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The Next Step in Covid-19 Vaccines May Be Through the Nose

Intranasal vaccines may help prevent transmission and hinder the evolution of new viral variants

By Claire Bugos

In a collective display of scientific advancement, the Covid-19 vaccines from Pfizer, Moderna and Johnson & Johnson seem to be astoundingly effective at preventing severe disease and death from Covid-19. All are intramuscular, meaning they are injected into the muscle tissue. Once the vaccine materials seep into the bloodstream, they induce the creation of antibodies, which then circulate in the blood throughout the body, protecting some of the most vital organs and creating what's called systemic immunity. This immune response protects the body from serious illness and death, but the response only builds after the virus has fully entered the body.

Their ability to protect the human body from Covid-19 illness is truly incredible, but the SARS-CoV-2 virus still has an entryway into the body left unprotected by the vaccines: the nose and mouth. Those two gateways, and their ability to transmit the virus, are what mask mandates are all about. Face coverings have been shown to impede the spread of the aerosol virus, protecting their wearers and those around them from infecting each other.

But what if a new, intranasal vaccine existed?

With a spritz up the nose, such a vaccine would travel through the upper respiratory tract, encouraging the body to produce protective antibodies there. If successful, this immune response would both neutralize the virus on its way in before making a person sick, and it would ensure that no live virus escapes when they exhale, cough or sneeze. While early data on efforts to promote mucosal immunity is promising, companies are still in early-stage clinical trials and a marketable, intranasal Covid-19 vaccine may be a year out.

"For real control of the pandemic, what we want to do is not just prevent serious disease and death—as good as that is in itself—but we want to be able to break the chains of transmission," says Michael Russell, a mucosal immunologist with the University of Buffalo.

The existing vaccines achieve systemic immunity by spurring the production of antibodies called immunoglobulin G, or IgG and killer T cells. These cells and proteins are highly effective at neutralizing the virus before seriously damaging our key organs. But to prevent the virus from entering into the body in the first place, scientists likely need to target the mucosal system. The moist tissue lining the nasal and mouth are part of the mucosal system, which stretches from there all the way through the gastrointestinal and reproductive tracts. Here, a different class of antibodies exude from the mucosa to neutralize viruses and other intruders. The mucosal system secretes specialized antibodies called Immunoglobulin A or IgA. When faced with an intruding virus or bacterium, the mucosa releases IgA to neutralize it.

If a Covid-19 vaccine can create a strong mucosal immune response, the body may be better equipped to stop the virus before it makes its way to essential organs, like the heart and lungs. Plus, secretory IgA antibodies in the mouth and nose are more potent against SARS-CoV-2 than the IgG antibodies induced by intramuscular vaccines, according to a study published in *Science Translational Medicine* in January. Proponents of intranasal vaccines are hopeful that boosting secretory IgA in this way would be a step up from the protection offered by the existing vaccines.

For the body to create the secretory IgA antibodies necessary to neutralize incoming virus, many scientists think a vaccine needs to be applied along the natural route of infection. This means administering the vaccine through the nose via a nasal spray and

letting it travel through the mucosa.

Injected Covid-19 vaccines don't appear to elicit much of an antibody response in the mucosa, says Michal Tal, an immunologist at Stanford University and team lead of the Stanford Saliva Study—an effort to track antibodies that are secreted in saliva from people who have been vaccinated. Many people who have been naturally infected with Covid-19 seem to create a mucosal immune response early in the infection, but for those relying on a vaccine to build their immunity, an intranasal vaccine may provide a necessary IgA supplement to their systemic immunity.

"To protect the nose from being a site where infection can get in and infection can get back out, you really have to have IgA there," Tal says.

Globally, five intranasal vaccine candidates are currently undergoing clinical trials, according to the World Health Organization. Scot Roberts, chief scientific officer of Altimmune, the only U.S. company with an intranasal vaccine in clinical trials, is betting that such an intranasal vaccine will be the best way to stop viral transmission while also protecting the body from disease. "You can only get this mucosal antibody response when you do intranasal administration, because it's a very localized immunity," he says.

Recent research indicates that the Pfizer and Moderna vaccines may reduce viral load and asymptomatic transmission. A study by the CDC published last month shows that health care workers in eight U.S. locations saw a 90 percent reduction in Covid-19 transmission rates after being fully vaccinated with one of the mRNA vaccines. Another study, by Israeli researchers and published in *Nature Medicine* in March, indicates that the Pfizer vaccine significantly reduced viral load 12 to 37 days after vaccination—a key indicator of diminished transmission.

Still, the current vaccines haven't proven to completely block transmission. Part of the reason why, Tal says, is because transmission can stem from different parts of the respiratory tract for different individuals. Some infected individuals, vaccinated or not, may not spread the virus unless they're in close contact with others. Tal says scientists think this kind of spread originates from virus living in the nose. But other people, who act as "superspreaders," may carry and spread aerosols of highly infectious virus from the lungs or the nose or both. Intramuscular vaccines can neutralize the virus in the lungs, but without mucosal immunity conferred through an intranasal vaccine, scientists say no way likely exists to fully stop transmission from the nose.

Tal adds that she was "a little surprised" to learn that most of the original Covid-19 candidates under Operation Warp speed were to be administered intramuscularly, despite dealing with a mucosal pathogen. But during that point in the pandemic, when death and hospitalization rates were skyrocketing, creating a formula to prevent death was paramount.

"From a public health perspective, the most important key mission is to bring down deaths and hospitalizations," Tal says. "So, you want to go with an intramuscular formulation where you know you're going to get really great circulating antibodies, which intranasal may not be as optimal for."

Now that more than 175 million doses of vaccine have been distributed in the U.S., scientists are looking to do more. Blocking transmission is especially important in attempts to rein in emerging viral variants. After entering the body, genetic mutations in the virus sometimes help it become more infectious or successful at evading immune responses. When this happens, the new version of the virus replicates and eventually becomes a new variant. However, if the virus is unable to breach the mucosal and systemic immune systems, it cannot live and replicate in the nasal passages or body. And if transmission is blocked, it becomes more difficult for

variants to spread through a population.

Intranasal and oral vaccines are not novel concepts. Intranasal flu vaccines like FluMist, developed by AstraZeneca, were used for decades in the U.S. In the last decade, however, they became variably effective against the circulating flu strains, causing the CDC to revoke its recommendation for their use for several years. Previous intranasal flu vaccines introduce some weakened virus and allow it to replicate in the respiratory tract to create an immune response. Roberts says his company's Covid vaccine, AdCOVID, will be safer because it introduces a larger amount of vaccine and the viral vector isn't able to replicate in the body and make someone sick.

History offers a precedent to a second wave of vaccines adding a layer of protection for public health. The initial Salk polio vaccine, for instance, was first introduced as a shot. Though it was effective at preventing illness, the shot didn't stop infection. The poliovirus mostly affects the intestines, which are lined with mucus. So, scientists, including Albert Sabin, developed an oral vaccine that, when swallowed, came in direct contact with the gut mucosa to boost the mucosal immunity and stop infection and transmission. A Covid-19 intranasal vaccine would directly affect the mucosa in the same way.

"That polio story is completely analogous to what we're doing, except we're doing it in the respiratory tract," Roberts says.

One of the major remaining unknowns about an intranasal vaccine is how well it will mount a lasting immune response. Russell says that the mucosal immune must constantly contend with our microbiota and the everything we eat and inhale in ways that the rest of the body does not. Thus, it's possible that the mucosal system's memory of, and response to, the virus may diminish more quickly than the systemic immune response will.

Roberts predicts AdCOVID will be available in early 2022. In regions of the world where many people have been vaccinated, it may serve as a sort of seasonal re-vaccination. Roberts says that, like the flu, Covid-19 may become a seasonal illness. For people with a systemic immune response, either from intramuscular vaccination or natural infection, the intranasal vaccine could act as a booster to support their mucosal immunity and protect against variants.

As pharmaceutical companies develop second generation vaccines and think about vaccine boosters, Tal says they have renewed opportunity to devise ways to boost mucosal immunity.

"Obviously, we've got to get out of the current situation we find ourselves in, but also provide a better preparedness to deal with the virus becoming endemic in the human population," Russell adds. "It seems very likely that we will not totally eliminate this virus, we're going to have to live with it forever in [the] future."

https://bbc.in/32lIbC4

Covid: Asthma drug 'speeds up recovery at home'

A cheap drug, commonly used to treat asthma, can help people at home recover more quickly from Covid-19, a UK trial has found.

By Philippa Roxby Health reporter

Two puffs of budesonide twice a day could benefit many over-50s with early symptoms around the world, said the University of Oxford research team.

There are also early signs the drug could reduce hospital admissions.

The NHS says it can now be prescribed by GPs to treat Covid on a case-by-case basis.

At present, there are few options for treating people with Covid who are not in hospital, apart from paracetamol.

This widely-available asthma drug works in the lungs, where coronavirus can do serious damage, and could improve the recovery of at-risk patients who are unwell with Covid at home.

Prof Stephen Powis, national medical director of NHS England,

said he was "delighted" by the trial results so far and added that GPs could prescribe it after "a shared decision conversation" with patients.

Community care

Prof Mona Bafadhel, a respiratory doctor who was involved in the Oxford-led Principle trial, said the results were "something we should be excited about".

"We are helping the patient as much as possible, as early as possible - in the community," she said.

Early in the pandemic, asthma patients were under-represented in severely-ill hospital patients with Covid - and the drugs they took to treat their condition were thought to be the reason.

The trial involved more than 1,700 people at high risk of becoming severely ill with Covid-19 - all aged over 50, either with an underlying health condition or aged over 65 with no health problems.

During the first two weeks of experiencing symptoms at home, 751 were given an inhaler containing budesonide to use twice a day.

This group recovered from Covid on average three days sooner than another group given normal care, which is advice to rest and take paracetamol, the trial data showed.

And a third of those taking inhaled budesonide recovered within the first 14 days of using it, compared to less than a quarter of those in the other group.

There were also early signs that slightly fewer people on the drug were admitted to hospital with Covid (8.5% compared to 10.3%) - but more data is needed before this, or any reduction in deaths from Covid, can be confirmed, the researchers said.

These are interim results from the trial up to the end of March, which have not yet been peer-reviewed or published in a journal.

Final results from the trial, which are likely to include more data, are expected at the end of April.

Budesonide, like other coricosteroids which are breathed into the lungs using an inhaler, "work at the site of the virus where it is likely to be causing the biggest effect and is widely known to reduce inflammation", Prof Bafadhel said.

Lab tests suggest the drug also reduces viral replication of the virus.

Associate Prof Gail Hayward, a GP and investigator on the trial, said patients at higher risk could be offered the inhaler as part of their treatment on the NHS. One inhaler is thought to cost about £14.

"We now have the evidence to treat my patients at home," she said.

A smaller, earlier-stage trial on the drug in February also reported promising results.

The Oxford-led Principle trial is the latest UK trial to release positive results in the search for Covid treatments. Last year, a steroid called dexamethasone was found to save lives among the most seriously-ill patients in hospital and a number of other drugs and treatments have also shown promise.

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Human screams communicate at least six emotions

Non-alarming screams are perceived and processed by the brain more efficiently than alarming screams

Human screams signal more than fear and are more acoustically diverse than previously thought, according to a study published April 13th 2021 in the open-access journal *PLOS Biology* by Sascha Frühholz of the University of Zurich, and colleagues. Remarkably, non-alarming screams are perceived and processed by the brain more efficiently than alarming screams.

In nonhuman primates and other mammalian species, scream-like calls are frequently used as an alarm signal exclusively in negative contexts, such social conflicts or the presence of predators or other environmental threats. Humans are also assumed to use screams to signal danger and to scare predators. But humans scream not only

when they are fearful and aggressive, but also when they experience other emotions such as despair and elation. Past studies on this topic largely focused on alarming fear screams, so the broader significance of various scream types has not been clear. In the new study, the researchers addressed this knowledge gap using four different psychoacoustic, perceptual decision-making, and neuroimaging experiments in humans.

Twelve participants were asked to vocalize positive and negative screams that might be elicited by various situations. A different group of individuals rated the emotional nature of the screams, classified the screams into different categories, and underwent functional magnetic resonance imaging (fMRI) while listening to the screams.

The results revealed six psycho-acoustically distinct types of scream calls, which indicated pain, anger, fear, pleasure, sadness, and joy. Perhaps surprisingly, listeners responded more quickly and accurately, and with higher neural sensitivity, to non-alarm and positive scream calls than to alarming screams. Specifically, less alarming screams elicited more activity across many auditory and frontal brain regions. According to the authors, these findings show that scream calls are more diverse in their signaling and communicative nature in humans than frequently assumed.

Dr. Frühholz notes "The results of our study are surprising in a sense that researchers usually assume the primate and human cognitive system to be specifically tuned to detect signals of danger and threat in the environment as a mechanism of survival. This has long been supposed to be the primary purpose of communicative signaling in screams. While this seems true for scream communication in primates and other animal species, scream communication seemed to have largely diversified in humans, and this represents is a major evolutionary step. Humans share with other species the potential to signal danger when screaming, but it seems like only humans scream to signal also positive emotions like extreme joy and pleasure. Signaling and perceiving these positive emotions in screams seemed to have gained priority in humans over alarm signaling. This change in priority might be likely due to the requirements of evolved and complex social contexts in humans."

Research article

Peer reviewed; Experimental study; Human

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Next Winter May Be Rough: Models Predict 'Considerable Surge' of COVID

It's likely the United States will see another surge of COVID-19 this winter

Ken Terry

It's likely the United States will see another surge of COVID-19 this winter, warned Christopher Murray, MD, director of the Institute for Health Metrics and Evaluation (IHME) at the University of Washington in Seattle.

Speaking at the national conference of State of Reform on April 8, Murray cited the seasonality of the SARS-CoV-2 virus, which wanes in the summer and waxes in the winter. The "optimistic forecast" of IHME, which has modeled the course of the pandemic for the past 13 months, is that daily deaths will rise a bit in the next month, then decline from May through August, he said.

"Summer should be fairly quiet in terms of COVID, if vaccinations rise and people don't stop wearing masks," Murray said.

But he added that "a considerable surge will occur over next

winter," because the new variants are more transmissible, and people will likely relax social distancing and mask wearing. The IHME predicts that the percentage of Americans who usually don masks will decline from 73% today to 21% by August 1.

With a rapid decline in mask use and a rise in mobility, there will still be more than 1000 deaths each day by July 1, Murray said. In a forecast released the day after Murray spoke, the IHME predicted that by August 1, there will be a total of 618,523 US deaths from COVID-19. Deaths could be as high as 696,651 if mobility among the vaccinated returns to pre-pandemic levels, the institute forecasts.

Based on cell phone data, Murray said, the amount of mobility in the United States has already risen to the level of March 2020, when the pandemic was just getting underway.

Decreased Infections

If there's one piece of good news in the latest IHME report, it's that the estimated number of people infected (including those not tested) will drop from 111,581 today to a projected 17,502 on August 1. But in a worst-case scenario, with sharply higher mobility among vaccinated people, the case count on that date would only fall to 73,842.

The SARS-CoV-2 variants are another factor of concern. Murray distinguished between variants like the one first identified in the UK (B.1.1.7) and other "escape variants."

B.1.1.7, which is now the dominant strain in the US, increases transmission but doesn't necessarily escape the immune system or vaccines, he explained.

In contrast, if someone is infected with a variant such as the South African or the Brazilian mutations, he said, a previous COVID-19 infection might not protect the person, and vaccines are less effective against those variants.

Cross-variant immunity may range from 0% to 60% for escape variants, based on the slim amount of data now available, Murray said. In his view, these variants will be the long-term driver of the pandemic in the US, while the UK variant is the short-term driver.

The latest data, he said, show that the Pfizer/BioNTech and Moderna vaccines are 75% effective against the escape variants, with lower efficacy for other vaccines. But booster shots may still be required to protect people against some variants.

Human Factors

Human behavior will also help determine the course of the pandemic, he noted. Vaccine hesitancy, for example, is still high in the US.

By the end of May, he predicted, about 180 million people will have received about two doses of vaccine. After that, he said, "vaccination will flatline due to lack of demand." The two unknowns are how much campaigns to promote vaccination will increase vaccine confidence, and when children will be vaccinated.

In the US, he said, 69% of adults have been vaccinated or want to get a shot. But that percentage has dropped 5 points since February, and vaccine confidence varies by state.

Murray emphasized that the winter surge he predicts can be blocked if people change their behaviors. These include a rise in vaccine confidence to 80% and continued mask wearing by most people.

However, if vaccine confidence and mask wearing decline, state governments continue to drop social distancing rules, and the uptake of boosters is low, the winter surge could be more serious, he said.

Double Surge

Murray also raised the possibility of a double surge of COVID-19 and influenza this winter. Widely expected last winter, this double surge never materialized here or elsewhere, partly because of mask wearing. But Murray said it could happen this year: History shows that the flu tends to be stronger in years after weak outbreaks.

He advised hospitals to prepare now for whatever might come later

this year. Public health authorities, he said, should speed up vaccination, monitor variants closely with additional sequencing, and try to modify behavior in high-risk groups.

Asked to explain the recent surge of COVID-19 cases in Michigan, Murray attributed it partly to the spread of the B.1.1.7 (UK) variant. But he noted that the UK variant has expanded even more widely in some other states that haven't had an explosive surge like Michigan's.

Moreover, he noted, Michigan doesn't have low mask use or high mobility. So the upward spiral of COVID-19 infections there is very concerning, he said.

In regard to the role of children as reservoirs of the virus, Murray pointed out that views on this have changed around the world. For a while, people thought kids didn't spread COVID-19 very much. That view shifted when UK data showed that child transmission of the B.1.1.7 variant increased by half to 9% of contacts in comparison with the original virus strain.

Dutch data, similarly, showed schools contributing to the latest outbreaks, and some European nations have closed schools. In the US, the trend is to open them.

https://bit.ly/3qgsKn6

The DNA of lettuce unraveled: 6000 years from weed to beloved vegetable

Descend from wild plants that were modified 6000 years ago in the Caucasus

Iceberg lettuce, oakleaf lettuce, romaine, and all other lettuces that we eat nowadays, descend from wild plants that were modified 6000 years ago in the Caucasus so that plant oil could be harvested from the seeds. After the ancient Greek and Romans further bred the plants to use them as leafy vegetables, lettuce also ended up on our plates over time. The special history of lettuce has been described in detail thanks to the DNA analysis of 445 types of lettuce, conducted by Wageningen University & Research and the Chinese BGI. Their research will be published today in the authoritative periodical *Nature Genetics* and opens the door to faster and more effective breeding of more resilient food crops.

Try to imagine a collection of 2500 different types of lettuce: approximately 1500 varieties that were ever grown by farmers somewhere in the world and roughly 1000 populations of wild lettuce plants from roadsides and nature reserves. Then try to imagine the DNA being collected from all these types of lettuce and used to determine how the lettuce on our plate came to be. The first wild plants were modified for cultivation 6000 years ago in the Caucasus. These first lettuces were only suitable for harvesting seeds to extract oil, and the ancient Greek and Romans further bred these plants (at that time, they still had thorns on the leaves) to be used as leafy vegetables. And the story told by the DNA continues, up to the Americans that needed properties from wild varieties to change soft, smooth butter lettuce into hard, puckered iceberg lettuce. We've learned all that information from the DNA in these lettuce types!

Slow Migration Through Europe

The Center for Genetic Resources, the Netherlands (CGN), which is the Dutch gene bank and part of Wageningen University & Research (WUR), manages this collection of 2500 lettuce types. This is the largest, most complete, and best documented lettuce collection in the world.

In collaboration with the Chinese BGI, the DNA order is being determined for all 2500 types, including an analysis of genetic variants and the differences and similarities between these variants. The results from the first 445 types of lettuce have led to a publication in *Nature Genetics* about the origins and breeding history of the crop.

It appears that a wealth of information became available. As it turns

out, the modern varieties of cultivated lettuces mostly resemble their wild predecessor Lactuca serriola from the Caucasus and the first cultivated lettuces must have been grown for seed and used for oil. The slow migration of lettuce throughout Europe via the Roman Empire, as well as the transition from seed crop to leaf crop, can also be reconstructed.

Iceberg Lettuce Versus "Ancient" Butterhead Lettuce

The study was also able to determine the point at which the more recent iceberg lettuce diverged from "ancient" butterhead lettuce in the genetic material of the wild Lactuca virosa, a fact that had long been suspected based on the genealogical data of these lettuce varieties.

Analysis of the relationship between the DNA information and traits of the cultivated lettuces shows that rigorous selection took place for traits that were desirable for production and consumption, the "domestication traits" like the absence of spines and thorns, which resulted in reduced diversity in the regions of the DNA where the genes for these traits are located. It also appears that determining the location of several genes in the DNA is possible by analysing the relationship between DNA variation and traits through so-called Genome Wide Association Studies (GWAS).

The Key to a Wealth of Genetic Material for Breeding

According to Rob van Treuren and Theo van Hintum, the two Wageningen co-authors of the publication, the research beautifully demonstrates how much information can be collected from DNA information in a genebank collection. It also shows how important the preservation and protection of biodiversity and genetic sources are for a sustainable food supply in times of climate change and a growing global population.

"Determining the DNA order of the material, in our collections and others, enables science to trace the traits hidden until now, in thousands of varieties and wild populations of lettuce and other crops. In doing so, we have obtained the key to an enormous treasure chest. For instance, imagine that research indicates that certain genes are important for resistance against drought or a certain disease. Then you would be able to search in the DNA data for genetic resources that have genes that look very similar and, using those resources, you could breed plants much quicker and more effective than what was previously possible. That is nothing short of revolutionary."

More information: *Tong Wei et al. Whole-genome resequencing of 445 Lactuca accessions reveals the domestication history of cultivated lettuce, Nature Genetics (2021). DOI: 10.1038/s41588-021-00831-0*

https://bit.ly/3tr6vyf

The chillest ape: How humans evolved a super-high cooling capacity

Penn Medicine discovery illuminates human sweat gland evolution

Philadelphia-- Humans have a uniquely high density of sweat glands embedded in their skin--10 times the density of chimpanzees and macaques. Now, researchers at Penn Medicine have discovered how this distinctive, hyper-cooling trait evolved in the human genome.

In a study published today in the *Proceedings of the National Academy of Sciences of the USA*, researchers showed that the higher density of sweat glands in humans is due, to a great extent, to accumulated changes in a regulatory region of DNA--called an enhancer region--that drives the expression of a sweat gland-building gene, explaining why humans are the sweatiest of the Great Apes.

"This is one of the clearest examples I've ever seen of pinpointing the genetic basis for one of the most extreme and distinctively human evolutionary traits as a whole," said the study's senior author, Yana Kamberov, PhD, an assistant professor of genetics at Penn

Medicine. "This kind of research is important not only because it shows how evolution actually works to produce species diversity but also because it gives us access into human biology that is often not possible to gain in other ways, essentially by learning from tweaking the biological system in a way that is actually beneficial, without breaking it."

Scientists broadly assume that humans' high density of sweat glands, also called eccrine glands, reflects an ancient evolutionary adaptation. This adaptation, coupled with the loss of fur in early hominins, which promoted cooling through sweat evaporation, is thought to have made it easier for them to run, hunt, and otherwise survive on the hot and relatively treeless African savannah, a markedly different habitat than the jungles occupied by other ape species.

Kamberov found in a 2015 study that the expression level of a gene called Engrailed 1--EN1 in humans--helps determine the density of eccrine glands in mice. EN1 encodes a transcription factor protein that, among many other functions, works during development to induce immature skin cells to form eccrine glands. Because of this property, Kamberov and colleagues hypothesized that perhaps one way in which humans could have built more sweat glands in their skin is to evolve genetic changes that increased the production of EN1 in the skin.

The activity of a gene is often affected by nearby regions of DNA called enhancer regions, where factors that activate the gene can bind and help drive the gene's expression.

In the study, Kamberov and her team identified an enhancer region called hECE18 that boosts the production of EN1 in skin, to induce the formation of more eccrine glands. The researchers showed that the human version of hECE18 is more active than that of ape or macaque versions, which would in turn drive higher levels of EN1 production.

Kamberov and her colleagues also teased apart the individual mutations that distinguish human hECE18, showing why some of them boost EN1 expression--and showing that rolling back those mutations to the chimp version of hECE18 brings the enhancer activity down to chimp levels.

Prior studies of evolved human-specific traits, such as language, generally have tied such traits to complex genetic changes involving multiple genes and regulatory regions.

In contrast, the work from Kamberov and her team suggest that the human "high-sweat" trait evolved at least in part through repeated mutations to just one regulatory region, hECE18. This means that this single regulatory element could have repeatedly contributed to a gradual evolution of higher eccrine gland density during human evolution.

While the study is mainly a feat of basic biology that shines a light on human evolution, it also should have some long-term medical relevance, Kamberov said.

"Severe wounds or burns often destroy sweat glands in skin, and so far we don't know how to regenerate them--but this study brings us closer to discovering how to do that," she said.

"The next step in this research would be to uncover how the multiple activity enhancing mutations in hECE18 interact with each other to increase EN1 expression and to use these biologically key mutations as starting points to figure out what DNA-binding factors actually bind at these sites. Basically, this provides us with a direct molecular inroad to discover the upstream factors that by activating EN1 expression get skin cells to start making sweat glands."

Support for the research was provided by the National Science Foundation (BCS-1847598) the National Institute of Arthritis and Musculoskeletal and Skin Diseases (R01AR077690), the McCabe Fund, the Penn Skin Biology and Disease Resource-based Center (P30AR069589), and the National Institute of Child Health and Human Development (F32HD101230).

https://bit.ly/3x3mrJt

We May Have Found a Cellular Difference That Protects Kids From COVID-19

Blood taken from children before the pandemic had a higher frequency of B cells that could bind to SARS-CoV-2 than adult blood did

Jacinta Bowler

The human immune system relies on an intricate army of T cells, B cells, macrophages and many more, all keeping us safe from invading pathogens. But that doesn't mean we all have the same set of protective gear in our blood.

B cells are responsible for 'remembering' what pathogens our bodies have previously encountered, so they can sound the alarm if they stumble upon these once more. Depending on which diseases you've already been exposed to and how the cell receptors - which hold this 'memory' - mutate and change, each person carries a different variation of immune cells.

A team of researchers has now looked into how these immune cells differ not just between individuals, but how they might change over a person's lifespan. Interestingly, they discovered that blood taken from children before the pandemic had a higher frequency of B cells that could bind to SARS-CoV-2 than adult blood did, even though they had never been exposed to this novel virus.

This research is still in the early stages, but it could go some way to explain why children seem to fare a lot better than adults when it comes to falling ill with COVID-19.

"Children usually have milder disease following SARS-CoV-2 infection than adults, potentially due to differences of viral receptor expression and immune responses," the team writes in their new paper. "Infected children, in contrast to adults, show lower antibody titers and more IgG specific for the spike protein."

A type of white blood cell, B cells hold the 'memory' of past pathogens in a wide range of receptors on their cell surface. These receptors allow B cells to bind to bits of potential pathogens they can recognize - called antigens - like a puzzle piece, launching an immune response against them.

These receptors are all built on the same backbone known as immunoglobulin sequences, but can be switched around or mutated to form a whole range of pathogen busting receptors before the bacteria or virus even enters the body.

"It is still unclear, however, how B cell memory to different antigens distributes in human tissues and changes during an individual's lifespan," the team notes.

This latter point is what the Stanford University researchers set to find out. They analyzed 114 blood samples from healthy human adults, 93 samples from 51 children between one and three years old, 12 umbilical cord blood samples, and blood, lymph nodes and spleen samples from 8 organ donors.

When the team looked at the B cell receptors and analyzed which antigens the cells can target, they found that children's B cells had more shared 'clones' for viruses and bacteria they'd already encountered than adults.

They also had more B cells that could 'switch' to become effective against SARS-CoV-2, without having been infected first.

The team thinks this could be because kids' immune systems are better at switching to a wide range of antigens after having been exposed to a different, less dangerous coronavirus than the one responsible for the current pandemic.

"We hypothesize that previous human coronavirus exposures may stimulate cross-reactive memory, and that such clonal responses may have their highest frequencies in childhood," the team writes.

"Childhood immune responses are particularly important in an individual's life, as they form the initial memory B cell pool that shapes future responses."

There's likely going to be a number of factors responsible for children having generally milder COVID-19 symptoms, so there's plenty more research to be done. Still, this is an interesting part of the conundrum and provides insight into the flexibility of B cells during our childhood, including setting us up for future immune responses.

The research has been published in *Science*.

https://wb.md/3gi0iRx

One in Six of the Papers You Cite in a Review Has Been Retracted. What Do You Do?

Recently became aware that 10 of the 63 references in her article were to papers by a researcher in third position on the retraction leaderboard

Retraction Watch Staff

The author of a 2014 review article about the role of vitamin D in Parkinson's disease has alerted readers to the fact that roughly one-sixth of her references have since been retracted. But she and the journal are not retracting the review itself.

The paper, "A review of vitamin D and Parkinson's disease," appeared in Elsevier's *Maturitas*, which is the official journal of the European Menopause and Andropause Society. The author is Amie Hiller, a neurologist at Oregon Health & Science University in Portland, and the work has been cited 26 times, according to Clarivate Analytics' Web of Science.

According to Hiller, she recently became aware that 10 of the 63 references in her article were to papers by Yoshihiro Sato, a bone researcher in Japan whose 103 retractions put him in the third position on the Retraction Watch leaderboard. Sato's misdeeds run from lack of IRB approval to fabrication of data, in articles dating back to the mid-1990s.

Hiller's letter on the subject, recently published in *Maturitas* but not linked from the original review, states that:

In light of the recent retraction of Yoshihiro Sato's publications due to findings of fraudulent data, I and the editors of Maturitas felt it appropriate to reassess the review I authored (then under the name Peterson) published in 2014 entitled 'A review of vitamin D and Parkinson's disease', in which Sato's publications played a prominent role.[1] Not all Sato's papers have been retracted at this time [nota bene : true, 103 is not all of them], but we feel it necessary to point out which assessments of the evidence contained in the review may have been affected had the publications from Sato not been included.

Out of 63 articles referenced in the paper, 10 were by Sato. The most affected areas of the review include section 3.2, Vitamin D levels are often low in persons with PD, where the review discussed the observation that vitamin D levels appear to be lower in persons with PD than in control populations. Most of the data for this claim were from three papers from Sato. These data were supported by two American studies and refuted by one Iranian study. If Sato's work had not been included in the review, this observation would have been considered more tenuous. Section 3.3, Vitamin D is related to bone health in PD, also referenced primarily studies by Sato. Two-thirds of the references in this section (10 of 15) were to work by Sato. The other references here do support a relationship between vitamin D and bone health in PD but, again, without Sato's work, there is much less evidence that this is the case. In section 3.6, Vitamin D appears to be related to the severity of PD symptoms, Sato's work played a less prominent role. Of the eight referenced papers, two were Sato's. With the inclusion of Sato's work, seven of eight referenced publications show a relationship between vitamin D levels and PD symptoms; with its exclusion, five of six showed this relationship.

Overall, the removal of all Sato's publications from this review calls into question our understanding that people with PD tend to have lower vitamin D levels and lower bone mineral density.

Hiller told us that the letter is "a notification/update" and that she has no plans to retract the paper, despite the unreliability of 16% of its references:

Both the editors and I felt it was reasonable to approach it this way. Rewriting the article with the time having passed would be a large endeavor in a field I have not kept up with.

Leon Flicker, the co-chief editor of the journal, told us:

In light of the Sato retractions we contacted the author of this review. This review is a narrative review and meta-analyses were not performed. We made the conservative assumption that none of Sato's papers were reliable. Some of these papers have not been formally retracted. The author carefully reviewed her paper and decided which of the many conclusions in the review may have been materially affected by the withdrawal of the Sato papers. We believe that this letter, that has been linked to the original review, updates our readers sufficiently to the current situation.

https://bit.ly/32qcvM8

Study finds that paid family leave does not hurt employers

Are businesses hurt when workers take time off with pay to care for a child or ailing family member?

by Krysten Crawford

With the battle over federal paid family leave heating up again, a new Stanford study has answers to a key question at the heart of the debate: Are businesses hurt when workers take time off with pay to care for a child or ailing family member?

The answer is no, according to research by Maya Rossin-Slater, an associate professor of medicine and a SIEPR faculty fellow. If anything, the policy makes it easier for employers to deal with lengthy employee absences, at least in the short-term. In a new working paper, Rossin-Slater and her co-authors find—among other insights—that a taxpayer-funded paid family leave policy implemented in 2018 in New York did not adversely affect employer's ratings of employee productivity, cooperation, or attendance. What's more, there was an improvement in employers' average rating of their ease of dealing with workers' absences, and the majority of employers support the policy.

Their analysis, released Monday by the National Bureau of Economic Research, is striking for both its timing and novelty.

President Joe Biden is expected to propose paid family leave as part of a revamp of what advocates call the nation's "care infrastructure." Polls have shown that a majority of Americans support paid family leave, and more than 200 businesses last month formally urged Congress to enact it. While several states have either passed or implemented paid family leave legislation, the United States is the only high-income country without a policy at the federal level.

[In addition to New York, states with paid family leave laws include California, Colorado, Connecticut, Massachusetts, New Jersey, Oregon, Rhode Island, Washington, and Washington, D.C.]

Rossin-Slater's research looks at the core argument against federal paid family leave: that it will hurt employers' bottom line, even if the money paid to workers comes from the government. Opponents also argue that employees will suffer as companies might avoid hiring anyone who they think might take the benefit, such as women of child-bearing age. But data on the impacts of paid family leave on employers are hard to come by, so nobody has known for sure if employers really do suffer and, if so, to what extent.

"The biggest roadblock so far to passing a paid family leave policy has been this open question about the indirect costs to employers," says Rossin-Slater, who is also a core faculty member at Stanford Health Policy. "While there are hundreds of studies showing benefits to workers and families, the evidence on employers has been very, very limited."

Her study—which she conducted with Columbia University's Ann Bartel, Meredith Slopen, and Jane Waldfogel, as well as Christopher Ruhm of the University of Virginia—is among the first to provide causal evidence of how paid family leave impacts

businesses. "We don't find any evidence of adverse effects on employers," Rossin-Slater says.

Direct evidence from employers

The history of family leave legislation in the United States dates to 1993, when the Family and Medical Leave Act (FMLA) was enacted to guarantee 12 weeks of unpaid job-protected leave for qualifying workers. Only larger business with 50 or more employees are covered by the FMLA, and take-up of the benefit has been low, especially among low-income workers who can't afford to take unpaid time off.

In 2004, California became the first state to pay workers on leave a portion of their salary through the state's employee-funded disability insurance program. Today, nine states and the District of Columbia offer some form of paid family leave. In 2019, the Trump administration extended the benefit to most federal employees. And when the COVID-19 pandemic hit, Congress passed a temporary provision for paid family leave.

Family leave policies have long been a focus of Rossin-Slater's research agenda. She has found that California's policy increases leave use among both mothers and fathers, and has studied implications of the FMLA for infant health. She detailed the impact of family leave laws in a 2018 SIEPR Policy Brief.

When New York passed a paid family leave law in 2016 that covered private sector workers and would be funded through a payroll tax, Rossin-Slater and her co-authors saw an opportunity. They set out to survey employers in the state with 99 or fewer workers over the two years before the law took effect in 2018 and in the two years following. For their control group, they surveyed comparable employers in Pennsylvania, which has never offered paid family leave. In all, nearly 4,600 firms participated in at least one of the four years.

In their survey, the researchers solicited data on potential indirect costs of the policy. They asked about the percentage of female and part-time employees, yearly turnover, and absenteeism rates. They also asked employers to rate five measures of employee performance, including productivity and attendance, and their ability to coordinate work schedules and employee absences of varying lengths.

For employees who took time off to care for family, the scholars tracked their gender and the precise reason for the leave of absence. They also measured the New York employers' views of the new law.

Benefits to employers

Their analysis yielded several key findings. They show, for example, that employer perceptions of their workers' performance—an indicator of profitability—did not change after the policy took effect. They also show that, in the law's first year, the businesses found it easier to manage leaves of absences of two weeks or longer. The improvement was driven by employers with 50-99 workers; the study found that employers with less than 50 employees did not initially see an increase in workers taking leave.

That began to change as the amount and duration of the benefit became more generous and employers had more time to look back on how their workers were using it. In the second year of the law, the researchers observed a large jump in leave-taking among the smaller businesses. Overall, employees in all the firms surveyed were 53.3 percent more likely to take leave, and this impact reflects increases in both women and men taking parental leaves, as well as men taking leaves to care for ill family members.

To Rossin-Slater, the increase in leave-taking among businesses with fewer than 50 employees was not surprising; companies of that size are exempt from the FMLA.

The study also shows that the law had no impact on the makeup of the employers' workforces. "We don't find evidence that firms are hiring or firing different types of workers due to the policy,"

Rossin-Slater says. Among other things, this suggests to Rossin-Slater that employers are not discriminating against workers most likely to take paid leave.

As for employer views of the policy, the researchers find that the majority of businesses were either very or somewhat supportive of paid family leave across all four years. However, opposition to the policy grew from 4.1 percent of employers to 9.5 percent over the same time period. Rossin-Slater says further research is needed to understand why objections rose. One possible explanation could be that small businesses are unhappy with the administrative burdens of complying.

Overall, Rossin-Slater says, the study suggests that paid family leave might help employers by—among other things—requiring them to develop standardized processes for managing longer worker absences. She says the findings are especially relevant today as COVID-19 has highlighted the need for standardized systems in the workplace when a larger-than-expected number of employees have to care for children or other family members.

"Our evidence," Rossin-Slater says, "is at least suggestive of the idea that having a family leave policy in place reduces the burden on employers, especially when dealing with unprecedented situations like a pandemic."

More information: *Ann Bartel et al. The Impact of Paid Family Leave on Employers: Evidence from New York, (2021). DOI: 10.3386/w28672*

https://bit.ly/2P3kBXU

Researchers map brain regions responsible for intoxicating effects of alcohol

Research could pave way for future treatments for alcohol use disorder

The slurred speech, poor coordination, and sedative effects of drinking too much alcohol may actually be caused by the breakdown of alcohol products produced in the brain, not in the liver as scientists currently think. That is the finding of a new study led by researchers from the University of Maryland School of Medicine (UMSOM) and the National Institute on Alcohol Abuse and Alcoholism. It was published recently in the journal *Nature Metabolism* and provides new insights into how alcohol may affect the brain and the potential for new treatments to treat alcohol misuse.

It is well known that the liver is the major organ that metabolizes alcohol, using the enzyme alcohol dehydrogenase to convert alcohol into a compound called acetaldehyde. Acetaldehyde, which has toxic effects, is quickly broken down into a more benign substance called acetate. This occurs through a different enzyme called acetaldehyde dehydrogenase 2 (ALDH2). Until now, alcohol and acetaldehyde, produced by the liver, have been considered important players in triggering the cognitive impairment associated with imbibing. Acetate, on the other hand, was considered relatively unimportant in producing effects like motor impairment, confusion, and slurred speech. Researchers also did not know which brain region or particular brain cells were most important for alcohol metabolism.

To learn more about the role played by the brain in alcohol metabolism, the researchers measured the distribution of ALDH2 enzyme in the cerebellum, using magnetic resonance (MR) scanners in both mice and in human tissue. They observed that ALDH2 was expressed in the cerebellum, in a type of nerve cell called an astrocyte, in both human brain tissue and in living mice.

The researchers found that this enzyme controlled the conversion of acetaldehyde into acetate in the brain. They also found alcohol-induced cellular and behavioral effects in specific regions of the brain where this enzyme was expressed. Acetate was found to interact with the brain messenger chemical called GABA, which is known to decrease activity in the nervous system. This decreased

activity can lead to drowsiness, impair coordination, and lower normal feelings of inhibition.

"We found ALDH2 was expressed in cells known as astrocytes in the cerebellum, a brain region that controls balance and motor coordination," said Qi Cao, PhD, Assistant Professor of Diagnostic Radiology and Nuclear Medicine at the University of Maryland School of Medicine. "We also found that when ALDH2 was removed from these cells, the mice were resistant to motor impairment inducted by alcohol consumption."

Su Xu, PhDHe and his team also found the enzyme ALDH2 in other brain regions responsible for emotional regulation and decision-making (both impaired by excess alcohol consumption), including in the hippocampus, amydala, and prefrontal cortex.

These findings suggest that certain brain regions are important for alcohol metabolism and that abnormalities in the enzyme production in these brain regions can lead to detrimental effects associated with alcohol misuse. They also suggest that acetate produced in the brain and in the liver differ in their ability to affect motor and cognitive function.

"Our next step is to determine whether these mechanisms observed in mice also exist in people," said Dr. Cao. "We would like to know whether alcohol metabolism is directly regulated in the human brain. If further research confirms this to be the case, it could lead to potential new targets for treating alcohol use disorder.

Su Xu, PhD, Professor of Diagnostic Radiology and Nuclear Medicine, was a co-author on this study.

E. Albert Reece, MD, PhD, MBA"This is an exciting basic research finding that elucidates important pathways involved in the body's metabolism of alcohol. It suggests that acetate serves as the important missing link connecting the body's metabolism of alcohol with cognitive changes in the brain," said E. Albert Reece, MD, PhD, MBA, Executive Vice President for Medical Affairs, UM Baltimore, and the John Z. and Akiko K. Bowers Distinguished Professor and Dean, University of Maryland School of Medicine.

"Replication of this research could eventually lead to new avenues for treatment of alcohol use disorder."

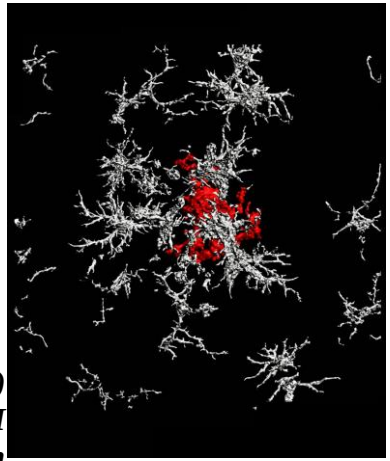
https://bit.ly/3qjZlbr

In surprising twist, some Alzheimer's plaques may be protective, not destructive

Salk scientists find brain's immune cells form some plaques as a defense in Alzheimer's, suggesting a new therapeutic direction

Salk Institute

La Jolla - One of the characteristic hallmarks of Alzheimer's disease (AD) is the buildup of amyloid-beta plaques in the brain. Most therapies designed to treat AD target these plaques, but they've largely failed in clinical trials. New research by Salk scientists upends conventional views of the origin of one prevalent type of plaque, indicating a reason why treatments have been unsuccessful.



A dense-core amyloid-beta plaque (red) surrounded by microglia that lack TAM receptors (white) in the brain of a mouse with Alzheimer's disease Credit: Salk Institute

The traditional view holds that the brain's trash-clearing immune cells, called microglia, inhibit the growth of plaques by "eating" them. The Salk scientists show instead that microglia promote the formation of dense-core plaques, and that this action sweeps wispy plaque material away from neurons, where it causes cell death. The research, which was published in *Nature Immunology* on April 15, 2021, suggests that dense-core plaques play a protective role, so treatments to destroy them may do more harm than good.

"We show that dense-core plaques don't form spontaneously. We believe they're built by microglia as a defense mechanism, so they may be best left alone," says Greg Lemke, a professor in Salk's Molecular Neurobiology Laboratory. "There are various efforts to

get the FDA to approve antibodies whose main clinical effect is reducing dense-core plaque formation, but we make the argument that breaking up the plaque may be doing more damage."

Alzheimer's disease is a neurological condition that results in memory loss, impairment of thinking, and behavioral changes, which worsen as we age. The disease seems to be caused by abnormal proteins aggregating between brain cells to form the hallmark plaques, which interrupt activity that keeps the cells alive.

There are numerous forms of plaque, but the two most prevalent are characterized as "diffuse" and "dense-core." Diffuse plaques are loosely organized, amorphous clouds. Dense-core plaques have a compact center surrounded by a halo. Scientists have generally believed that both types of plaque form spontaneously from excess production of a precursor molecule called amyloid precursor protein (APP).

But, according to the new study, it is actually microglia that form dense-core plaques from diffuse amyloid-beta fibrils, as part of their cellular cleanup.

This builds on a 2016 discovery by the Lemke lab, which determined that when a brain cell dies, a fatty molecule flips from the inside to the outside of the cell, signaling, "I'm dead, eat me." Microglia, via surface proteins called TAM receptors, then engulf, or "eat" the dead cell, with the help of an intermediary molecule called Gas6. Without TAM receptors and Gas6, microglia cannot connect to dead cells and consume them.

The team's current work shows that it's not only dead cells that exhibit the eat-me signal and Gas6: So do the amyloid plaques prevalent in Alzheimer's disease. Using animal models, the researchers were able to demonstrate experimentally for the first time that microglia with TAM receptors eat amyloid plaques via the eat-me signal and Gas6. In mice engineered to lack TAM receptors, the microglia were unable to perform this function.

Digging deeper, they traced the dense-core plaques using live imaging. Much to their surprise, the team discovered that after a microglial cell eats a diffuse plaque, it transfers the engulfed amyloid-beta to a highly acidic compartment and converts it into a highly compacted aggregate that is then transferred to a dense-core plaque. The researchers propose that this is a beneficial mechanism, organizing diffuse into dense-core plaque and clearing the intercellular environment of debris.

"Our research seems to show that when there are fewer dense-core plaques, there seem to be more detrimental effects," says Youtong Huang, first author on the paper. "With more-diffuse plaques, there's an abundance of dystrophic neurites, a proxy for neuronal damage. I don't think there's a distinct clinical decision on which form of plaque is more or less detrimental, but through our research, we seem to find that dense-core plaques are a bit more benign."

Their findings suggest new ways of developing a treatment for Alzheimer's disease, such as boosting expression of TAM receptors on microglia to accelerate dense-core plaque formation. The team would like to conduct cognitive studies to see if increasing the activity of microglial TAM receptors would alleviate the effects of AD.

Lemke, who holds the Françoise Gilot-Salk Chair, believes that the current failure rate of most Alzheimer's drug trials is about to end. "Some people are saying that the relative failure of trials that bust up dense-core plaques refutes the idea that amyloid-beta is a bad thing in the brain," says Lemke. "But we argue that amyloid-beta is still clearly a bad thing; it's just that you've got to ask whether dense-core plaques are a bad thing."

Lemke suggests that scientists looking for a cure for Alzheimer's should stop trying to focus on breaking up dense-core plaques and start looking at treatments that either reduce the production of amyloid-beta in the first place or therapies that facilitate transport

of amyloid-beta out of the brain altogether.

Other authors on the study are Kaisa E. Happonen, Patrick G. Burrola, Carolyn O'Connor, Nasun Hah, Ling Huang, and Axel Nimmerjahn of Salk.

The work was supported by grants from the US National Institutes of Health; the Cure Alzheimer's Fund; the Coins for Alzheimer's Research Trust; the Leona M. and Harry B. Helmsley Charitable Trust; UC San Diego Goeddel's Chancellor's, Marguerite Vogt, and the H.A. and Mary K. Chapman Charitable Trust graduate fellowships; and Anderson, NOMIS Foundation and Sweden-America Foundation postdoctoral fellowships.

https://bit.ly/3ty5LHN

Confirmed: Island gigantism and dwarfism result of evolutionary island rule

Island rule effects are widespread in mammals, birds and reptiles

It is an old-standing theory in evolutionary ecology: animal species on islands have the tendency to become either giants or dwarfs in comparison to mainland relatives. Since its formulation in the 1960s, however, the 'island rule' has been severely debated by scientists. In a new publication in *Nature Ecology and Evolution* on April 15, researchers solved this debate by analysing thousands of vertebrate species. They show that the island rule effects are widespread in mammals, birds and reptiles, but less evident in amphibians.

A juvenile Brookesia micra standing on a human finger tip Frank Glaw, Jörn Köhler, Ted M. Townsend, Miguel Vences, CC BY 2.5, via Wikimedia Commons

Dwarf hippos and elephants in the Mediterranean islands are examples of large species who exhibited dwarfism. On the other hand, small mainland species may have evolved into giants after colonizing islands, giving rise to such oddities as the St Kilda field mouse (twice the size of its mainland ancestor), the infamous dodo of Mauritius (a giant pigeon), and the Komodo dragon.

In 1973, Leigh van Valen was the first that formulated the theory, based on the study by mammologist J. Bristol Foster in 1964, that animal species follow an evolutionary pattern when it comes to their body sizes. Species on islands have the tendency to become either giants or dwarfs in comparison to mainland relatives. "Species are limited to the environment on an island. The level of threat from predatory animals is much lower or non-existent", says Ana Benítez-Lopez, who carried out the research at Radboud University, now researcher at Doñana Biological Station (EBD-CSIC, Spain). "But also limited resources are available." However, until now, many studies showed conflicting results which led to severe debate about this theory: is it really a pattern, or just an evolutionary coincidence?

Island rule confirmed

The team of scientists at Radboud University, Doñana Biological Station, National Museum of Natural Sciences and Imperial College London has revisited the island rule, aiming to solve this debate by performing a meta-analysis of over a thousand vertebrate species. They show that island rule effects are widespread in mammals, birds and reptiles, but less evident in amphibians, which mostly tend towards gigantism. The study also indicates that the magnitude of insular dwarfism and gigantism is more pronounced in smaller, more remote islands for mammals and reptiles.

Size is context-dependent

They also found an effect of climate and seasonality on the island rule. Small mammal and bird species grew larger and large species stayed the same size to conserve heat in colder, harsher insular environments. Furthermore, when seasons are present, availability of resources become less predictable for reptiles, leading smaller reptile species to become larger. Benítez-López: "Using a wealth of data from museum and live specimens, we were able to rigorously demonstrate for the first time that insular gigantism and dwarfism across vertebrates is a generalized pattern and not just an

evolutionary coincidence."

https://bit.ly/3x6s5um

How many T. rexes were there? Billions.

How many Tyrannosaurus rexes roamed North America during the Cretaceous period?

That's a question Charles Marshall pestered his paleontologist colleagues with for years until he finally teamed up with his students to find an answer.

What the team found, to be published this week in the journal *Science*, is that about 20,000 adult T. rexes probably lived at any one time, give or take a factor of 10, which is in the ballpark of what most of his colleagues guessed.

A cast of a T. rex skeleton on display outside the UC Museum of Paleontology at the University of California, Berkeley. The original, a nearly complete skeleton excavated in 1990 from the badlands of eastern Montana, is at the Museum of the Rockies in Bozeman, Montana. **Credit: Keegan Houser, UC Berkeley**

What few paleontologists had fully grasped, he said, including himself, is that this means that some 2.5 billion lived and died over the approximately 2 1/2 million years the dinosaur walked the earth. Until now, no one has been able to compute population numbers for long-extinct animals, and George Gaylord Simpson, one of the most influential paleontologists of the last century, felt that it couldn't be done.

Marshall, director of the University of California Museum of Paleontology, the Philip Sandford Boone Chair in Paleontology and a UC Berkeley professor of integrative biology and of earth and planetary science, was also surprised that such a calculation was possible.

"The project just started off as a lark, in a way," he said. "When I hold a fossil in my hand, I can't help wondering at the improbability that this very beast was alive millions of years ago, and here I am holding part of its skeleton—it seems so improbable. The question just kept popping into my head, 'Just how improbable is it? Is it one in a thousand, one in a million, one in a billion?' And then I began to realize that maybe we can actually estimate how many were alive, and thus, that I could answer that question."

Marshall is quick to point out that the uncertainties in the estimates are large. While the population of T. rexes was most likely 20,000 adults at any give time, the 95% confidence range—the population range within which there's a 95% chance that the real number lies—is from 1,300 to 328,000 individuals. Thus, the total number of individuals that existed over the lifetime of the species could have been anywhere from 140 million to 42 billion.

"As Simpson observed, it is very hard to make quantitative estimates with the fossil record," he said. "In our study, we focused in developing robust constraints on the variables we needed to make our calculations, rather than on focusing on making best estimates, per se."

He and his team then used Monte Carlo computer simulation to determine how the uncertainties in the data translated into uncertainties in the results.

The greatest uncertainty in these numbers, Marshall said, centers around questions about the exact nature of the dinosaur's ecology, including how warm-blooded T. rex was. The study relies on data published by John Damuth of UC Santa Barbara that relates body mass to population density for living animals, a relationship known as Damuth's Law. While the relationship is strong, he said, ecological differences result in large variations in population densities for animals with the same physiology and ecological niche. For example, jaguars and hyenas are about the same size, but

hyenas are found in their habitat at a density 50 times greater than the density of jaguars in their habitat.

"Our calculations depend on this relationship for living animals between their body mass and their population density, but the uncertainty in the relationship spans about two orders of magnitude," Marshall said. "Surprisingly, then, the uncertainty in our estimates is dominated by this ecological variability and not from the uncertainty in the paleontological data we used."

As part of the calculations, Marshall chose to treat T. rex as a predator with energy requirements halfway between those of a lion and a Komodo dragon, the largest lizard on Earth.

The issue of T. rex's place in the ecosystem led Marshall and his team to ignore juvenile T. rexes, which are underrepresented in the fossil record and may, in fact, have lived apart from adults and pursued different prey. As T. rex crossed into maturity, its jaws became stronger by an order of magnitude, enabling it to crush bone. This suggests that juveniles and adults ate different prey and were almost like different predator species.

This possibility is supported by a recent study, led by evolutionary biologist Felicia Smith of the University of New Mexico, which hypothesized that the absence of medium-size predators alongside the massive predatory T. rex during the late Cretaceous was because juvenile T. rex filled that ecological niche.

What the fossils tell us

The UC Berkeley scientists mined the scientific literature and the expertise of colleagues for data they used to estimate that the likely age at sexual maturity of a T. rex was 15.5 years; its maximum lifespan was probably into its late 20s; and its average body mass as an adult—its so-called ecological body mass,—was about 5,200 kilograms, or 5.2 tons. They also used data on how quickly T. rexes grew over their life span: They had a growth spurt around sexual maturity and could grow to weigh about 7,000 kilograms, or 7 tons.

From these estimates, they also calculated that each generation lasted about 19 years, and that the average population density was about one dinosaur for every 100 square kilometers.

Then, estimating that the total geographic range of T. rex was about 2.3 million square kilometers, and that the species survived for roughly 2 1/2 million years, they calculated a standing population size of 20,000. Over a total of about 127,000 generations that the species lived, that translates to about 2.5 billion individuals overall.

With such a large number of post-juvenile dinosaurs over the history of the species, not to mention the juveniles that were presumably more numerous, where did all those bones go? What proportion of these individuals have been discovered by paleontologists? To date, fewer than 100 T. rex individuals have been found, many represented by a single fossilized bone.

"There are about 32 relatively well-preserved, post-juvenile T. rexes in public museums today," he said. "Of all the post-juvenile adults that ever lived, this means we have about one in 80 million of them."

"If we restrict our analysis of the fossil recovery rate to where T. rex fossils are most common, a portion of the famous Hell Creek Formation in Montana, we estimate we have recovered about one in 16,000 of the T. rexes that lived in that region over that time interval that the rocks were deposited," he added. "We were surprised by this number; this fossil record has a much higher representation of the living than I first guessed. It could be as good as one in a 1,000, if hardly any lived there, or it could be as low as one in a quarter million, given the uncertainties in the estimated population densities of the beast."

Marshall expects his colleagues will quibble with many, if not most, of the numbers, but he believes that his calculational framework for estimating extinct populations will stand and be useful for estimating populations of other fossilized creatures.

"In some ways, this has been a paleontological exercise in how much we can know, and how we go about knowing it," he said. "It's surprising how much we actually know about these dinosaurs and, from that, how much more we can compute. Our knowledge of T. rex has expanded so greatly in the past few decades thanks to more fossils, more ways of analyzing them and better ways of integrating information over the multiple fossils known."

The framework, which the researchers have made available as computer code, also lays the foundation for estimating how many species paleontologists might have missed when excavating for fossils, he said.

"With these numbers, we can start to estimate how many short-lived, geographically specialized species we might be missing in the fossil record," he said. "This may be a way of beginning to quantify what we don't know."

More information: *C.R. Marshall el al., "Absolute abundance and preservation rate of Tyrannosaurus rex," Science (2021).* *science.sciencemag.org/cgi/doi ... 1126/science.abc8300*

https://bit.ly/3snR74s

99.992% of fully vaccinated people have dodged COVID, CDC data shows

No vaccine is 100% effective. But the COVID vaccines seem pretty darn good.

Beth Mole - 4/16/2021, 6:46 AM

Cases of COVID-19 are extremely rare among people who are fully vaccinated, according to a new data analysis by the Centers for Disease Control and Prevention.

Among more than 75 million fully vaccinated people in the US, just around 5,800 people reported a “breakthrough” infection, in which they became infected with the pandemic coronavirus despite being fully vaccinated.

The numbers suggest that breakthroughs occur at the teeny rate of less than 0.008 percent of fully vaccinated people—and that over 99.992 percent of those vaccinated have not contracted a SARS-CoV-2 infection.

The figures come from a nationwide database that the CDC set up to keep track of breakthrough infections and monitor for any concerning signs that the breakthroughs may be clustering by patient demographics, geographic location, time since vaccination, vaccine type, or vaccine lot number. The agency will also be keeping a close eye on any breakthrough infections that are caused by SARS-CoV-2 variants, some of which have been shown to knock back vaccine efficacy.

So far, the vaccines appear to be highly effective and working as expected, according to the CDC’s analysis—which the agency provided to Ars via email.

The vast majority of people in the US have been vaccinated with one of the mRNA vaccines, made by Moderna and Pfizer-BioNTech, which both had around 95 percent efficacy in Phase III clinical trials. Less than five percent of vaccinated people in the US have received the Johnson & Johnson adenovirus-based vaccine, which had a slightly lower efficacy of 72 percent in the US.

The extraordinary calculation that 99.992 percent of vaccinated people have not contracted the virus may reflect that they all simply have not been exposed to the virus since being vaccinated. Also, there are likely cases missed in reporting. Still, the data is a heartening sign.

“COVID-19 vaccines are effective and are a critical tool to bring the pandemic under control,” the agency said in its email. “To date, no unexpected patterns have been identified in case demographics or vaccine characteristics.”

Keep masking up for now

Many of the breakthroughs occurred in older people, who are well-known to be more vulnerable to COVID-19. More than 40 percent

were in people ages 60 and above. However, the agency noted that there were breakthrough infections scattered through every age group that is currently eligible for vaccination.

"We see [breakthroughs] with all vaccines," top infectious disease expert Anthony Fauci said in a press briefing earlier this week. "No vaccine is 100 percent efficacious or effective, which means that you will always see breakthrough infections regardless of the efficacy of your vaccine."

Vaccines can fail in some people because of a variety of factors, including immune status, health status, age, and medications they're on. There's also the possibility that something went wrong with the vaccines themselves, such as improper storage, delivery, or composition, Fauci explained.

"However," Fauci added, "even if a vaccine fails to protect against infection, it often protects against serious disease." He highlighted the case of the 2019-2020 flu vaccine, which was only about 39 percent effective.

Despite this, and the fact that only about 52 percent of people got their immunization, the vaccine was estimated to have prevented 105,000 flu hospitalizations and 6,300 flu deaths.

In the CDC's data on breakthrough COVID-19 infections, the agency found that 29 percent of the infections were asymptomatic. Only seven percent of the 5,800 breakthrough cases resulted in hospitalization and there were only 74 deaths. That suggests the death rate among breakthrough cases is around one percent and, among all fully vaccinated people, around 0.0001 percent.

Though the risk is small, there is still risk. The CDC emphasized that everyone should get vaccinated when its their turn and, once vaccinated, should continue following health precautions for now, such as "wearing a mask, staying at least 6 feet apart from others, avoiding crowds and poorly ventilated spaces, and washing their hands often."

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A rich marine algal ecosystem 600 million years earlier than previously thought

Biomarker evidence from fossilised algae remains

The first photosynthetic oxygen-producing organisms on Earth were cyanobacteria. Their evolution dramatically changed the Earth allowing oxygen to accumulate into the atmosphere for the first time and further allowing the evolution of oxygen-utilizing organisms including eukaryotes. Eukaryotes include animals, but also algae, a broad group of photosynthetic oxygen-producing organisms that now dominate photosynthesis in the modern oceans. When, however, did algae begin to occupy marine ecosystems and compete with cyanobacteria as important phototrophic organisms?

In a new study Zhang et al use the molecular remains of ancient algae (so-called biomarkers) to show that algae occupied an important role in marine ecosystems 1400 million years ago, some 600 million years earlier than previously recognized.

The specific biomarkers explored by Zhang et al are a group of sterane molecules derived from sterols that are prominent components of cell membranes in eukaryotic organisms. A particular difficulty in analyzing for ancient steranes is that samples are easily contaminated with steranes from other sources. The sources of contamination range from steranes introduced during the sampling, transport and processing of the samples, to geological contamination of steranes as fluids have flow through the rocks.

Zhang et al carefully controlled for each of the sources of contamination and found, as have others, that no steranes were liberated when using standard protocols to extract biomarkers from such ancient rocks, in this case the 1400 million-year-old Xiamaling Formation in North China.

However, Shuichang Zhang, the lead author of the study speculated that "There is some fossil evidence for eukaryotic algae 1400

million years ago, or even earlier, so we wondered whether any steranes in these rocks might be more tightly bound to the kerogens and not easily released during standard biomarker extraction". Therefore, Zhang et al utilized a stepwise heating protocol where samples were slowly heated in gold tubes in 9 steps from 300°C to 490°C. The organic molecules liberated in each of the nine steps were extracted and steranes indicating the presence of both red and green algae were liberated, especially at the higher temperatures.

Zhang continues "Many will be concerned that the steranes we found were a product of some kind of contamination. We were also worried about this, but we ran in parallel samples that have been heated to high temperatures during their geologic history and that, therefore, contained no biomarkers. We found no steranes in these. This means that our protocols were clean, and we are therefore confident that the steranes we found were indigenous to the rock".

It's still not completely clear why the steranes were so tightly bound to the kerogen and not released during standard protocols. But, the findings of Zhang et al. show that both green and red algal groups were present in marine ecosystems by 1400 million years ago. This is 600 million years earlier than evident from previous biomarker studies. This work shows that the red and green algal lineages had certainly evolved by 1400 million years ago, and this should be a useful constraint in timing the overall history of eukaryote evolution. This work also shows that at least some ancient marine ecosystems functioned more similarly to modern ecosystems than previously thought, at least with respect to the types of photosynthetic organisms producing organic matter. This means furthermore that there was sufficient nutrients and oxygen available to drive the presence of algae-containing ecosystems.

Professor Don Canfield, Nordic Center for Earth Evolution, University of Southern Denmark, a co-author on the study adds: "We hope that our study will inspire others to utilize similar techniques to better unravel the full history of eukaryote evolution through geologic time".

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Pharma, US Government Plan for COVID-19 Booster Shots

It's unclear how long protections against infection will last from the initial vaccinations, and health authorities say additional jabs will likely be necessary.

Jef Akst

To stay protected against COVID-19, people may need booster shots within 12 months of receiving their initial vaccinations, David Kessler, the chief science officer for President Joe Biden's COVID-19 response task force, said at a congressional committee meeting on Thursday (April 15), Reuters reports. Pfizer CEO Albert Bourla agrees with that timeline, according to comments he made to *CNBC* earlier this month.

So far, the evidence suggests that Pfizer/BioNTech's and Moderna's COVID-19 vaccines will protect against SARS-CoV-2 infection for at least six months. Beyond that, the data simply aren't available yet.

"Unfortunately, many people have misunderstood that to mean that it lasts only six months, [when] all that information means is that we know that it lasts six months, and we expect it to last longer," allergist and clinical immunologist Susan Bailey, the president of the American Medical Association, tells *National Geographic*.

Pfizer and BioNTech are now testing the efficacy of adding a third dose to their two-shot regimen, and Moderna announced this week that it was also working on a booster, which it hopes to have ready by the fall, according to *CNBC*. Meanwhile, Johnson & Johnson is testing the effects of adding a second jab to its one-and-done protocol. All of these companies are also working to develop updated formulations to target emerging SARS-CoV-2 variants.

"It's highly likely" that booster shots or new vaccines will be "required in the future," the University of Maryland School of Medicine's Matthew Frieman, who is involved in the development of Novavax's COVID-19 vaccine candidate, tells *National Geographic*. "How frequently we need them—and if they're needed worldwide or in specific populations—is what we don't know."

https://bit.ly/32toCbe

Scientists Develop New Blood Test That Could Diagnose Your Level of Depression

A newly developed system that monitors for blood biomarkers linked to mood disorders could lead to new ways to diagnose and treat depression and bipolar disorder, all beginning with a simple blood test.

Peter Dockrill

While depression has been recognized for centuries and affects hundreds of millions of people worldwide, the traditional diagnosis still depends on clinical assessments by doctors, psychologists, and psychiatrists.

Blood tests might inform such health assessments, to check whether symptoms of depression might be related to other factors, but they're not used in clinical practice to objectively and independently diagnose the condition itself. The new research suggests this could be a practical option in the future.

In the new study, researchers have identified 26 biomarkers – measurable and naturally occurring indicators – in patients' blood variably linked to the incidence of mood disorders including depression, bipolar disorder, and mania.

"Blood biomarkers are emerging as important tools in disorders where subjective self-report by an individual, or a clinical impression of a health care professional, are not always reliable," says psychiatrist and neuroscientist Alexander B. Niculescu from Indiana University. "These blood tests can open the door to precise, personalized matching with medications, and objective monitoring of response to treatment."

Niculescu has explored this territory for several years, developing similar blood biomarker-based tests to help predict suicidality in patients, diagnose severe pain, and gauge levels of PTSD.

In the new study, conducted over the course of four years, the researchers worked with hundreds of patients at the Richard L. Roudebush VA Medical Center in Indianapolis, conducting a series of tests to identify and confirm gene expression biomarkers in blood that might be tied to mood disorders.

In visits with patients with depression who agreed to take part, their mood (ranging from low to high) was tracked in each session, with samples of their blood taken at the time.

Comparing the samples against a massive database comprised of information gleaned from 1,600 studies on human genetics, gene expression, and protein expression, the team identified a series of biomarkers linked to mood disorders, shortening the list to 26 biomarker candidates after validating their results in a second cohort of patients.

In a final test, the researchers investigated another group of psychiatric patients to see whether the 26 identified biomarkers could determine mood, depression, and mania in the participants and also predict outcomes such as future hospitalizations.

After all these steps were taken, the researchers say 12 of the biomarkers provide particularly strong links to depression, with six of the same tied to bipolar disorder, and two biomarkers that can indicate mania.

"Not all changes in expression in peripheral cells are reflective of or germane to brain activity," the researchers write in their paper.

"By carefully tracking a phenotype with our within-subject design in the discovery step, and then using [convergent functional genomics] prioritization, we are able to extract the peripheral

changes that do track and are relevant to the brain activity studied, in this case mood state, and its disorders."

According to the researchers, their precision medicine approach doesn't just identify propensity for depression and other mood disorders in patients but can help bioinformatically highlight specific drugs that might best treat their conditions.

In this study, the results suggested a range of existing non-antidepressant medicines – including pindolol, ciprofibrate, pioglitazone, and adiphenine – might function if used as antidepressants, while the natural compounds asiaticoside and chlorogenic acid could also warrant further consideration.

Of the top biomarker genes linked to mood disorders, the team says eight are involved with circadian functioning, which could help provide a molecular underpinning to explain the ties between conditions like depression and factors such as sleep disorders.

"That explains why some patients get worse with seasonal changes, and the sleep alterations that occur in mood disorders," Niculescu says.

While the blood test as described is a scientific proof of concept for now – meaning there's no telling when a test like this will become available more broadly – the researchers hope their results will convince the psychiatry community that precision medicine has a place in depression diagnostics and treatment.

Ultimately, existing doctor-assessed methods of diagnosing depression and other mood disorders are insufficient, they suggest, lagging behind the kinds of objective testing systems that are commonplace across other medical specialties.

"This is part of our effort to bring psychiatry from the 19th century into the 21st century, to help it become like other contemporary fields such as oncology," Niculescu says.

"Ultimately, the mission is to save and improve lives."

The findings are reported in *Molecular Psychiatry*.