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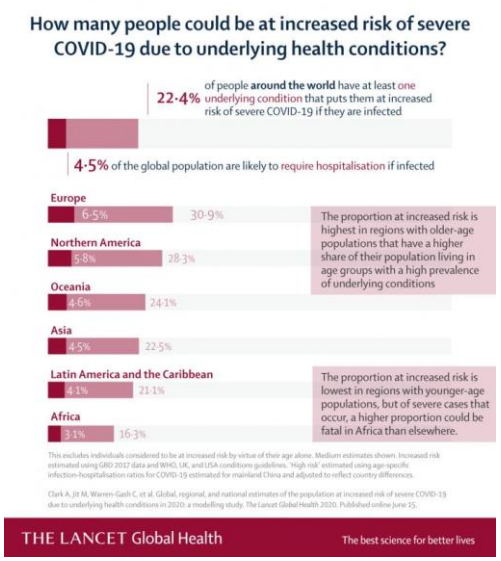
Estimates suggest one in five people worldwide have an underlying health condition that could increase their risk of severe COVID-19 if infected

How many people could be at increased risk of severe COVID-19 due to underlying health conditions?

An estimated 1.7 billion people, 22% of the world population, have at least one underlying health condition that could increase their risk of severe COVID-19 if infected, according to a modelling study that uses data from 188 countries, published in *The Lancet Global Health* journal.

"As countries move out of lockdown, governments are looking for ways to protect the most vulnerable from a virus that is still circulating. We hope our estimates will provide useful starting points for designing measures to protect those at increased risk of severe disease. This might involve advising people with underlying conditions to adopt social distancing measures appropriate to their level of risk, or prioritising them for vaccination in the future," says Associate Professor Andrew Clark from the London School of Hygiene & Tropical Medicine (LSHTM), UK. [2]



Although the estimates provide an idea of the number of people governments should prioritise for protective measures, not all individuals with these conditions would go on to develop severe symptoms if infected. The authors estimate that 4% of the world's population (349 million of 7.8 billion people) would require hospitalisation if infected, suggesting that the increased risk of severe COVID-19 could be quite modest for many with underlying conditions.

Guidelines published by the WHO and by public health agencies in the UK and USA identify risk factors for severe COVID-19, including cardiovascular disease, chronic kidney disease, diabetes and chronic respiratory disease. The new study provides global, regional and national estimates for the number of people with underlying health conditions. The authors caution that they focused on underlying chronic conditions and didn't include other possible risk factors for COVID-19 that are not yet included in all guidelines, such as ethnicity and socioeconomic deprivation. Their estimates are therefore unlikely to be exhaustive, but serve as a starting point for policy-makers.

The authors based their estimates on disease prevalence data from the Global Burden of Diseases, Injuries and Risk Factors Study (GBD) 2017, UN population estimates for 2020 and the list of underlying health conditions relevant to COVID-19, as defined by current guidelines. The authors point out that the GBD prevalence estimates are likely to be higher than those from national databases, because they're designed to capture cases that might be undiagnosed or not severe enough to be included in electronic health records. They analysed the number of people with an underlying condition by age group, sex and country for 188 countries.

To help determine the degree of increased risk, the researchers also provided separate estimates of the proportion of all people (with and without underlying conditions) who would require hospitalisation if infected. The authors calculated those at high risk using infection hospitalisation ratios for COVID-19 [3] and made adjustments for differences between countries.

Countries and regions with younger populations have fewer people with at least one underlying health condition, while those with older populations have more people with at least one condition. For example, the proportion of the population with one or more health condition ranges from 16% in Africa (283 million people out of 1.3 billion) to 31% in Europe (231 million out of 747 million).

However, Associate Professor Clark cautions that the evidence needs to be carefully communicated to avoid complacency about risk in Africa: "The share of the population at increased risk of severe COVID-19 is generally lower in Africa than elsewhere due to much younger country populations, but a much higher proportion of severe cases could be fatal in Africa than elsewhere." [2]

Small island nations with high diabetes prevalence, such as Fiji and Mauritius, have among the highest proportion of people with an underlying condition. In Africa, countries with the highest HIV/AIDS prevalence, such as eSwatini and Lesotho, have a greater proportion of people with an underlying condition than countries with lower prevalence, such as Niger.

Globally, less than 5% of people aged under 20 years, but more than 66% of those aged 70 and above, have at least one underlying condition that could increase their risk of severe COVID-19. Among the working age population (15 to 64 years), 23% are estimated to have at least one underlying condition. The prevalence of one or more condition listed on current guidelines is similar between the sexes, but the authors assumed males were twice as likely as females to require hospitalisation if infected.

The authors estimate that 349 million people worldwide are at high risk of severe COVID-19, meaning they would require hospital treatment if infected. This risk varies from less than 1% of people under 20 to nearly 20% of those aged 70 or older, rising to more than 25% in males over 70. In all age groups under 65, around twice the number of men as women would require hospitalisation. Above 65 years, the ratio becomes less marked because women are over-represented in older age groups due to longer life expectancy.

"Our estimates suggest that age-based thresholds for shielding could play a role in reducing deaths and reducing the number of people who require hospital treatment, but the choice of threshold needs to be balanced against the proportion of people of working age affected, as well as the health and economic consequences that might be associated with long periods of isolation," says Dr Rosalind Eggo from LSHTM. [21]

Writing in a linked Comment, lead author Professor Nina Schwalbe, MPH, (who was not involved in the study) from Columbia University Mailman School of Public Health, USA, says: "An increased understanding of risk factors, including the effects of social determinants and their interplay, provides an opportunity to target mitigation strategies and helps to allay the popular misconception that everyone is at equal risk of severe illness. As the authors note, it is time to evolve from a one-size-fits-all approach to one that centres on those most at risk. This will need to happen at both the individual and community level. Considering the relevance of social determinants, such an approach requires urgently improving communication about COVID-19; increasing access to health services, including palliative care, for those already socially vulnerable; and providing economic support to cope with the mitigation."

NOTES TO EDITORS

This study was funded by the UK's Department for International Development (DFID) and the Wellcome Trust. It was conducted by researchers from the London School of Hygiene & Tropical Medicine, the University of Edinburgh, Sun Yat-Sen University, the University of Washington, Imperial College London and the University College London.

The labels have been added to this press release as part of a project run by the Academy of Medical Sciences seeking to improve the communication of evidence. For more information, please see: http://www.sciencemediacentre.org/wp-content/uploads/2018/01/AMS-press-release-labelling-system-GUIDANCE.pdf if you have any questions or feedback, please contact The Lancet press office pressoffice@lancet.com

[1] *For example, self-isolating, avoiding workplaces and using home-delivered food and medical care*

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

[3] *https://doi.org/10.1016/S1473-3099(20)30243-7*

Peer-reviewed / Modelling study / People

Country-level data and infographic available below - with interactive embeddable map available on request

https://bit.ly/3hC2W2O

Diluting blood plasma rejuvenates tissue, reverses aging in mice

New study suggests that plasma exchange could be the key to unlocking the body's regenerative capacities

Berkeley -- In 2005, University of California, Berkeley, researchers made the surprising discovery that making conjoined twins out of young and old mice -- such that they share blood and organs -- can rejuvenate tissues and reverse the signs of aging in the old mice. The finding sparked a flurry of research into whether a youngster's blood might contain special proteins or molecules that could serve as a "fountain of youth" for mice and humans alike.

But a new study by the same team shows that similar age-reversing effects can be achieved by simply diluting the blood plasma of old mice -- no young blood needed.

In the study, the team found that replacing half of the blood plasma of old mice with a mixture of saline and albumin -- where the albumin simply replaces protein that was lost when the original blood plasma was removed -- has the same or stronger rejuvenation effects on the brain, liver and muscle than pairing with young mice or young blood exchange. Performing the same procedure on young mice had no detrimental effects on their health.

This discovery shifts the dominant model of rejuvenation away from young blood and toward the benefits of removing age-elevated, and potentially harmful, factors in old blood.

"There are two main interpretations of our original experiments: The first is that, in the mouse joining experiments, rejuvenation was due to young blood and young proteins or factors that become diminished with aging, but an equally possible alternative is that, with age, you have an elevation of certain proteins in the blood that become detrimental, and these were removed or neutralized by the young partners," said Irina Conboy, a professor of bioengineering at UC Berkeley who is the first author of the 2005 mouse-joining paper and senior author of the new study. "As our science shows, the second interpretation turns out to be correct. Young blood or factors are not needed for the rejuvenating effect; dilution of old blood is sufficient."

In humans, the composition of blood plasma can be altered in a clinical procedure called therapeutic plasma exchange, or plasmapheresis, which is currently FDA-approved in the U.S. for treating a variety of autoimmune diseases. The research team is currently finalizing clinical trials to determine if a modified plasma exchange in humans could be used to improve the overall health of older people and to treat age-associated diseases that include muscle wasting, neuro-degeneration, Type 2 diabetes and immune deregulation.

"I think it will take some time for people to really give up the idea that that young plasma contains rejuvenation molecules, or silver bullets, for aging," said Dobri Kiprov, a medical director of Apheresis Care Group and a co-author of the paper. "I hope our results open the door for further research into using plasma exchange -- not just for aging, but also for immunomodulation."

The study appears online in the journal *Aging*.

A molecular 'reset' button

In the early 2000s, Conboy and her husband and research partner Michael Conboy, a senior researcher and lecturer in the Department of Bioengineering at UC Berkeley and co-author of the new study,

had a hunch that our body's ability to regenerate damaged tissue remains with us into old age in the form of stem cells, but that somehow these cells get turned off through changes in our biochemistry as we age.

"We had the idea that aging might be really more dynamic than people think," Conboy said. "We thought that it could be caused by transient and very reversible declines in regeneration, such that, even if somebody is very old, the capacity to build new tissues in organs could be restored to young levels by basically replacing the broken cells and tissues with healthy ones, and that this capacity is regulated through specific chemicals which change with age in ways that become counterproductive."

After the Conboys published their groundbreaking 2005 work, showing that making conjoined twins from the old mouse and a young mouse reversed many signs of aging in the older mouse, many researchers seized on the idea that specific proteins in young blood could be the key to unlocking the body's latent regeneration abilities.

However, in the original report, and in a more recent study, when blood was exchanged between young and old animals without physically joining them, young animals showed signs of aging. These results indicated that that young blood circulating through young veins could not compete with old blood.

As a result, the Conboys pursued the idea that a buildup of certain proteins with age is the main inhibitor of tissue maintenance and repair, and that diluting these proteins with blood exchange could also be the mechanism behind the original results. If true, this would suggest an alternative, safer path to successful clinical intervention: Instead of adding proteins from young blood, which could do harm to a patient, the dilution of age-elevated proteins could be therapeutic, while also allowing for the increase of young proteins by removing factors that could suppress them.

To test this hypothesis, the Conboys and their colleagues came up with the idea of performing "neutral" blood exchange. Instead of exchanging the blood of a mouse with that of a younger or an older animal, they would simply dilute the blood plasma by swapping out part of the animal's blood plasma with a solution containing plasma's most basic ingredients: saline and a protein called albumin. The albumin included in the solution simply replenished this abundant protein, which is needed for overall biophysical and biochemical blood health and was lost when half the plasma was removed.

"We thought, 'What if we had some neutral age blood, some blood that was not young or not old?'" said Michael Conboy. "We'll do the exchange with that, and see if it still improves the old animal. That would mean that by diluting the bad stuff in the old blood, it made the animal better. And if the young animal got worse, then that would mean that that diluting the good stuff in the young animal made the young animal worse."

After finding that the neutral blood exchange significantly improved the health of old mice, the team conducted a proteomic analysis of the blood plasma of the animals to find out how the proteins in their blood changed following the procedure. The researchers performed a similar analysis on blood plasma from humans who had undergone therapeutic plasma exchange.

They found that the plasma exchange process acts almost like a molecular reset button, lowering the concentrations of a number of pro-inflammatory proteins that become elevated with age, while allowing more beneficial proteins, like those that promote vascularization, to rebound in large numbers.

"A few of these proteins are of particular interest, and in the future, we may look at them as additional therapeutic and drug candidates," Conboy said. "But I would warn against silver bullets. It is very unlikely that aging could be reversed by changes in any

one protein. In our experiment, we found that we can do one procedure that is relatively simple and FDA-approved, yet it simultaneously changed levels of numerous proteins in the right direction."

Therapeutic plasma exchange in humans lasts about two to three hours and comes with no or mild side effects, said Kiprov, who uses the procedure in his clinical practice. The research team is about to conduct clinical trials to better understand how therapeutic blood exchange might best be applied to treating human ailments of aging.

Co-authors of the paper include Melod Mehdipour, Colin Skinner, Nathan Wong, Michael Lieb, Chao Liu, Jessy Etienne and Cameron Kato of UC Berkeley.

This work was supported by the National Institutes of Health under grants R56 AG058819, R01 EB023776, R01 HL139605; by an Open Philanthropy Project award; and by the National Institutes of Health T32 and Cooke fellowships.

https://bit.ly/2V1hu2l

Tuberculosis spread from animals to humans may be greater than previously thought

Cases of TB transmitted from animals, as opposed to human-to-human transmitted, may be much higher than previously estimated

University Park, Pa. -- The number of human tuberculosis (TB) cases that are due to transmission from animals, as opposed to human-to-human transmission, may be much higher than previously estimated, according to an international team of researchers. The results could have implications for epidemiological studies and public health interventions.

"Tuberculosis kills 1.4 million people every year, making it the most deadly disease arising from a single infectious agent," said Vivek Kapur, professor of microbiology and infectious diseases and Huck Distinguished Chair in Global Health, Penn State. "India has the largest burden of human tuberculosis globally, with more than 2.6 million cases and 400,000 deaths reported in 2019. Additionally, the cattle population in India exceeds 300 million, and nearly 22 million of these were estimated to be infected with TB in 2017.

Kapur noted that the World Health Organization, World Organisation for Animal Health and Food and Agriculture Organization of the United Nations define zoonotic TB as human infection with Mycobacterium bovis, a member of the Mycobacterium tuberculosis complex (MTBC).

To evaluate the use of M. bovis as a proxy for zoonotic tuberculosis and to investigate the potential role of other MTBC subspecies, Kapur and his colleagues analyzed 940 bacterial samples -- both pulmonary (from lung fluid or tissue) and extrapulmonary (from tissues other than the lungs) -- collected from patients who were visiting a large reference hospital for TB in southern India. The researchers used PCR to speciate M. tuberculosis complex organisms and then sequenced all the non-M. tuberculosis samples. Next, they compared the sequences to 715 sequences from cattle and humans that had previously been collected in south Asia and submitted to public databases.

"Surprisingly, we did not find any evidence for the presence of M. bovis in any of the samples," said Sreenidhi Srinivasan, postdoctoral scholar in the Huck Institutes of the Life Sciences. "Instead, we found that seven of the patient samples contained M. orygis. Six of these came from patients with extrapulmonary TB."

They describe their findings in a paper published June 1 in *The Lancet Microbe*.

As expected, most of the remainder of the sequences from the patients belonged to M. tuberculosis -- the TB bacterium that is generally thought to be transmitted only among humans.

"Our findings suggest that M. bovis might be uncommon in India, and that its detection may not be an adequate proxy for zoonotic TB infection in humans," said Srinivasan. "These data indicate that

members of the TB complex other than M. bovis might be more prevalent in livestock in India."

Kapur added that the operational definition of zoonotic TB should be broadened to include other MTBC subspecies capable of causing human disease. "By 2035, the World Health Organization is aiming to reduce the incidence of tuberculosis by 90% as a part of its End TB Strategy," he said.

"The increasing evidence supporting M. orygis endemicity in south Asia and the identification of M. tuberculosis in cattle highlight the importance of using a One Health approach, involving multisectoral collaboration across the veterinary and clinical sectors, to meet the WHO's goal in India."

The Bill & Melinda Gates Foundation and the Canadian Institutes for Health Research supported this research.

Other authors on the paper include Shannon Duffy, Sarah Danchuk, and Marcel Behr, McGill University; Megan Schilling, Robab Katani, and Shubhada Chothe, Penn State; Tod Stuber and Suelee Robbe-Austerman, USDA APHIS; Joy Michael and Manigandan Venkatesan, Christian Medical College Vellore; Nitish Bansal, Naresh Jindal, Deepika Chaudhary, and Sushila Maan, Lala Lajpat Rai University of Veterinary and Animal Sciences; Premanshu Dandapat, Indian Council of Agricultural Research; Maroudam Veerasami, Cisgen Biotech Discoveries; and Nicholas Juleff, Bill & Melinda Gates Foundation.

https://bit.ly/2YT7SHU

Astronomers Say There Could Be 36 Communicating Extraterrestrial Civilizations in Milky Way

The nearest is 17,000 light-years away and most likely hosted by a red dwarf star

Using the assumption that intelligent life develops on exoplanets in a similar way as it does on Earth, a duo of researchers from the School of Physics and Astronomy at the University of Nottingham has obtained an estimate for the number of communicating extraterrestrial intelligent (CETI) civilizations within our Milky Way Galaxy. They calculate that there could be 36 active CETI civilizations in the Galaxy; the nearest is 17,000 light-years away and most likely hosted by a red dwarf star, likely far surpassing our ability to detect it for the foreseeable future, and making interstellar communication impossible.

“There should be at least a few dozen active CETI civilizations in our Galaxy under the assumption that it takes 5 billion years for intelligent life to form on other planets, as on Earth,” said Professor Christopher Conselice, senior author of the study.

“The idea is looking at evolution, but on a cosmic scale. We call this calculation the Astrobiological Copernican Limit.”

“The classic method for estimating the number of intelligent civilizations relies on making guesses of values relating to life, whereby opinions about such matters vary quite substantially,” added Dr. Tom Westby, first author of the study. “Our new study simplifies these assumptions using new data, giving us a solid estimate of the number of civilizations in our Galaxy.”

The two Astrobiological Copernican limits are that intelligent life forms in less than 5 billion years, or after about 5 billion years — similar to on Earth where a communicating civilization formed after 4.5 billion years.

In the strong criteria, whereby a metal content equal to that of the Sun is needed, the authors calculate that there should be around 36 active CETI civilizations in the Milky Way. They show that the number of civilizations depends strongly on how long they are actively sending out signals of their existence into space, such as radio transmissions from satellites, television, etc.

If other technological civilizations last as long as ours which is currently 100 years old, then there will be about 36 ongoing intelligent technical civilizations throughout our Galaxy.

However, the average distance to these civilizations would be 17,000 light-years away, making detection and communication very difficult with our present technology. It is also possible that we are

the only civilization within our Galaxy unless the survival times of civilizations like our own are long.

“Our new research suggests that searches for extraterrestrial intelligent civilizations not only reveal the existence of how life forms, but also give us clues for how long our own civilization will last,” Professor Conselice said.

“If we find that intelligent life is common then this would reveal that our civilization could exist for much longer than a few hundred years, alternatively if we find that there are no active civilizations in our Galaxy it is a bad sign for our own long-term existence.”

“By searching for extraterrestrial intelligent life — even if we find nothing — we are discovering our own future and fate.”

The team’s paper was published in the *Astrophysical Journal*.

Tom Westby & Christopher J. Conselice. 2020. The Astrobiological Copernican Weak and Strong Limits for Intelligent Life. ApJ 896, 58; doi: 10.3847/1538-4357/ab8225

https://bit.ly/37KStOq

Directly printing 3D tissues within the body

Researchers take a step closer to 3D printing living tissues in patients

Los Angeles - In the TV series Westworld, human body parts are built on robotic frames using 3D printers. While still far from this scenario, 3D printers are being increasingly used in medicine.

Image of a 3D lattice structure of a tissue implanted directly onto a soft living tissue. **Ohio State University**

For example, 3D printing can be used to produce parts of the body such as orthopedic joints and prosthetics, as well as portions of bone, skin and blood vessels. However, the majority of these tissues are created in an apparatus outside of the body and surgically implanted. Such a procedure may involve making large surgical incisions, posing the added risk of infection and increased recovery time for the patient. And since there is a time lapse between when the tissue is created and when it is implanted in the patient, further complications may occur. To prevent these complications, a team of scientists have developed a technology to print tissues directly in the body.

There are two basic components needed to produce an engineered tissue: (1) a fluid-like "bio-ink" that consists of a framework material mixed with living cells, and (2) growth factors to help the cells grow and develop into regenerated tissue.

When developing tissues for direct implantation into the body, there are other things to consider: the construction of tissue would have to be conducted at body temperature (37°C), the tissue needs to be attached effectively to soft, live organ tissue and any procedural steps should not be harmful to the patient. One such harmful step in current methods is the application of harmful UV light necessary to solidify the constructed tissue.

A collaboration among Ali Khademhosseini, Ph.D., Director and CEO of the Terasaki Institute, David J Hoelzle, Ph.D., from the Ohio State University Department of Mechanical and Aerospace Engineering and Amir Sheikhi, Ph.D. from the Pennsylvania State University Department of Chemical Engineering, has produced a specially-formulated bio-ink designed for printing directly in the body.

"This bio-ink formulation is 3D printable at physiological temperature, and can be crosslinked safely using visible light inside the body." said first author Ali Asghari Adib, Ph.D. In order to build the tissue, they used robotic 3D printing, which uses robotic machinery affixed with a nozzle. Bio-ink may be dispensed through the nozzle, much like an icing tube squeezes out writing gel, only in a highly-precise, programmable manner.

The team also worked on methods to attach pieces of the tissue formed with this bio-ink onto soft surfaces. In experiments attempting to attach the tissue onto pieces of raw chicken strips and agarose, the team employed a unique interlock technique using the robotic 3D printer and their specially-formulated bio-ink. The nozzle tip was modified to be able to penetrate the soft surfaces and fill the punctured space with bio-ink as it withdrew; this created an anchor for the tissue construct. As the nozzle tip reached the surface, it dispensed an additional blob of bio-ink to "lock in" the anchor. "The interlocking mechanism enables stronger attachments of the scaffolds to the soft tissue substrate inside the patient body," said Asghari Adib.

Such improvements in tissue engineering are instrumental in providing lower-risk, minimally-invasive laparoscopic options for procedures such as the repair of tissue or organ defects, engineering/implanting patches to enhance ovarian function, or creating bio-functional hernia repair meshes. Such options would be safer for the patient, save time and be more cost-effective. Further modifications in tissue engineering design and the adjustment of other conditions may increase the potential for customization, thus leading the way to limitless possibilities for enhancing patient health.

"Developing personalized tissues that can address various injuries and ailments is very important for the future of medicine. The work presented here addresses an important challenge in making these tissues, as it enables us to deliver the right cells and materials directly to the defect in the operating room," said Khademhosseini, "This work synergizes with our Personalized Implant Technology Platform at the Terasaki Institute which aims to develop approaches that address the variability in tissue defects in patients."

Additional authors on the article include Melika Shahhosseini, Andrej Simeunovic, Ph.D., Shuai Wu, Carlos Castro, Ph.D., and Ruike Zhao, Ph.D. Financial support came from the National Science Foundation under grants CMMI-1552358 CAREER and IIP-1919204.

https://bit.ly/3dqHLQF

Squid skin is naturally anti-microbial

This new finding makes squid skin a potentially valuable medical product, and could reduce waste from commercial fisheries

Lauren Sara McKee

Many types of squid have the ability to alter the color of skin cells called chromatophores, in order to blend in with their environment. This allows them to hide from predators, and is often triggered when the squid feels threatened. These same squids, including the Humboldt squid (*Dosidicus gigas*), are commercially fished in parts of North and South America.

Now, researchers working in Spain and Mexico have identified the pigments in Humboldt squid chromatophores as ommochromes. Chemical analysis showed that the main violet-coloured ommochrome is a compound called xanthommatin, which the researchers found to have strong anti-microbial properties. Their study showed that xanthommatin could inhibit the growth of several microorganisms that can cause disease in humans, including the fungus *Candida albicans* (which causes thrush and yeast infections) and bacteria like *Salmonella enterica*.

Skin from the squid is often discarded as waste from fisheries, but this new research tells us that it could be used to produce valuable medical compounds. The dumping of squid skin as waste "generates pollution problems in the coasts," says study co-author Jesús Enrique Chan in a news release, "so research like this, in which we inform about how these wastes could be used, helps to revalue them."

Humboldt squid aren't the only squid that produces this pigment. The tiny Hawaiian bobtail squid (*Euprymna scolopes*) also produces the anti-microbial xanthommatin pigment, as do many other species.

https://wb.md/2AY5Tds

Gardasil-9 Approved for Prevention of Head and Neck Cancers

FDA has expanded the indication for Gardasil-9 to include prevention of oropharyngeal and other head and neck cancers caused by HPV

Roxanne Nelson, RN, BSN

The US Food and Drug Administration (FDA) has expanded the indication for the Gardasil-9 (Merck) vaccine to include prevention of oropharyngeal and other head and neck cancers caused by HPV types 16, 18, 31, 33, 45, 52, and 58.

This new indication is approved under the FDA's accelerated approval program and is based on the vaccine's effectiveness in preventing HPV-related anogenital disease. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial, which is currently underway.

"At Merck, working to help prevent certain HPV-related cancers has been a priority for more than two decades," said Alain Luxembourg, MD, director, clinical research, Merck Research Laboratories, in a statement. "Today's approval for the prevention of HPV-related oropharyngeal and other head and neck cancers represents an important step in Merck's mission to help reduce the number of men and women affected by certain HPV-related cancers."

This new indication doesn't affect the current recommendations that are already in place. In 2018, a supplemental application for Gardasil 9 was approved to include women and men aged 27 through 45 years for preventing a variety of cancers including cervical, vulvar, vaginal, and anal cancer as well as genital warts. But cancers of the head and neck were not included.

The original Gardasil vaccine came on the market in 2006, with an indication to prevent certain cancers and diseases caused by HPV types 6, 11, 16, and 18. It is no longer distributed in the United States. In 2014, the FDA approved Gardasil 9, which extends the vaccine coverage for the initial four HPV types as five additional types (31, 33, 45, 52, and 58), and its initial indication was for use in both men and women between the ages of 9 through 26 years.

Head and Neck Cancers Surpass Cervical Cancer

More than 2 decades ago, researchers first found a connection between HPV and a subset of head-and-neck cancers (*Curr Opin Oncol.* 1999;11(3):191-199). The cancers associated with HPV also appeared to have a different biology and disease pattern, as well as a better prognosis, compared with those that were unrelated. HPV is now responsible for the majority of oropharyngeal squamous cell cancers diagnosed in the United States.

A study published last year found that oral HPV infections were occurring with significantly less frequency among sexually active female adolescents who had received the quadrivalent vaccine, as compared with those who were unvaccinated.

These findings provided evidence that HPV vaccination was associated with a reduced frequency of HPV infection in the oral cavity, suggesting that vaccination could decrease the future risk of HPV-associated head and neck cancers.

The omission of head and neck cancers from the initial list of indications for the vaccine is notable because, according to data from the Centers for Disease Control and Prevention (CDC), oropharyngeal cancers are now the most common malignancy caused by HPV, surpassing cervical cancer.

Who Will Benefit?

An estimated 14 million new HPV infections occur every year in the United States, according to the CDC, and about 80% of individuals who are sexually active have been exposed at some

point during their lifetime. In most people, however, the virus will clear on its own without causing any illness or symptoms.

In a *Medscape* videoblog, Sandra Adamson Fryhofer, MD, MACP, FRCP, helped clarify the adult population most likely to benefit from the vaccine. She pointed out that the HPV vaccine doesn't treat HPV-related disease or help clear infections, and there are currently no clinical antibody tests or titers that can predict immunity.

"Many adults aged 27-45 have already been exposed to HPV early in life," she said. Those in a long-term mutually monogamous relationship are not likely to get a new HPV infection. Those with multiple prior sex partners are more likely to have already been exposed to vaccine serotypes. For them, the vaccine will be less effective." Fryhofer added that individuals who are now at risk for exposure to a new HPV infection from a new sex partner are the ones most likely to benefit from HPV vaccination.

Confirmation Needed

The FDA's accelerated approval is contingent on confirmatory data, and Merck opened a clinical trial this past February to evaluate the efficacy, immunogenicity, and safety of the 9-valent HPV vaccine in men 20 to 45 years of age. The phase 3 multicenter randomized trial will have an estimated enrollment of 6000 men.

https://bit.ly/3fCSc2m

New Study Reveals COVID-19 Causes Serious Neurological Symptoms Shockingly Often

About half of hospitalized coronavirus patients experience neurological symptoms

Anna Medaris Miller, Business Insider

About half of hospitalized coronavirus patients experience neurological symptoms including dizziness, difficulty concentrating, a loss of smell and taste, seizures, strokes, and weakness, according to a new review of research published in the *Annals of Neurology*.

The findings illustrate that COVID-19, the disease the coronavirus causes, is far more than a respiratory infection and rather one that poses "a global threat" to the whole nervous system, including the brain, spinal cord, and nerves, the study authors say.

"It's important for the general public and physicians to be aware of this, because a SARS-CoV-2 infection may present with neurological symptoms initially, before any fever, cough or respiratory problems occur," lead study author Igor Koralnik, professor of neurology at Northwestern University Feinberg School of Medicine, said in a press release.

Some of the other neurological symptoms patients experienced included headache, decreased alertness, and muscle pain.

It makes sense that the nervous system can be affected by COVID-19 if, for example, the virus's wear on the lungs and heart make it tough to get enough oxygen to the brain. That in turn can contribute to the strokes some COVID-19 patients have experienced.

The virus may also infect the brain directly, the study authors say, and the immune system's reaction to it can cause inflammation that damages the brain and nerves.

It's too soon to know much about if or how long the neurological consequences persist and for whom, but Koralnik and his colleagues are planning to find out by continuing to follow COVID-19 survivors who were treated at their hospital.

Other studies and experts have called attention to the short- and long-term cognitive consequences

The current study helps frame and begin to explain something many doctors, patients, and mental-health providers have called attention to: The seemingly large rates and persistence of short- and long-term cognitive complications of COVID-19.

One study suggested as many as 65 percent of COVID-19 patients experience delirium, an often terrifying post-ICU effect that can involve vivid hallucinations, disorientation, irritability, and

range of other startling cognitive changes. One expert called delirium an "epidemic" on its own.

Hospitalized COVID-19 patients may also be susceptible to anxiety and panic attacks, as well as post-ICU syndrome, or PICS, a cluster of symptoms including generalized weakness, cognitive challenges, and poor mood.

Unlike medical post-traumatic stress disorder, which is also a concern for COVID-19 patients, PICS typically isn't debilitating enough to reach a clinical level of depression or anxiety but can drain survivors and their family members for months or years, Craig Weinert, a pulmonologist and critical-care physician at the University of Minnesota who's studied mental health outcomes of ICU patients, told Business Insider.

Any life-threatening illness that's landed people in intensive care can lead to cognitive and psychological complications including delirium and PICS due to limited oxygen intake, sedative medication, and being in a strange environment where patients don't know day from night.

But experts say aspects of COVID-19 are likely to make these consequences more prevalent, including the way it may infect the brain, the length of time on a ventilator, the heavy doses of sedative medications, and importantly, the physical isolation from family members during treatment. "This is unprecedented – the inability to have family around you as you are experiencing and recovering from this severe illness," Weinert said.

This article was originally published by Business Insider.

https://bbc.in/37wWEgo

Coronavirus: Dexamethasone proves first life-saving drug

A cheap and widely available drug can help save the lives of patients seriously ill with coronavirus.

By Michelle Roberts Health editor, BBC News online

The low-dose steroid treatment dexamethasone is a major breakthrough in the fight against the deadly virus, UK experts say.

The drug is part of the world's biggest trial testing existing treatments to see if they also work for coronavirus.

It cut the risk of death by a third for patients on ventilators. For those on oxygen, it cut deaths by a fifth. Had the drug had been used to treat patients in the UK from the start of the pandemic, up to 5,000 lives could have been saved, researchers say. And it could be of huge benefit in poorer countries with high numbers of Covid-19 patients. The UK government has 200,000 courses of the drug in its stockpile and says the NHS will make dexamethasone available to patients.

Prime Minister Boris Johnson said there was a genuine case to celebrate "a remarkable British scientific achievement", adding: "We have taken steps to ensure we have enough supplies, even in the event of a second peak."

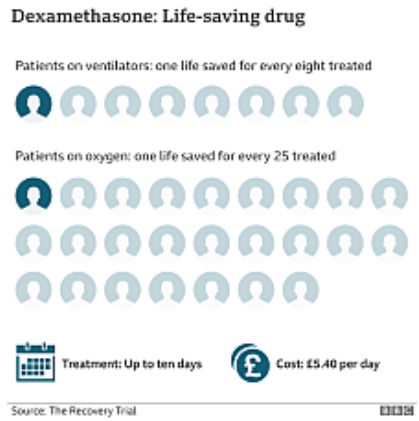
Chief Medical Officer for England Prof Chris Whitty said it would save lives around the world. About 19 out of 20 patients with coronavirus recover without being admitted to hospital. Of those who are admitted, most also recover but some may need oxygen or mechanical ventilation. And these are the high-risk patients dexamethasone appears to help.

The drug is already used to reduce inflammation in a range of other conditions, including arthritis, asthma and some skin conditions.

And it appears to help stop some of the damage that can happen when the body's immune system goes into overdrive as it tries to fight off coronavirus. This over-reaction, a cytokine storm, can be deadly.

In the trial, led by a team from Oxford University, about 2,000 hospital patients were given dexamethasone and compared with more than 4,000 who were not. For patients on ventilators, it cut the risk of death from 40% to 28%.

For patients needing oxygen, it cut the risk of death from 25% to 20%.



Chief investigator Prof Peter Horby said: "This is the only drug so far that has been shown to reduce mortality - and it reduces it significantly. It's a major breakthrough."

Lead researcher Prof Martin Landray said the findings suggested one life could be saved for:

- ***every eight patients on a ventilator***
- ***every 20-25 treated with oxygen***

"There is a clear, clear benefit," he said.

"The treatment is up to 10 days of dexamethasone and it costs about £5 per patient. "So essentially it costs £35 to save a life. "This is a drug that is globally available." When appropriate, hospital patients should now be given it without delay, Prof Landray said.

But people should not go out and buy it to take at home.

Dexamethasone does not appear to help people with milder symptoms of coronavirus who do not need help with their breathing.

The Recovery Trial, running since March, also looked at the malaria drug hydroxychloroquine, which has subsequently been ditched amid concerns it increases fatalities and heart problems.

The antiviral drug remdesivir, meanwhile, which appears to shorten recovery time for people with coronavirus, is already being made available on the NHS.

The first drug proven to cut deaths from Covid-19 is not some new, expensive medicine but an old, cheap-as-chips steroid. That is something to celebrate because it means patients across the world could benefit immediately. And that is why the top-line results of this trial have been rushed out - because the implications are so huge globally.

Dexamethasone has been used since the early 1960s to treat a wide range of conditions, such as rheumatoid arthritis and asthma.

Half of all Covid patients who require a ventilator do not survive, so cutting that risk by a third would have a huge impact.

The drug is given intravenously in intensive care and in tablet form for less seriously ill patients.

So far, the only other drug proven to benefit Covid patients is remdesivir, which has been used for Ebola. That has been shown to reduce the duration of coronavirus symptoms from 15 days to 11.

But the evidence was not strong enough to show whether it reduced mortality. Unlike dexamethasone, remdesivir is a new drug with limited supplies and a price has yet to be announced.

https://bit.ly/2BlQqfT

Researchers discover the origins of the beloved guinea pig

New University of Otago research sheds light on guinea pig domestication and how and why the small, furry animals became distributed around the world.

by Liane Topham-Kindley, University of Otago

Just published in the international science journal, *Scientific Reports*, the researchers use ancient DNA from archaeological guinea pig remains which reveals the transition from the animals being used as a wild food source 10,000 years ago to their domestication and later role as beloved pets and medical animal models.

It builds on previous research over many years by Professor of Biological Anthropology, Lisa Matisoo-Smith, tracing the DNA from plants and animals that Pacific settlers carried in their canoes and using that as a proxy for identifying human population origins and tracking their movement around the Pacific.

As part of her Otago Master's thesis research in Professor Matisoo-Smith's lab, Edana Lord, now at Stockholm University, Sweden and

Dr. Catherine Collins from Otago's Department of Anatomy and other international researchers, set about finding out where the guinea pigs that were introduced to the islands of the Caribbean came from.

Professor Matisoo-Smith explains it is generally accepted that modern guinea pigs were domesticated in the Andes region of what is now Peru. As an important food item that was also included in religious ceremonies, they were transported and traded around South America.

Sometime around AD500, guinea pigs were taken out to the islands of the Caribbean, through at least one of several established trade networks. The researchers expected that the guinea pigs found in the Caribbean would came from Colombia, one of the closer locations in South America to the Caribbean.

Using ancient DNA of guinea pigs remains excavated from several sites in the Caribbean, Peru, Colombia, Bolivia, Europe and North America, they found the guinea pigs on the islands did not originate in Colombia, but most likely originated in Peru.

What was a bigger surprise to the team was that the guinea pig remains found in the Colombian Highlands appeared to be from a totally different species. This suggests that guinea pig domestication likely took place independently in both Peru and Colombia.

The genetic information, along with archaeological contexts, also shows how the guinea pigs had different roles through time.

"They were and still are important food item in many parts of South America and cultures that derived from South America—people took them live to introduce to new islands where they were not native or they traded them for other goods," Professor Matisoo-Smith explains.

"The guinea pig was brought to Europe in the late 1500s or early 1600s by the Spanish and to North America in the early 1800s as part of the exotic pet trade. In the 18th century guinea pigs began to be used by medical researchers as laboratory animals because they have many biological similarities to humans, thus the origin of the phrase 'being a guinea pig' in research.

"All guinea pigs today—pets, those that are sold for meat in South America and Puerto Rico, and those used in medical research—are derived from the Peruvian domesticated guinea pigs."

Why the guinea pig was viewed as a pet in some cultures and a food source in others can likely be attributed to long-established cultural notions of what is acceptable as food.

Professor Matisoo-Smith says the research demonstrates that the history of guinea pigs is more complex than previously known and has implications for other studies regarding mammal domestication, translocation and distribution.

"Identifying the origins of the guinea pig remains from the Caribbean helps us to understand how the human trade networks in the region moved in the past 1000 years or so.

"Through this analysis of ancient guinea pig DNA, we better understand the history of human social interactions over thousands of years and across three continents. It also provides a critical historical perspective of the genetic diversity in guinea pigs and the relationship humans have had with this important domestic animals."

More information: *E. Lord et al. Ancient DNA of Guinea Pigs (Cavia spp.) Indicates a Probable New Center of Domestication and Pathways of Global Distribution, Scientific Reports (2020). DOI: 10.1038/s41598-020-65784-6*

https://bit.ly/2zQwEjJ

COVID-19 death rate cut by cheap steroid, according to unpublished data

Researchers have yet to release data on the trial, but many are optimistic.

Beth Mole

Researchers at the University of Oxford announced Tuesday that a cheap, readily available steroid drug lowered the risk of death in COVID-19 patients who were enrolled in a randomized clinical trial and required either ventilation or oxygen during their treatment.

According to unpublished data, the steroid dexamethasone reduced the risk of death from 41 percent to about 27 percent in patients who were ventilated, and from 25 percent to 20 percent in patients on oxygen.

If the finding holds up, it would mark the first time in the five-month-old pandemic that researchers have identified a therapeutic that reduces mortality from infections with the novel coronavirus, SARS-CoV-2.

Upon hearing the news Tuesday, many experts were optimistic and excited about the reduction of mortality—and that it came from a drug that would be affordable and easy to deliver to patients all over the world.

But many experts also urged caution, noting that the clinical trial data has not yet been published or reviewed by outside scientists. The Oxford researchers merely announced the news and a small amount of supporting data in a press release.

This has become a frustrating trend during the pandemic, which researchers have repeatedly recommended against. The trial authors noted in the press release that "given the public health importance of these results, we are now working to publish the full details as soon as possible."

Here's what we know so far

The unpublished results are from the RECOVERY (Randomised Evaluation of COVid-19 thERapY) trial, a large randomized clinical trial involving more than 11,500 patients at 175 hospitals in the UK. It's funded by the University of Oxford, UK government grants, and nonprofits and charities, including Wellcome and The Bill and Melinda Gates Foundation.

The trial has multiple treatment arms, meaning that doctors are using the trial to test several potential therapeutics at once. These include the HIV treatment lopinavir-ritonavir, the anti-malaria treatment hydroxychloroquine (which has since been abandoned), the anti-inflammatory tocilizumab, and convalescent plasma.

One of the drugs was dexamethasone, a synthetic corticosteroid known to have anti-inflammatory and immune-suppressing effects and which is able to make its way into the central nervous system. Researchers have hypothesized that such drugs could help with severe cases of COVID-19 because they are thought to involve out-of-control immune responses, as seen in "cytokine storms." So far, dexamethasone is used to treat a variety of conditions, including shock, multiple sclerosis, allergies, cerebral edema, asthma, and contact dermatitis.

According to the press release, the trial's dexamethasone arm included a total of 2,104 randomly assigned COVID-19 patients who took a 6-milligram dose of dexamethasone once per day (either by mouth or by intravenous injection) for ten days. The fates of these patients after 28 days were compared to those of 4,321 randomly assigned COVID-19 patients who only received standard care, no experimental treatments.

Among the patients in the standard care group, some percentage of them required ventilation and of those ventilated patients, 41 percent had died after 28 days. Of the standard-care patients who required only oxygen, 25 percent died. There were also patients who did not require any respiratory intervention and, of those, 13 percent died.

"Dexamethasone reduced deaths by one-third in ventilated patients (rate ratio 0.65 [95% confidence interval 0.48 to 0.88]; p=0.0003) and by one fifth in other patients receiving oxygen only (0.80 [0.67 to 0.96]; p=0.0021)," the press release stated. "There was no benefit

among those patients who did not require respiratory support (1.22 [0.86 to 1.75]; p=0.14)."

Put another way, dexamethasone decreased the risk of death in those ventilated by 35 percent and in those needing oxygen by 20 percent.

The press release hashed this out further, saying, "Based on these results, 1 death would be prevented by treatment of around 8 ventilated patients or around 25 patients requiring oxygen alone."

Rosy reviews

The release also included some splashy quotes, unbridled in their excitement:

"Dexamethasone is the first drug to be shown to improve survival in COVID-19. This is an extremely welcome result," said Peter Horby, professor of emerging infectious diseases at Oxford and one of the chief investigators for the trial. "The survival benefit is clear and large in those patients who are sick enough to require oxygen treatment, so dexamethasone should now become standard of care in these patients. Dexamethasone is inexpensive, on the shelf, and can be used immediately to save lives worldwide."

Martin Landray, another Oxford research on the trial, added,

"These preliminary results from the RECOVERY trial are very clear—dexamethasone reduces the risk of death among patients with severe respiratory complications. COVID-19 is a global disease—it is fantastic that the first treatment demonstrated to reduce mortality is one that is instantly available and affordable worldwide."

The UK government's chief scientific adviser, Sir Patrick Vallance, called the press release announcement "tremendous news" and a "ground-breaking development."

Caution

But other experts were not so enthusiastic.

Surgeon and public health researcher Atul Gawande tweeted:

It will be great news if dexamethasone, a cheap steroid, really does cut deaths by 1/3 in ventilated patients with COVID19, but after all the retractions and walk backs, it is unacceptable to tout study results by press release without releasing the paper.

Dr Penny Ward, an expert in pharmaceutical medicine and a visiting professor at King's College London called the announcement "good news" in a statement but noted:

Clinicians will need to see the detailed results of the trial, particularly those in patients not requiring oxygen therapy/ventilator support, as the breakdown of outcomes by disease stage suggests that the timing for start of steroid use may be relevant to use the treatment most efficiently. That said, for patients going onto a ventilator, good news today.

On Twitter, Nahid Bhadelia, an infectious disease doctor at Boston University, likewise called for the full data to help treating physicians understand which COVID-19 patients would most likely benefit from the treatment and what other standard treatments patients in the trial received. And Jeremy Faust, a Harvard emergency medicine doctor, noted that additional information on outcomes for patients is needed to truly assess the benefits of the drug—not just survival.

Columbia University virologist Angela Rasmussen implored colleagues to release data alongside such announcements in the future: "I urge scientists and physicians—especially those working on studies with implications for clinical practice—to PLEASE not disclose results by press release with no accompanying data," she wrote on Twitter.

"Evidence-based medicine requires evidence. It's not optional."

https://wb.md/2YVGBow

Is COVID-19 Risk Linked to Blood Type?

Blood type may be associated with the risk for coronavirus infection and death from COVID-19

F. Perry Wilson, MD, MSCE

Welcome to Impact Factor, your weekly dose of commentary on a new medical study. I'm Dr F. Perry Wilson.

One of the things that has really bothered me about COVID-19 is the dramatic variability in presentation, from being asymptomatic to having sniffles, complete respiratory failure requiring ECMO, and, of course, death. I've seen all of these firsthand at this point. And sure, we know that there are risk factors for bad outcomes, such as older age and comorbidities. But ask any of us who have cared for these patients and we'll tell you that there is clearly other stuff going on. I've seen a 35-year-old man with no comorbidities fighting for his life on ECMO.

It seems logical that genetics may play a role here, but those studies are just in the early phases. Nevertheless, some tantalizing clues are emerging—and some from really unlikely places.

Okay. A couple of months ago, my family did tests to figure out our blood type. We did this for no scientific or medical reason; we were bored, stuck at home, wanted some fun science-y stuff to do with the kids, and found some cheap kits on Amazon.

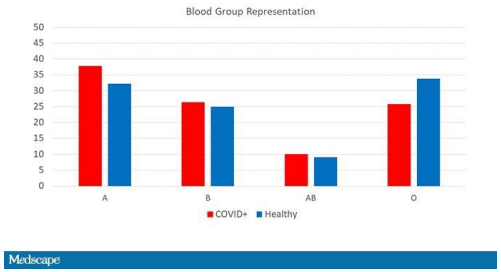
I am type O. My wife, type A.

And that was that. Until I started seeing that blood type may be associated with the risk for coronavirus infection and death from COVID-19.

This supposition immediately raised red flags for me. Correlating blood type with various outcomes has long straddled the border between regular science and pseudoscience—and often had a racially tinged flavor. I am pretty sure blood type does not correlate with various personality traits, for example. So why would blood type dictate susceptibility to a respiratory virus?

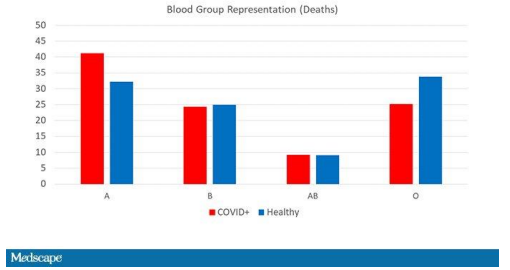
But, since I am often wrong and love to find out when I'm wrong, I looked into it. And I honestly think there may be something here. Caveats: Data are really limited, and studies are sort of trickling out in preprint form and in various esoteric journals. But I'll point out a couple that hold water for me.

The first, a preprint out of China, looked at just over 2000 COVID-positive individuals and reported that there was a higher infection rate in people with type A blood. What you see here is that there was a higher-than-expected rate of individuals with blood group A diagnosed with COVID-19 than in the general population.

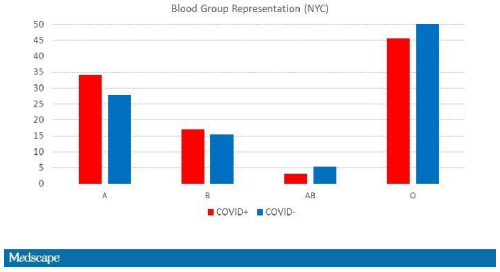


Conversely, fewer-than-expected individuals with blood group O appeared in the pool of those infected. Similar results were seen when the analysis was restricted to the 206 individuals who died from COVID-19. Again, blood group A was overrepresented.

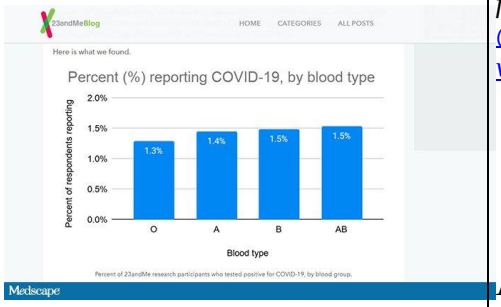
One study, especially in preprint form, is never definitive, but we now have this study from New York City to add to the data. This study looked at 1559 patients who were tested for COVID-19; 682 were positive. And check out the distribution of blood types in the positive vs negative groups. Again, blood group A is overrepresented and blood group O is underrepresented among the infected.



The commercial DNA testing company 23andMe has reported that their analysis of over 750,000 genomes shows a similar pattern by blood group. They haven't published their data yet, but you can see here that the self-reported infection rate was lower in type



O individuals and higher in type A individuals, though overall rates are still low.



These data don't come totally out of the blue. Back in the SARS era, a Hong Kong study reported that type A individuals were at higher risk for infection from that coronavirus.

But what's the biological rationale here? Even if we believe the epidemiology, the question is, why?

There are a few theories floating around out there, but most of them focus on antibodies. An in vitro study of the SARS coronavirus from 2008 found that anti-A antibodies inhibited the ability of the viral spike protein to bind to its receptor, ACE2.

So, a leading theory is that people with blood type O, like me, might be protected if they have some anti-A antibodies floating around. Of course, people with type B blood also have anti-A antibodies, and we haven't seen protection in them so far.

The other possibility is that the antibodies generated *against* the virus are cross-reactive with the blood group A antigen, so when someone with blood group A is generating those antibodies, they might also be making antibodies that make their platelets a bit stickier, leading to some of the thrombotic events we've seen in COVID-19 patients. Of course, this doesn't explain why the risk for infection would be higher, only the risk for bad outcome after infection.

I'm left a bit puzzled. Am I convinced that there is something here? Yes—but I'm not sure what it is. Whether it's a direct biologic effect of blood type, or whether blood type is a marker for something else—a nearby gene, for instance—or maybe even socioeconomic status—is ongoing work. As we get more answers, we'll tell you about them here.

F. Perry Wilson, MD, MSCE, is an associate professor of medicine and director of Yale's Program of Applied Translational Research. His science communication work can be found in the Huffington Post, on NPR, and here on Medscape. He tweets @methodsmanmd and hosts a repository of his communication work at www.methodsman.com.

https://bit.ly/2V23yoX

Liver perfusion could save 7 in 10 rejected donor livers

Could have significant implications for the liver transplant waiting list

A major study investigating the effectiveness of liver perfusion as a technique to improve the function of donor livers that would have otherwise been rejected has shown that up to 7 in every 10 could be used after just 4-6 hours of the assessment.

The study, 'Transplantation of discarded livers following viability testing with normothermic machine perfusion', published today in *Nature Communications*, could have significant implications for the liver transplant waiting list and the commissioning of local transplant services.

Currently, across the UK, a third of donated livers don't meet desired transplant criteria and aren't used.

Chronic liver disease in the UK is rising annually, a result of obesity and increasing alcohol misuse causing approximately 8500 deaths per year.

For those with end-stage liver disease, a transplant is the only hope for survival, but demand for livers suitable for transplantation far outstrips supply.

According to the latest NHS Blood and Transplant report, up to 20% of people awaiting a transplant operation died or were removed from waiting lists due to ill health.

A growing proportion of donated livers are coming from high-risk donors with a history of alcohol misuse, obesity or elderly people with comorbidities, often when a patient has suffered cardiac arrest

that is unexpected and when the patient cannot or should not be resuscitated.

These livers are of lower quality and pose risks to recipients. Consequently, the majority are not transplanted.

Funded by the Wellcome Trust, experts from the University of Birmingham's Centre for Liver and Gastrointestinal Research, University Hospitals Birmingham NHS Foundation Trust and the NIHR Birmingham Biomedical Research Centre have found that just 4-6 hours of normothermic machine perfusion assessment enabled 70 per cent of currently discarded livers to recover enough to allow successful transplantation into a recipient.

Mr Hynek Mergental, Honorary Senior Lecturer at the University of Birmingham and Consultant Surgeon at the UHB Liver Unit said:

"Whilst liver transplantation is one of the most advanced surgical procedures, up to now, there has been no objective mean to assess suitability of donor livers for transplantation. The VITTAL trial validated our pre-clinical research and pilot clinical observations and these viability criteria can now guide transplant teams worldwide to provide access to the life-saving transplantation to more patients in need. "

VITTAL project lead, Professor Darius Mirza, Consultant Transplant Surgeon at University Hospitals Birmingham NHS Foundation Trust, added:

"This challenging study was designed to assess function of discarded livers in the real-life situation, using the normothermic machine perfusion. The major challenge in this pioneering clinical trial was to assure patients safety while pushing the envelope of sub-optimal liver utilisation."

Mr Thamara Perera, Consultant Transplant Surgeon at UHB explains: "This ground breaking trial has proven that objective parameters can be used for making a decision to use a borderline liver. The observed 100% study participants post-transplant survival was reassuring and provided our patients and the surgical team with confidence to implement and further expand this approach, which now helps the sickest patients on our waiting list to underwent transplantation sooner and safer."

Dr Simon Afford, Reader in Liver Immunobiology at the University of Birmingham's Institute of Immunology and Immunotherapy, said: "It has long been recognised that as a consequence of our population aging the quality of donated livers keeps declining. Based on our latest discoveries we believe that in the near future the machine perfusion platform will facilitate therapeutic interventions to improve liver viability. We expect we will be able salvage even more organs than 70% observed in the VITTAL trial, including livers from donors with known alcohol misuse or obesity."

Tim Knott, Head of Innovation Programmes at the Wellcome Trust, said: "Many more patients who need liver transplants will benefit from this technology. Giving surgeons the tools to assess if a liver transplant will be viable will help the thousands of people who have chronic liver disease globally."

John Forsythe, Medical Director of Organ Donation and Transplantation for NHS Blood and Transplant, said: "New techniques of Organ perfusion and preservation are a vital developing area of organ donation and transplantation. We are delighted that a number of doctors and scientists in the UK are leading the way in this field of research.

"Each year a small number of donated organs are not transplanted for a variety of reasons. Transplant success relies on a significant amount of activity taking place in a short space of time. New techniques are already allowing us to transplant donated organs that would not have been possible in the past. More research in this area is likely to increase that ability."

https://bit.ly/3hMbpQZ

UConn researchers overcome a vexing problem in vaccine research

A vaccine for VED community acquired pneumonia has been sought after since the illness can pose problems for closed community settings

Researchers at UConn's Center of Excellence in Vaccine Research (CEVR) have made a breakthrough in vaccine development for a common and difficult to treat pneumonia-causing pathogen. Their research was recently published in the Nature Partner Journal - *Vaccines*.

For Mycoplasma pneumoniae, vaccine development has been stalled since the 1960s due to a phenomena called vaccine-enhanced disease (VED) or vaccine induced disease exacerbation. A vaccine for this type of community acquired pneumonia has been sought after since the illness can pose problems for closed community settings such as military bases, hospitals, ships, college dormitories, and prisons.

"Two different vaccines were developed by the National Institutes of Health," says Assistant Professor in Pathobiology and Veterinary Science Steven Szczepanek. "In trials, most vaccinated subjects were protected from infection and showed no symptoms. However, for some vaccinated and infected subjects, symptoms were actually worse than those observed in people that did not receive the vaccine. This is vaccine-enhanced disease and is of course really bad."

A vaccine must strike a balance. The formulation needs just enough potency to ensure the immune system will be able to recognize a pathogen and easily kill it if the patient re-encounters it. If all goes according to plan, vaccinated patients are able to easily clear a reinfection without even knowing they were re-exposed. However, a vaccine can sometimes lead to an overreaction by the immune system upon reinfection. This vaccine-enhanced disease has been seen with other pathogens such as respiratory syncytial virus (RSV), Dengue fever, and in animals models in SARS vaccine research, says Steven Geary Department Head of Pathobiology and Veterinary Science and Director of CEVR.

VED is contradictory to the very basis of vaccination.

"We're trying to develop prophylactic vaccines to prevent infections from occurring in healthy people. If the vaccines we develop will actually make infections worse in 1/3 people that get the vaccine, then most people are not going to take the vaccine - and rightfully so," says Szczepanek. "We're not talking about cancer therapeutics where the subject is already sick, where the potential benefit of finding a cure often outweighs the risk of an adverse event occurring. The medical community, and people in general, have very little tolerance for adverse events occurring in a product that is given to otherwise healthy individuals."

To get to the root cause of VED with M. pneumoniae vaccination, the researchers analyzed the building blocks of the bacteria -- the proteins, lipids, and lipoproteins -- to determine if they elicited an immune response.

"We decided to systematically tear the bug apart using different chemical and physical approaches and test different components as vaccines to see if we could identify what, exactly, was causing VED after infection. Before we started this process, we hypothesized that it was the membrane bound surface lipoproteins that were causing VED," says Szczepanek.

The team also studied details about the host immune system and what qualities of the pathogen would lead to the occurrence of VED. "That's the $64,000 question. The short answer is that we don't know the full picture. Chemical signals used by the immune system called "cytokines" help to drive specific types of immune responses to different pathogens," says Szczepanek.

A confounding trend the researchers have found is the cytokines that play a key role in vaccine protection to another pneumonia-causing bacteria, Streptococcus pneumoniae, are the same cytokines driving VED with M. pneumoniae. This is an example of the nuances and complexities behind vaccine development explains Szczepanek. "We can't even use what we know about immunity from one bacterial pathogen that causes a similar disease to understand what happens during infection with a different species. Each pathogen is complex and unique, so it seems that we will stay employed for many years to come."

The researchers were able to narrow down the candidates to certain lipoproteins on the surface of the bacteria to test their hypothesis about the immune-inducing culprit.

"After some pretty extensive testing we found out that we were right," says Szczepanek. "Chemical removal of the lipid portion of purified M. pneumoniae lipoproteins eliminated VED, and even drove some level of protection from infection. We still have some work to do to fully optimize the efficacy of a vaccine formulation, but we have identified and eliminated the cause of the nagging roadblock of VED that plagued the field for over half a century. Safety problems are no longer a concern for M. pneumoniae vaccines."

The road to a safe and effective vaccine is a long one, but the researchers at CEVR are excited to be moving forward after overcoming the difficult hurdle of VED, says Geary. "We have to prepare and refine candidate M. pneumoniae vaccines that do not contain lipoproteins, and test them in our animal model. We will also be testing different adjuvants (compounds that are added to vaccines to increase the proper immune response). Once we have defined the precise vaccine formulation we will proceed with a phase 1 clinical trial in humans. If successful, we will continue on the FDA proscribed phase 2 and 3 clinical trials required for all human vaccines and hopefully then find a partner to produce and market it."

It is a team effort Geary adds, "The majority of the hands-on experimentation and data evaluation to date has been conducted by PhD candidates Arlind Mara and Tyler Gavitt, who will continue to perform the immunologic and vaccine efficacy analysis as this project progresses to the point of a successful vaccine."

UConn has filed a provisional patent application and the technology is available for licensing or partnering. For further information please contact Amit Kumar at a.kumar@uconn.edu.

https://bit.ly/3ennUQZ

What it means when animals have beliefs

Chimpanzees, some dog species and even scrub jay and crows have beliefs. Philosophers from Bochum have been debating how to define the term.

Humans are not the only ones who have beliefs; animals do too, although it is more difficult to prove them than with humans. Dr. Tobias Starzak and Professor Albert Newen from the Institute of Philosophy II at Ruhr-Universität Bochum have proposed four criteria to understand and empirically investigate animal beliefs in the journal "Mind and Language". The article was published online on 16 June 2020.

Flexible use of information about the world

The first criterion for the existence of beliefs worked out by the philosophers is that an animal must have information about the world. However, this must not simply lead to an automatic reaction, like a frog instinctively snapping at a passing insect.

Instead, the animal must be able to use the information to behave in a flexible manner. "This is the case when one and the same piece of information can be combined with different motivations to produce different behaviours," explains Albert Newen. "For example, if the

animal can use the information that there is food available at that moment for the purpose of eating or hiding the food."

Information can be relinked

The third criterion says that the information is internally structured in a belief; accordingly, individual aspects of that information can be processed separately. This has emerged, for example, in experiments with rats that can learn that a certain kind of food can be found at a certain time in a certain place. Their knowledge has a what-when-where structure.

Fourthly, animals with beliefs must be able to recombine the information components in novel ways. This reassembled belief should then lead to flexible behaviour. Rats can do this too, as the US researcher Jonathan Crystal demonstrated in experiments in an eight-armed labyrinth. The animals learned that if they received normal food in arm three of the maze in the morning, chocolate could be found in arm seven at noon.

Crows and scrub jays meet all criteria

The authors from Bochum also cite crows and scrub jays as examples of animals with beliefs. British researcher Nicola Clayton carried out conclusive experiments with scrub jays. When the birds are hungry, they initially tend to eat the food. When they are not hungry, they systematically hide the leftovers. In the process, they encode which food - worm or peanut - they have hidden where and when. If they are hungry in the following hours, they first look for the worms they prefer. After the period of time has elapsed that takes worms to become inedible, they head for the peanut hiding places instead.

"What best explains this change in behaviour is the birds' belief about the worms being spoiled and their beliefs about the location of other food items," says Tobias Starzak. The animals also react flexibly in other situations, for example if they notice that they are being watched by rivals while hiding; if this is the case, they hide the food again later.

Flexible behaviour, which can be interpreted as caused by beliefs, has also been shown in rats, chimpanzees and border collies. "But probably many more species have beliefs," supposes Albert Newen.

https://bit.ly/2YSDzRL

Without intervention, a 70% reduction in strokes or death in patients with brain AVMs

Interventional treatment could be more dangerous than the disease itself.

Montreal - For people with a brain arteriovenous malformation, a congenital vascular system defect, fate has a name: stroke. To avoid this risk, patients sometimes undergo interventions to remove the malformation. But is this very beneficial? Not necessarily. According to an international clinical trial, co-directed by researchers from the University of Montreal Hospital Research Centre (CRCHUM), interventional treatment--by neurosurgery, neuroradiology or radiation therapy--could be more dangerous than the disease itself.

In a study published in *The Lancet Neurology*, Dr. Christian Stapf, a vascular neurologist at the CHUM and the co-author of the article, and his colleagues show that the risk of having a stroke or dying falls by 68% when doctors let the malformation follow its natural course.

"In other words, the risk of patients having a stroke or dying is at least three times lower," stated Dr. Stapf, a researcher at the CRCHUM and professor at the Université de Montréal. "We wondered what was better for the patient: to remove the malformation to prevent a stroke or to live with the malformation for several years? The results of our study are clear: in the long term, standard medical care is more beneficial for the patient than

any intervention. This certainly shakes up conventional thinking about how to prevent stroke in these patients."

Before joining the neurovascular program at CHUM in 2015, Dr. Stapf worked at Lariboisière Hospital (Paris, France). He was already the principal co-author of this study and in charge of the European component.

A second phase of the study sought to evaluate whether early surgical intervention might reduce the risk of neurological deficits. "After a five-year follow-up period, we showed that there were twice as many patients with a disabling deficit after the interventions than medical management alone," pointed out Dr. Stapf.

An Extraordinary Study

In this international clinical trial named ARUBA (acronym for A Randomized trial of Unruptured Brain AVMs), 226 adult participants with an average age of 44 were recruited between 2007 and 2013 in 39 hospital centres located in nine countries. Among the members of this collaborative network, the CHUM was the most active centre in terms of recruitment in Canada. There were two other centres in Ontario.

These volunteer patients, who had never had a stroke and whose malformation was sometimes discovered by chance, were divided into two groups: the first would get standard medical care, while the second would receive standard care combined with invasive therapies (by neurosurgery, interventional neuroradiology or radiation therapy). They were followed for average periods of between 33 and 50 months.

In 2014, under the supervision of Dr. Jean Raymond (interventional neuroradiologist), the CHUM launched TOBAS, an international study whose aim was to see whether the conclusive findings of the clinical trial ARUBA might also be valid for all patients with a neurovascular malformation, including those who had had a stroke in the past.

To date, the CHUM's neurovascular health program is the largest in Quebec and among the biggest in Canada: more than 800 stroke patients are admitted to the program every year. With its Centre de Référence des Anomalies Neurovasculaires Rares (referral centre for rare neurovascular abnormalities or iCRANIUM), the CHUM also offers a specialized multidisciplinary clinic dedicated to patients with several types of vascular malformations of the brain.

This research was supported by the National Institutes of Health/National Institute of Neurological Disorders and Stroke and the Vital Projects Fund.

Further reading: "Medical management with interventional therapy versus medical management alone for unruptured brain arteriovenous malformations (ARUBA): final follow-up of a multicentre, non-blinded, randomised controlled trial" by Jay P. Mohr et al. in Lancet Neurol 2020; 19:573-81

https://bit.ly/3hPU1Lt

Hookworm trial offers new hope to MS patients

Parasitic worms could offer a new treatment hope for patients suffering from the autoimmune disease multiple sclerosis, according to experts from the University of Nottingham.

The findings of the research, published in the journal *JAMA Neurology,* show that infecting MS patients with a safe dose of the hookworm parasite Necator americanus induces immunoregulatory responses and boosts the number of cells which help keep the immune system under control.

The research was led by Cris Constantinescu, Professor of Neurology in the University's School of Clinical Sciences and a leading MS expert, and David Idris Pritchard, Professor of Parasite Immunology in the University's School of Pharmacy, who has spent decades studying the biology of the hookworm. The study was funded by the Multiple Sclerosis Society.

MS is a condition that can affect the brain and spinal cord, causing a wide range of potential symptoms, including problems with vision,

arm or leg movement, sensation or balance. Whilst treatments are available, there is currently no cure.

The study aimed to show that the presence of hookworms in the body switches off the mechanism by which the body's immune system becomes overactive -- the main cause of MS -- reducing both the severity of symptoms and the number of relapses experienced by the patients. 71 patients were recruited for a controlled clinical trial who suffer from the most common type of the disease, relapsing remitting MS (RRMS).

Symptoms in patients such as vision problems, dizziness and fatigue, appear and then fade away either partially or completely, and secondary progressive MS with superimposed relapses.

Half of the patients on the trial, received a low dose of the hookworms --25 of the microscopic larvae -- on a plaster applied to the arm, while the other half received a placebo plaster.

At the beginning of the trial, the participants underwent an MRI scan to record the scarring or lesions on the brain which are present in MS patients. Over the course of nine months, all the patients were scanned on a regular basis for new or worsening lesions which can be a tell-tale sign of relapse.

The results at the end of the trial showed that the total number of new MRI lesions did not differ significantly between patients receiving hookworm and those receiving placebo. However, more than half the patients on hookworm had no new lesions at all.

In addition, the scientists found an increase in the percentage of regulatory T cells found within patients who received the hookworm. These cells help to keep the immune system under control, and are deficient in MS patients. The results showed that the hookworm increases this type of cell which could be beneficial in the treatment of MS.

Professor Constantinescu said: "The findings of our study are encouraging. Whilst the results are modest in comparison to the current very potent and highly effective treatments available, some patients with milder disease or more inclined for natural treatments may consider this as an option.

"On the more biological level, it is worth harnessing immunoregulatory mechanisms, for example increasing regulatory T cells in MS (and possibly other autoimmune diseases). Further studies are now needed to establish whether different protocols can enhance this benefit. For instance, would a booster infection in around nine months enhance the regulatory T cells responses and enhance the clinical/radiological benefit?"

Professor Pritchard is equally encouraged by the results of the trial. He said: "In essence, we were able to safely and easily deliver a living drug to humans, an organism which has long lasting modulatory effects on the immune system, given the time the adult parasite is resident in the small intestine (years). Clearly, this study has set the scene for follow up trials, where I would envisage booster infections being given to enhance the immune modulation already recorded. The dosage used in the current study (25 larvae) was the maximum permitted under regulatory guidelines, therefore boosting with this dose would be preferable to increasing the level of primary exposure." A full copy of the study can be found here.

https://bit.ly/2YSnLOY

Study shows sedentary behavior independently predicts cancer mortality

Replacing sitting time with 30 minutes of activity associated with lower risk of cancer death

Houston -- In the first study to look at objective measures of sedentary behavior and cancer mortality, researchers from The University of Texas MD Anderson Cancer Center found that greater inactivity was independently associated with a higher risk of dying from cancer. The most sedentary individuals had an 82% higher risk of cancer mortality compared to the least sedentary individuals. An

accelerometer was used to measure physical activity, rather than relying on participants to self-report their activity levels

"This is the first study that definitively shows a strong association between not moving and cancer death," said Susan Gilchrist, M.D., associate professor of Clinical Cancer Prevention and lead author of the study, published today in *JAMA Oncology*. "Our findings show that the amount of time a person spends sitting prior to a cancer diagnosis is predictive of time to cancer death."

Researchers also found that replacing 30 minutes of sedentary time with physical activity was associated with a 31% lower risk of cancer death for moderate-intensity activity, such as cycling, and an 8% lower risk of cancer death for light-intensity activity, such as walking.

"Conversations with my patients always begin with why they don't have time to exercise," said Gilchrist, who leads MD Anderson's Healthy Heart Program. "I tell them to consider standing up for 5 minutes every hour at work or taking the stairs instead of the elevator. It might not sound like a lot, but this study tells us even light activity has cancer survival benefits."

Study design

This study involved a cohort of participants from the nationally representative REGARDS study, which recruited more than 30,000 U.S. adults over the age of 45 between 2003 and 2007 to study long-term health outcomes.

To measure sedentary behavior, 8,002 REGARDS participants who did not have a cancer diagnosis at study enrollment wore an accelerometer on their hip during waking hours for seven consecutive days. The accelerometer data was gathered between 2009 and 2013. After a mean follow-up of 5 years, 268 participants died of cancer. Longer duration of sedentary behavior was independently associated with a greater risk of cancer death.

The study also found that engaging in either light or moderate to vigorous physical activity made a difference. Investigators assessed sedentary time, light-intensity physical activity (LIPA) and moderate to vigorous physical activity (MVPA) in the same model and found that LIPA and MVPA, not sedentary behavior, remained significantly associated with cancer mortality.

"From a practical perspective, this means that individuals who replaced either 10 to 30 minutes of sedentary time with either LIPA or MVPA had a lower risk of cancer mortality in the REGARDS cohort," Gilchrist said.

The study had several limitations, including a potentially healthier participant sample compared to the full REGARDS cohort and a lack of site-specific cancer data, including type of tumor and treatment.

"Our findings reinforce that it's important to 'sit less and move more' and that incorporating 30 minutes of movement into your daily life can help reduce your risk of death from cancer," Gilchrist said. "Our next step is to investigate how objectively measured sedentary behavior impacts site-specific cancer incidence and if gender and race play a role."

The research was supported by several institutes of the National Institutes of Health. A full list of co-authors and funding support is available on the paper.

https://bit.ly/2V0xmCc

MMR vaccine could protect against the worst symptoms of COVID-19

Administering the vaccine could serve as a preventive measure to dampen septic inflammation associated with COVID-19 infection

Washington, DC - Administering the MMR (measles, mumps, rubella) vaccine could serve as a preventive measure to dampen septic inflammation associated with COVID-19 infection, say a team of experts in this week's *mBio*, a journal of the American Society for Microbiology. Long-time collaborators and spouses Dr. Paul Fidel,

Jr., Department Chair, Oral and Craniofacial Biology, and Associate Dean for Research, Louisiana State University Health School of Dentistry and Dr. Mairi Noverr Professor of Microbiology & Immunology at Tulane University School of Medicine in New Orleans co-authored the perspective article based on ideas stemming from research in their labs. Vaccination with MMR in immunocompetent individuals has no contraindications and may be especially effective for health care workers who can easily be exposed to COVID-19, say the researchers.

"Live attenuated vaccines seemingly have some nonspecific benefits as well as immunity to the target pathogen. A clinical trial with MMR in high-risk populations may provide a low-risk-high-reward preventive measure in saving lives during the COVID-19 pandemic," said Dr. Fidel. "While we are conducting the clinical trials, I don't think it's going to hurt anybody to have an MMR vaccine that would protect against the measles, mumps, and rubella with this potential added benefit of helping against COVID-19."

Mounting evidence demonstrates that live attenuated vaccines provide nonspecific protection against lethal infections unrelated to the target pathogen of the vaccine by inducing trained nonspecific innate immune cells for improved host responses against subsequent infections. Live attenuated vaccines induce nonspecific effects representing "trained innate immunity" by training leukocyte (immune system cells) precursors in the bone marrow to function more effectively against broader infectious insults.

In Dr. Noverr's laboratory, in collaboration with Dr. Fidel, vaccination with a live attenuated fungal strain-induced trained innate protection against lethal polymicrobial sepsis. The protection was mediated by long-lived myeloid-derived suppressor cells (MDSCs) previously reported inhibiting septic inflammation and mortality in several experimental models. The researchers say that an MMR vaccine should be able to induce MDSCs that can inhibit or reduce the severe lung inflammation/sepsis associated with COVID-19. Mortality in COVID-19 cases is strongly associated with progressive lung inflammation and eventual sepsis.

Recent events provide support for the researchers' hypothesis. The milder symptoms seen in the 955 sailors on the U.S.S Roosevelt who tested positive for COVID-19 (only one hospitalization) may have been a consequence of the fact that the MMR vaccinations are given to all U.S. Navy recruits. In addition, epidemiological data suggest a correlation between people in geographical locations who routinely receive the MMR vaccine and reduced COVID-19 death rates. COVID-19 has not had a big impact on children, and the researchers hypothesize that one reason children are protected against viral infections that induce sepsis is their more recent and more frequent exposures to live attenuated vaccines that can also induce the trained suppressive MDSCs that limit inflammation and sepsis.

The researchers propose a clinical trial to test whether the MMR vaccine can protect against COVID-19, but in the meantime, they suggest that all adults, especially health care workers and individuals in nursing homes get the MMR vaccine. "If adults got the MMR as a child they likely still have some level of antibodies against measles, mumps, and rubella, but probably not the myeloid-derived suppressor cells," said Dr. Fidel. "While the MDSCs are long-lived, they are not life-long cells. So, a booster MMR would enhance the antibodies to measles, mumps, and rubella and reinitiate the MDSCs. We would hope that the MDSCs induced by the MMR would have a fairly good life-span to get through the critical time of the pandemic."

Dr. Noverr was recently awarded a "Fast Grant" (part of Emergent Ventures at the Mercatus Center, George Mason University) to test the efficacy of MMR directly in a nonhuman primate model of COVID-19 infection.

https://bit.ly/2Njk6EE

Trump administration paid millions for test tubes, got unusable mini soda bottles

Tubes don't even fit the racks used to analyze samples, may be contaminated anyway.

J. David McSwayne and Ryan Gabrielson, ProPublica

Since May, the Trump administration has paid a fledgling Texas company $7.3 million for test tubes needed in tracking the spread of the coronavirus nationwide. But, instead of the standard vials, Fillakit LLC has supplied plastic tubes made for bottling soda, which state health officials say are unusable.

The state officials say that these "preforms," which are designed to be expanded with heat and pressure into 2-liter soda bottles, don't fit the racks used in laboratory analysis of test samples. Even if the bottles were the right size, experts say, the company's process likely contaminated the tubes and could yield false test results. Fillakit employees, some not wearing masks, gathered the miniature soda bottles with snow shovels and dumped them into plastic bins before squirting saline into them, all in the open air, according to former employees and ProPublica's observation of the company's operations.

"It wasn't even clean, let alone sterile," said Teresa Green, a retired science teacher who worked at Fillakit's makeshift warehouse outside of Houston for two weeks before leaving out of frustration.

The Federal Emergency Management Agency signed its first deal with Fillakit on May 7, just six days after the company was formed by an ex-telemarketer repeatedly accused of fraudulent practices over the past two decades. Fillakit has supplied a total of more than 3 million tubes, which FEMA then approved and sent to all 50 states. If the company fulfills its contractual obligation to provide 4 million tubes, it will receive a total of $10.16 million.

Officials in New York, New Jersey, Texas, and New Mexico confirmed they can't use the Fillakit tubes. Three other states told ProPublica that they received Fillakit supplies and have not distributed them to testing sites. FEMA has asked health officials in several states to find an alternative use for the unfinished soda bottles.

"We are still trying to identify an alternative use," said Janelle Fleming, a spokeswoman for the New Jersey Department of Health.

Fillakit owner Paul Wexler acknowledged that the tubes are normally used for soda bottles but otherwise declined to comment.

It's my first day

The Fillakit deal shows the perils of the Trump administration's frantic hiring of first-time federal contractors with little scrutiny during the pandemic. The federal government has awarded more than $2 billion to first-time contractors for work related to the coronavirus, a ProPublica analysis of purchasing data shows. Many of those companies, like Fillakit, had no experience with medical supplies.

The United States has lagged behind many European countries in its rate of testing people for the coronavirus, partly because of supply shortages or inadequacies. Epidemiologists say testing is vital to tracking the virus and slowing transmission. In at least one state, the shipment of unusable Fillakit tubes contributed to delays in rolling out widespread testing.

"They're the most unusable tubes I've ever seen," said a top public health scientist in that state, who asked to remain anonymous to protect his job. "They're going to sit in a warehouse and no one can use them. We won't be able to do our full plan."

In a written response to questions, FEMA said it inspects testing products "to ensure packaging is intact to maintain sterility; that the

packing slip matches the requested product ordered, and that the vials are not leaking." It said that "product validation" that medical supplies are effective "is reinforced at the state laboratories."

The agency did not answer questions about the size and lack of sterilization of Fillakit's tubes or about why it sought an alternative use for them.

Fillakit is one of more than 300 new federal contractors providing supplies related to COVID-19. A ProPublica analysis last month found about 13 percent of total federal government spending on pandemic-related contracts went to first-time vendors. FEMA said last month that it only pays for products once they have been delivered, minimizing the risk of wasting taxpayer dollars.

"FEMA does not enter into contracts unless it has reason to believe they will be successfully executed," it said.

How do preforms perform?

Preforms, the small tubes also known in the plastics industry as "baby soda bottles" or "blanks," have a following among elementary school science teachers and amateur scientists, but they don't meet rigorous laboratory standards. They're much cheaper than glass vials and can be sealed off with a soda bottle cap. When inflated with high-pressure air, the soft plastic expands to the size of a 2-liter soda bottle.

The preforms arrive at Fillakit's warehouse in a huge shipping container. The tubes are then shoveled into smaller bins. Workers add the saline solution and screw on caps. The tubes are then loosely piled in bags and sent to FEMA, which forwards them to the states. Typically, test tubes are individually packaged to guard against contamination.

Washington state, an epicenter of the first outbreak of the virus, got more than 76,000 Fillakit vials from FEMA. None can be used.

"They were packaged unusually," said Frank Ameduri, a spokesman for the state Health Department. "Not in a way we're used to seeing, and they were not labeled. Some of them have been sent to our lab for quality control. None of the vials will be used until we've identified what's in them and that they are safe for use."

About 140,000 Fillakit tubes are also shelved in Texas, where officials were slow to roll out testing. The number of confirmed cases in Texas has increased by more than one-third in the past two weeks, according to data gathered by The COVID Tracking Project.

"There were issues with the labeling, and they use saline rather than viral transport medium, so we have not used them for our testing efforts," said Chris Van Deusen, a spokesman for the Texas health department.

The only solution

The US Food and Drug Administration has only validated one solution, known as viral transport medium, as reliable in preserving the coronavirus RNA from decay or destruction by substances in the container. However, because that medium is in short supply, the FDA has also granted an emergency authorization for other products it believes can keep the virus intact for up to three days.

Fillakit has been squirting one of the alternatives into its tubes, phosphate buffered saline, which the FDA says should be placed into "a sterile glass or plastic vial."

A spokeswoman for the Maryland-based Association of Public Health Laboratories, a membership organization that writes best practices and helps connect public health labs with government agencies, said it has heard rumblings about Fillakit's tubes but "nothing deadly."

"The bigger issue is the size of the tubes," said the spokeswoman, Michelle Forman. "They are an unusual shape so they don't fit racks, and we are getting lots of pushback about how difficult it is to work with them from our clinical partners."

Richard Loeb, a contract law expert at the University of Baltimore, said FEMA has the power to claw back money paid to contractors,

remove them from the government's list of approved vendors or refer them to the agency's inspector general.

"It's outrageous enough that they [FEMA] ordered something to test for COVID-19, and they got something that can't be used to test for COVID-19," Loeb said. "I still am a little bit troubled as to why FEMA accepted them. ... They may have stupidly accepted something that was nonconforming."

Law, real estate, and... medical supplies?

Wexler, Fillakit's owner, has a background in law and real estate, not medical supplies. In 2012, the Federal Trade Commission accused Wexler and his telemarketing firm of illegal robocalling, making unauthorized charges to consumers' bank accounts and falsely claiming to be a nonprofit organization. Wexler's firm allegedly misrepresented itself as a credit counseling service for several years, charging customers for work it did not do, according to court records.

Wexler, who denied the charges, settled the case a year later. The settlement banned him from offering debt relief services—but not from being a federal contractor—and imposed a $2.7 million judgment. Fillakit and another Wexler company, Cleargate Labs, operate out of the same warehouse in The Woodlands, a sprawling Houston suburb.

Cleargate describes itself as a "network of primary clinical laboratories" on its website. Last year, the company cold-called an elderly Iowa woman, told her that it was marketing a DNA screening for cancer genes and offered to send her testing supplies in exchange for her Medicare number, the Tampa Bay Times reported. Suspecting a scam, the woman reported the company to local law enforcement. Cleargate did not bill her and was not charged with a crime.

Three former Fillakit employees said that its process was unsterile. Workers shoveled up the tubes from unsanitary surfaces. The liquid that they added to each tube to preserve samples for lab analysis was kept in trays exposed to the air, which was whipped around by large fans.

Standards were compromised in the rush to meet productivity goals, Green said. "At the beginning, they were being picky, saying, 'You have to make sure it's at least 2 milliliters.' And sometimes there were tubes that didn't have any [solution] in there," she said.

"Cuss and scream"

Wexler would come in and "cuss and scream at everybody in this warehouse about how nobody's paying attention to what they're doing," she said. Wexler and Stephen Wachtler, a manager at Cleargate and Fillakit, "were telling us, 'Yeah, we gotta have four bins by lunch,'" Green said. "'We gotta have 10 bins before you leave at 5 o'clock. Work faster, work faster.'"

Green said that few employees at the company had backgrounds in science or medicine. In May, during Fillakit's first week of operations, the company did not provide workers with face masks, she said, raising concerns that fluid from their noses and mouths could land inside the tubes. Later, supervisors did hand out masks but did not require employees to wear them.

On June 10, a ProPublica reporter observed workers, some not wearing masks, standing over snow shovels and bins of tiny soda bottles. Wexler and workers loaded a shipment of tubes into an Enterprise rental truck, which lacked the refrigeration that the Centers for Disease Control and Prevention say is needed to safely transport legitimate testing supplies.

Wexler denied a request to tour the warehouse. Asked about the lack of sterile conditions and the use of soda preforms, Wexler screamed, "What's your problem, man?"

Michelle Hardy, a retired nurse who worked at Fillakit through June 10, said her concerns about contamination were dismissed by Wachtler. He did not respond to requests for comment.

“Is this supposed to be, like, clean?”

“I kind of said to Stephen, ‘Is this supposed to be, like, clean technique, or sterile technique or what?’” Hardy said. “He’s like: ‘No, it’s fine. It’s fine what you’re doing because they’re just testing for COVID, and so if there’s any other bacteria or viruses in there then it’s not going to show up.’”

That’s not true, according to Vjollca Konjufca, an associate professor of microbiology at Southern Illinois University. If Fillakit employees were infected, they might have contaminated the tubes with their own virus, potentially causing false test results, she said.

Konjufca was part of a team at her university that manufactured the viral transport solution validated by the FDA. She said they followed strict protocols to ensure tests aren’t contaminated.

“We filter-sterilize, and then we add antibiotics,” Konjufca said. “The whole work is handled under a biosafety hood ... so it does not allow any sort of air from the room, particulates or whatever, to get into your vials.” There are many ways to mess up medical testing, so careful manufacturing is vital. Some substances in saliva or the plastic vials can damage virus RNA and alter test results, Konjufca said. “You cannot just makeshift use soda bottles to make tubes,” she said. “You have enzymes in there and you have contaminants that can mess up the results.”

https://bit.ly/2BwhVKZ

WHO Is Hoping For Hundreds of Millions of COVID-19 Vaccine Doses Before 2021

With a view to two billion doses by the end of 2021

The World Health Organization said Thursday that a few hundred million COVID-19 vaccine doses could be produced by the end of the year - and be targeted at those most vulnerable to the virus.

The UN health agency said it was working on that assumption, with a view to two billion doses by the end of 2021, as pharmaceutical firms rush to find a vaccine.

WHO chief scientist Soumya Swaminathan said researchers were working on more than 200 vaccine candidates around the world, including 10 that are in human testing. "If we're very lucky, there will be one or two successful candidates before the end of this year," she told a virtual press conference. She identified three groups most in need of the first wave of vaccine doses.

They are front-line workers with high exposure, such as medics and police officers; those most vulnerable to the disease, such as the elderly and diabetics; and people in high-transmission settings, such as urban slums and care homes.

"You have to start with the most vulnerable and then progressively vaccinate more people," Swaminathan said. "We are working on the assumption that we may have a couple of hundred million doses at the end of this year, very optimistically," she said. "We're hoping that in 2021 we will have two billion doses of one, two or three effective vaccines to be distributed around the world. But there's a big 'if' there, because we don't yet have any vaccine that's proven.

"But because of all the investments going into this, let's say we have two billion doses by the end of 2021 - we should be able to vaccinate at least these priority populations."

Pharmaceutical company executives said late last month that one or several COVID-19 vaccines could begin rolling out before 2021, but warned that an estimated total of 15 billion doses would be needed to suppress the virus.

Swaminathan said scientists were analysing 40,000 sequences of the new coronavirus and while all viruses mutate, this one was doing so far less than influenza, and had not yet mutated in the key areas that would alter the severity of disease or the immune response.

Hydroxychloroquine halt

On Wednesday, the WHO decided to halt its trials of hydroxychloroquine as a treatment for hospitalised COVID-19

patients, after evidence from its own work and others that it had no effect on reducing the mortality rate. A decades-old malaria and rheumatoid arthritis drug, hydroxychloroquine has been at the centre of political and scientific controversy.

But Swaminathan said ongoing non-WHO trials were trying to establish whether it might help protect against developing the disease, either before or after exposure to the virus.

It is being tested on healthcare workers and others with heightened exposure to the virus in large, randomised trials.

"Hydroxychloroquine does not have - we know for sure now - does not have an impact" on the mortality rate for hospitalised COVID-19 patients, she said.

"Where there is still a gap is: does it have any role at all in prevention, or in minimising the severity in early infection?

"For prophylaxis... the last word is not yet out," she said.

Hydroxychloroquine was one of four drug or drug combinations in the WHO's Solidarity Trial: randomised clinical trials - considered the gold standard for clinical investigation - spanning hospital patients in several countries.

The trials aim to discover rapidly whether certain drugs slow disease progression or improve survival chances.

https://bit.ly/3fKAw4X

Smartphone app uses voice recordings to detect fluid in the lungs

Smartphone app identifies lung congestion in heart failure patients

Sophia Antipolis - Voice analysis by a smartphone app identifies lung congestion in heart failure patients, allowing early intervention before their condition deteriorates. The small study is presented today on HFA Discoveries, a scientific platform of the European Society of Cardiology (ESC).1

"Speech is personal and as such, very small changes (related to the same person) can be detected - for example, the ability of parents to notice health issues by listening to their kids," said study author Professor Offer Amir, director of the Heart Institute, Hadassah Medical Centre, Jerusalem, Israel. "Today we report results of the first easy to use, non-invasive, personalised heart failure monitoring device. It requires a simple 30-second recording each day, in any language."

Heart failure is one of the leading causes of morbidity and mortality, affecting more than 26 million people worldwide, and is the leading cause of hospitalisation in the US and Europe. Tight surveillance of patients could reduce related hospitalisations and deaths.

In patients with heart failure, the pumping function of the heart is not working as it should. The most common symptom is shortness of breath, which is caused by water congestion in the lungs. Congestion can be life-threatening and early identification is crucial. Lung congestion causes subtle changes in speech patterns, which may be a tool for assessing clinical status. Speech processing is currently used in a number of ways, for example converting text to speech and automatic voice recognition. This study examined the ability of a novel mobile application to distinguish between congested and non-congested states.2

The study included 40 patients admitted to hospital with acute heart failure and lung congestion. Patients were asked to record five sentences into a standard smartphone upon admission and then again just prior to discharge when they were no longer congested. The duration of each recording was 2-5 seconds. The researchers found that the technology successfully distinguished between the congested state at admission and the non-congested state at discharge.

Professor Amir said the system could be used to monitor heart failure patients at home. Physicians prescribe the app, patients

download it to their smartphone and submit voice recordings when they feel well so the app can create a personalised "healthy" model. Each day patients add a recording, which the app compares to the healthy model. Small deviations denoting the start of fluid accumulation generate an alert, which physicians pick up from a designated web portal.

"Those with early signs of lung congestion could receive adjustments to their treatment, thereby preventing the need for hospitalisation," said Professor Amir. "As more speech samples are obtained, the model becomes increasingly sensitive to changes."

He added: "During the current COVID-19 pandemic healthcare professionals are transitioning many outpatient visits for heart failure patients to telemedicine platforms, highlighting the importance of remote monitoring to reduce the risk of exposure to coronavirus."

https://bit.ly/2YkM7li

11-Year-Old Girl Cries Blood in Incredibly Rare Medical Case, Confusing Doctors

Strange and incredibly rare medical phenomenon known as haemolacria

Mike McRae

The sight of blood spontaneously pouring from a child's eyes would shock just about any parent. For one unnamed mother in India, discovering crimson streaks running down her daughter's face was a truly horrifying experience.

She was not in pain. **(Das et al., BMJ Case Reports, 2020)**

A recent case study by opthamologists from the All India Institute of Medical Sciences in New Delhi details the strange and incredibly rare medical phenomenon known as haemolacria in an 11-year-old girl.

According to the girl's mother, the bouts of bloody tears had been a daily occurrence over the previous week. Without pain or intense emotion, red streaks would suddenly trickle down the child's cheeks for several minutes, two to three times each day.

"I am scared about my daughter's health," the mother is reported to have told staff. "The blood coming from her eyes is horrifying. I hope there will not be any similar episodes in future."

The clinic ran a battery of tests to find the cause, coming up empty handed each time. The patient had no history of trauma or illness. Her tear glands appeared to be intact, her blood results were clear, and other than blood cells, the fluids being emitted from her tear ducts weren't unusual in any way.

Experts at the clinic could not come up with a single clue that might help them understand the case. Still, while under observation for the next few days, the child would continue to weep bloody tears.

As rare as cases like hers are, the shocking nature of haemolacria means there's no shortage of examples of the condition through medical history.

The Greek physician Aëtius of Amida might have been referring to something similar when he described childhood diseases that involved blood leaking from the corner of the eye. Other historical medical writers such as Antonio Brassavola and Rembertus Dodoens have also allegedly reported cases associated with menstruation in adolescent women.

In more recent times, reports of bloody tears in young women have drawn a mix of both medical interest and media sensationalism.

Ten years ago, *National Geographic* documented a similar case in a 14-year-old Indian girl named Twinkle Dwivedi, whose condition was famously questioned as a hoax at the hands of the girl's mother.

In 2019, a medical study described a case of haemolacria similar to this recent one, in a 16-year-old girl admitted to a hospital in Bangladesh.

It's possible that in at least some cases, hormones could be playing a role. A 1991 study that tested for hidden or 'occult' blood in the tears of 125 healthy volunteers found traces of blood in nearly one fifth of them, most often during their menstrual cycle.

But the condition is by no means restricted to one gender; just two years ago, a middle-aged man showed up in an Italian emergency department with blood gushing from his eyes.

In that case, a possible cause was found: he appeared to have conjunctival hyperaemia, a slight excess of blood in the membrane covering his eyeball.

There are plenty of other health conditions that could also help explain some incidences of the bloody phenomenon, such as the blood clotting disease haemophilia, or the blood vessel disorder Osler-Weber-Rendu syndrome.

Some medications can also cause blood to leak into tear glands; and of course, there is always the possibility of some kind of trickery.

Unfortunately, in the case of this poor 11-year-old and her upset mother, none of these explanations offer peace of mind. Her diagnosis of haemolacria remains 'idiopathic' (of unknown cause), which more or less means 'one of those strange things'.

The good news is there's no reason to think the tears of blood are a cause for ongoing concern; in fact, they could easily vanish just as strangely and suddenly as they started.

This case study was published in *BMJ Case Reports*.

https://bit.ly/3dkW0E4

Canine bone cancer successfully treated with vaccine made from dog's own tumor

Exciting new method for treating osteosarcoma in dogs

Ruby had always been an active dog.

So when Kristen Constable and her family returned home from vacation and discovered their beloved greyhound limping, they assumed Ruby had simply injured herself while playing. Nothing too serious.

But a trip to the family veterinarian led to a referral to the University of Missouri College of Veterinary Medicine, which resulted in a devastating diagnosis—Ruby had osteosarcoma, a common type of bone cancer in dogs. The prognosis was grim, probably less than a year to live after amputation of the cancerous limb and several rounds of chemotherapy, not to mention all the side effects that go with it.

The Constables were crestfallen.

But Brian Flesner, an assistant professor of oncology, and Jeffrey Bryan, a professor of oncology, at the MU College of Veterinary Medicine and their team offered the family an alternative. Ruby could enroll in a first-of-its-kind study to help advance a patient-specific, precision medicine treatment for bone cancer in dogs.

That was more than three years ago.

Today, 12-year-old Ruby is living proof that Bryan and his research team have advanced an exciting new method for treating osteosarcoma in dogs that can significantly prolong the life of some patients without the use of chemotherapy. By creating a vaccine from a dog's own tumor, MU scientists worked with ELIAS Animal Health, the developers, to target specific cancer cells and avoid the toxic side effects of chemotherapy, while also opening the door to future human clinical trials. The U.S. Food and Drug Administration recently placed the process on the fast track for treatment of a form of cancer in humans called glioblastoma multiforme or GBM.

"What we learned in this dog study—the successes and failures—is already informing what is being done in human studies," Bryan said. "We hope to expand the types of cancer that we treat using this method."

Precision medicine—or treatments tailored to the patient like the vaccine and cell treatment Ruby received—will be a key component of the NextGen Precision Health Initiative by helping accelerate medical breakthroughs for both patients in Missouri and beyond. Precision medicine can be based on someone's own DNA or—in Ruby's case—based on specific tumors growing in one's body.

Bryan will serve as the Cancer Faculty Research Lead at the NextGen Precision Health Institute slated to open in Fall 2021. Today marked a topping-off ceremony for the facility.

Osteosarcoma is not common in humans, representing only about 800-900 new cases a year in the U.S. About half of those cases are reported in children and teens. The disease is much more common in dogs—especially big dogs—with more than 10,000 cases a year in the U.S.

In Bryan's study, researchers used the dog's own tumor to create a vaccine that was then injected into the patient to stimulate anti-tumor lymphocytes. The lymphocytes were then collected and expanded outside the body by ELIAS to create a transfusion of the patient's immune cells.

"Essentially, the lymphocytes are exposed to chemicals that make them very angry and ready to attack the targeted cells," Bryan said. "Then, we transfuse them back into the patient's blood like we would a blood transfusion."

The result: angry lymphocytes hunt down the cancer cells and kill them. The whole process is over in about seven to eight weeks. Overall, the dogs like Ruby who received the vaccine had more than 400 days of remission compared to about 270 days for dogs receiving chemotherapy in a separate study by the National Cancer Institute.In the near future, Bryan said researchers plan to launch a similar patient-specific, precision medicine study aimed at treating melanoma in dogs.

For Constable, the gratitude of still having Ruby is eclipsed only by the joy of watching her race across the yard and leap into the air for a toy.

"Honestly," she said, "you couldn't ask for a better dog than Ruby."

https://wb.md/2V3JLFG

Endos Discuss Diabetic Ketoacidosis in COVID-19, Dexamethasone

Concerns and considerations regarding diabetic ketoacidosis (DKA) in the setting of COVID-19, and dexamethasone

Miriam E. Tucker

A new article in the *Journal of Clinical Endocrinology & Metabolism* (*JCEM*) addresses unique concerns and considerations regarding diabetic ketoacidosis (DKA) in the setting of COVID-19.

Corresponding author Marie E. McDonnell, MD, director of the diabetes program at Brigham and Women's Hospital, Boston, Massachusetts, discussed the recommendations with *Medscape Medical News* and also spoke about the news this week that the corticosteroid dexamethasone reduced death rates in severely ill patients with COVID-19.

The full *JCEM* article, by lead author Nadine E. Palermo, DO, Division of Endocrinology, Diabetes, and Hypertension, also at Brigham and Women's Hospital, covers DKA diagnosis and triage, and emphasizes that usual hospital protocols for DKA management may need to be adjusted during COVID-19 to help preserve personal protective equipment and ICU beds.

"Hospitals and clinicians need to be able to quickly identify and manage DKA in COVID patients to save lives. This involves determining the options for management, including when less intensive subcutaneous insulin is indicated, and understanding how to guide patients on avoiding this serious complication," McDonnell said in an Endocrine Society statement.

What About Dexamethasone for Severe COVID-19 in Diabetes?

The new article briefly touches on the fact that upward adjustments to intensive intravenous insulin therapy for DKA may be necessary in patients with COVID-19 who are receiving concomitant corticosteroids or vasopressors.

But it was written prior to the June 16 announcement of the "RECOVERY" trial results with dexamethasone. The UK National Health Service immediately approved the drug's use in the COVID-19 setting, despite the fact that there has been no published article on the findings yet.

McDonnell told *Medscape Medical News* that she would need to see formal results to better understand exactly which patients were studied and which ones benefitted.

"The peer review will be critical. It looks as if it only benefits people who need respiratory support, but I want to understand that in much more detail," she said. "If they all had acute respiratory distress syndrome (ARDS)," that's different.

"There are already some data supporting steroid use in ARDS," she noted, but added that not all of it suggests benefit.

She pointed to one of several studies now showing that diabetes, and hyperglycemia among people without a prior diabetes diagnosis, are both strong predictors of mortality in hospitalized patients with COVID-19.

"There was a very clear relationship between hyperglycemia and outcomes. We really shouldn't put people at risk until we have clear data," she said.

If, once the data are reviewed and appropriate dexamethasone becomes an established treatment for severe COVID-19, hyperglycemia would be a concern among all patients, not just those with previously diagnosed diabetes, she noted.

"We know a good number of people with prediabetes develop hyperglycemia when put on steroids. They can push people over the edge. We're not going to miss anybody, but treating steroid-induced hyperglycemia is really hard," McDonnell explained.

She also recommended 2014 guidance from Diabetes UK and the Association of British Clinical Diabetologists, which addresses management of inpatient steroid-induced DKA in patients with and without pre-existing diabetes.

Another major concern, she said, is "patients trying to get dexamethasone when they start to get sick," because this is not the right population to use this agent.

"We worry about people who do not need this drug. If they have diabetes they put themselves at risk of hyperglycemia, which then increases the risk of severe COVID-19. And then they're also putting themselves at risk of DKA. It would just be bad medicine," she said.

Managing DKA in the Face of COVID-19: Flexibility Is Key

In the *JCEM* article, Palermo and colleagues emphasizes that the usual hospital protocols for DKA management may need to be adjusted during COVID-19 in the interest of reducing transmission risk and preserving scare resources.

They provide evidence for alternative treatment strategies, such as the use of subcutaneous rather than intravenous insulin when appropriate.

"We wanted to outline when exactly you should consider nonintensive management strategies for DKA," McDonnell further explained to *Medscape Medical News*.

"That would include those with mild or some with moderate DKA...The idea is to remind our colleagues about that, because hospitals tend to operate on a protocol-driven algorithmic methodology, they can forget to step off the usual care pathway even if evidence supports that," she said.

But on the other hand, she also said that in some very complex or severely ill patients with COVID-19, classical intravenous insulin therapy makes the most sense even if their DKA is mild.

The Outpatient Setting: Prevention and Preparation

The new article also addresses several concerns regarding DKA prevention in the outpatient setting.

As with other guidelines, it includes a reminder that patients with diabetes should be advised to discontinue sodium-glucose cotransporter 2 (SGLT2) inhibitors if they become ill with COVID-19, especially if they're not eating or drinking normally, because they raise the risk for DKA.

Also, for patients with type 1 diabetes, particularly those with a history of repeated DKA, "this is the time to make sure we reach out to patients to refill their insulin prescriptions and address issues related to cost and other access difficulties," McDonnell said.

The authors also emphasize that insulin starts and education should not be postponed during the pandemic. "Patients identified as meeting criteria to start insulin should be referred for urgent education, either in person or, whenever possible and practical, via video teleconferencing," they urge.

McDonnell has reported receiving research funding from Novo Nordisk. The other two authors have reported no relevant financial relationships.

J Clin Endocrinol Metab. Published online June 18, 2020. Abstract

https://bit.ly/37QSqcn

Immunity to COVID-19 may wane just 2-3 months after infection, study suggests

It may not mean the end of immunity, but experts know little about immune responses.

Beth Mole

Protective immune responses that build up during a SARS-CoV-2 infection may weaken just two to three months later—particularly if the infection didn't come with any symptoms, a new study suggests. The finding does not necessarily mean that people will no longer be immune to the novel coronavirus after a few months. The lower levels of the immune responses measured in the study may still be enough to thwart the virus, and there are other types of immune responses not examined in the study that play a role in immunity. Overall, there are still many unknowns about potential immunity to SAR-CoV-2 infections, including who is most protected and how long that protection may last.

But the authors of the new study say that their findings are enough to raise more concerns about the potential use of so-called "immunity passports"—documents indicating someone is immune based on past infection. The authors—a team of researchers in Chongqing, China—also suggest that their findings support the continued use of physical distancing and other prevention efforts until we have a clearer understanding of immunity.

"The strength and duration of immunity after infection are key issues for 'shield immunity' and for informing decisions on how and when to ease physical distancing restrictions," the write. Their study appeared Thursday in Nature Medicine.

Case tracking

For the study, the team looked at immune responses in asymptomatic and symptomatic COVID-19 patients shortly after their infection and then two to three months later. The study was small, only including 37 asymptomatic cases, but it is among the first to look at detailed immune responses in people who never develop symptoms in the course of their infection.

The asymptomatic cases were identified by contact tracing from known cases, then isolated in a hospital for the entirety of their infection. The 37 were identified out of a total of 178 cases in the Wanzhou District of Chongqing, for an asymptomatic case rate of 21 percent. Though none developed noticeable symptoms, more

than half had abnormalities in their chest scans during their infection.

The researchers compared their immune responses to those from 37 people who had cases of symptomatic COVID-19. These symptomatic controls were matched to the asymptomatic cases by sex, age, and underlying health conditions.

Asymptomatic cases shed viral genetic material from their throats longer than the symptomatic cases—a median of 19 days compared with 14 days, respectively. However, presence of viral genetic material doesn't necessarily reflect infectious viral particles, so it's unclear if asymptomatic cases were infectious for longer than symptomatic cases.

Troubling declines

About three to four weeks after each case's initial exposure, the researchers looked for antibodies—that is, Y-shaped proteins that the immune system makes to identify and disarm germs the body has already encountered. Overall, the asymptomatic cases had lower levels of anti-coronavirus antibodies than their symptomatic counterparts. They also had lower levels of inflammatory immune signals.

When the researchers looked at antibody levels again eight weeks after each case was discharged from the hospital, they found that both groups had significant declines in antibodies. In the asymptomatic group, 40 percent had no detectable levels of one type of antibody—IgG—while 13 percent of symptomatic cases had no detectable levels. For comparison, in people who had been infected with SARS-CoV-2's relative, SARS-CoV (the coronavirus that causes SARS), researchers have seen sustained IgG levels for more than two years.

Further Reading

Antibody testing suggests immune response post-COVID is very variable

But not all antibodies are equally effective at thwarting invading viruses, like SARS-CoV-2. The most effective are called neutralizing antibodies. The researchers of the new study specifically looked for these antibodies using an engineered pseudovirus designed to mimic SARS-CoV-2 as bait. The researchers found that eight weeks after recovering, neutralizing antibody levels were still present—but they had declined in 81 percent of asymptomatic cases and 62 percent of symptomatic cases. What this means for immunity is not yet clear. Another study published Thursday in Nature found that some neutralizing antibodies present at low levels are also the most potent—potentially hinting that low levels may be enough to protect against infection. But, researchers do not know this yet.

The authors of the Nature Medicine study say that more antibody studies "profiling more symptomatic and asymptomatic individuals are urgently needed to determine the duration of antibody-mediated immunity."

Nature Medicine, 2020. DOI: 10.1038/s41591-020-0965-6 (About DOIs).

https://wb.md/37WuU4X

Headache May Predict Clinical Evolution of COVID-19

Headache may be a key symptom of COVID-19 that predicts the disease's clinical evolution in individual patients, new research suggests.

Erik Greb

An observational study of more than 100 patients showed that headache onset could occur during the presymptomatic or symptomatic phase of COVID-19 and could resemble tension-type or migraine headache.

Headache itself was associated with a shorter symptomatic period, while headache and anosmia (loss of sense of smell) were associated with a shorter hospitalization period.

In a subgroup of participants, headache persisted even after the symptoms of COVID-19 had been resolved.

Investigators note that understanding the pathophysiology of headache in COVID-19 could improve understanding of migraine and other headache disorders.

"It seems that those patients who start early on, during the asymptomatic or early symptomatic period of COVID-19, with headache have a more localized inflammatory response that may reflect the ability of the body to better control and respond to the infection by SARS-CoV2," lead investigator Patricia Pozo-Rosich, MD, PhD, head of the Headache and Craniofacial Pain Unit at Vall d'Hebron University Hospital, Barcelona, Spain, told *Medscape Medical News.*

She presented the findings at the American Headache Society (AHS) Annual Meeting 2020, which was virtual this year because of the COVID-19 pandemic.

Systemic Inflammation

Headache is one of the main symptoms of COVID-19. A recent study of 214 patients with COVID-19 showed that approximately 13% of the participants had headache and 5% had anosmia.

SARS-CoV2 penetrates the cells through the ACE2 receptor, which is present throughout the body.

"SARS-CoV2 enters the body through the nasal cavity and it probably penetrates the nervous system in the periphery through afferent branches of the olfactory and trigeminal nerve," Pozo-Rosich said.

It travels to the lungs and, later, the bloodstream. This generates systemic inflammation that may turn into a cytokine storm. Evidence has identified cortical hyperintensities and olfactory bulb hyperintensities in patients with COVID-19, suggesting that the virus directly infects the central nervous system.

Interleukin-6 (IL-6), one of the main inflammatory molecules, has been proven to be related to COVID-19 and has become a therapeutic target. Levels of IL-6 may be lower and tend to be more stable in patients with both COVID-19 and headache than in patients with COVID-19 only.

The researchers observed 130 patients (51% women; mean age, 54 years) with COVID-19 who were attended by neurologists at Vall d'Hebron. In this group, 74.4% had headache.

Patients with headache tended to be younger than those without headache (mean age, 50 years vs 63 years, respectively) and tended to be women (58.6% vs 29.4%).

Approximately one third of patients with headache had a history of migraine. Most reported mild to moderate pain that resembled tension-type headache. In participants with severe pain and migraine-like features, headache more often began during the asymptomatic phase of COVID-19.

Disease Evolution Predictor?

The investigators followed up on 100 of the 130 patients with COVID-19, of whom 74 had headache. About 38% of these patients had ongoing headache after 6 weeks, which suggests that some patients may develop a new daily persistent headache once a 3-month period has elapsed.

Half of this group had no previous headache history. Headache had been the prodromal symptom of COVID-19 for 21.4% of these patients.

Results showed that headache predicted the clinical evolution of COVID-19. The symptomatic phase of COVID-19 was 7 days shorter for patients with headache than for those without headache.

In addition, the period of hospitalization was 7 days shorter for patients with headache and anosmia compared with patients who had neither headache nor anosmia.

Most therapies, including ibuprofen, candesartan, and anti-CGRP monoclonal antibodies, are safe for treating headache in COVID-19, the investigators note.

"We should just try to initially avoid steroids to avoid interference with the body's reaction to SARS-CoV2," Pozo-Rosich said.

Researchers at Thomas Jefferson University in Philadelphia are currently studying intranasal vazegepant, an anti-CGRP therapy, as a way to potentially blunt the severe inflammatory response in the lungs of patients with COVID-19, she noted, adding that this peptide may have a future role not only in headache, but also in COVID-19.

Historical Link to Viral Infections

Commenting on the study for *Medscape Medical News*, Matthew S. Robbins, MD, associate professor of neurology at Weill Cornell Medicine, New York City, said the findings associating headache with a shorter symptomatic phase of COVID-19 were "interesting."

"Headache is common with mild viral infections. More severe viral infections may simply feature more overwhelming respiratory symptoms and fever that lead to underreporting or underascertainment of headache," said Robbins, who was not involved with the research.

He noted that the finding showing an association of headache and COVID-19 with a younger age and in women "may be related to a higher prevalence of migraine biology in such patients, and being triggered by the virus or the psychological stress associated with it."

Robbins added that viral illnesses have long been associated with new daily persistent headache, "dating back to the early 1980s," when it was first described in association with Epstein-Barr virus. These infections have also been implicated in the progression of migraine to chronic migraine in adolescents.

"In my view, treatment should be aimed at the symptomatic headache type for which new daily persistent headache resembles, regardless of the potential inciting factor," Robbins said.

Pozo-Rosich has received consulting fees from Allergan, Amgen, Almirall, Biohaven, Chiesi, Eli Lilly, Medscape, Novartis, and Teva Pharmaceuticals. Robbins has disclosed no relevant financial relationships.

American Headache Society (AHS) Annual Meeting 2020: Presented June 13, 2020.