krylova and Earn, PLOS Biology, 2020)

"Our analysis also suggests that greater use of control measures and changes in public health policies were correlated with changes in the frequency of the epidemics."

Smallpox has a long and rich history, with current thinking associating it with a rodent disease that made the leap in Africa a few thousand years ago. Over millennia, as the world became more globalised, it appears this virus took off, spreading and growing alongside human civilisations and their trade routes.

In the Middle Ages of Europe, the virus frequently caused epidemics. Colonisation then spread it to Africa, Australia and North America.

Before the development of vaccines, people in Africa, India and China began relying on variolation to control the spread of smallpox. This entailed a small cut on the arm or leg, in which a tiny amount of the smallpox virus was introduced, taken from the pustules or scabs of those already infected.

The remarkable idea ultimately came to Europe in the 18th Century through trade with Turkey, and it was quickly taken up by physicians.

In 1796, a scientist by the name of Edward Jenner figured out that cowpox, which is born from a similar virus to smallpox, could protect humans against epidemics of this infectious disease. When he inoculated patients with this animal virus, it provided immunity in a safer, cheaper and more effective way than inoculation with the human virus.

By 1800, his work helped produce a smallpox vaccine in England. By 1840, inoculation was a thing of the past.

But that wasn't the end of smallpox. It wasn't until the late 19th century that scientists realised vaccine immunity was not lifelong and that people needed to be re-vaccinated.

After that, a global campaign from the World Health Organisation was able to successfully eradicate the virus in a decade. The last remaining samples are now stored in the US and Russia.

Throughout this long timeline, London was going through its own set of major cultural and historic changes. The Industrial Revolution, for instance, may have played a role in smallpox epidemics as urbanisation spread and social demographics changed. Wars were also another possible mechanism for spread.

"Further research using mathematical models is needed to quantify the impacts of interventions and historical events on the smallpox outbreaks," says Krylova.

This extensive timeline can hopefully allow scientists to do just that. By honing in on specific events and their effects, we might come to better understand how contagious infections can fluctuate over time, and what we can do to beat them back in the end.

"The long history of documenting smallpox mortality in London provides an extraordinary opportunity to learn from the past about changing patterns in infectious disease transmission," the authors conclude.

Now it's time to dig into the data.

The study was published in *PLOS Biology*.