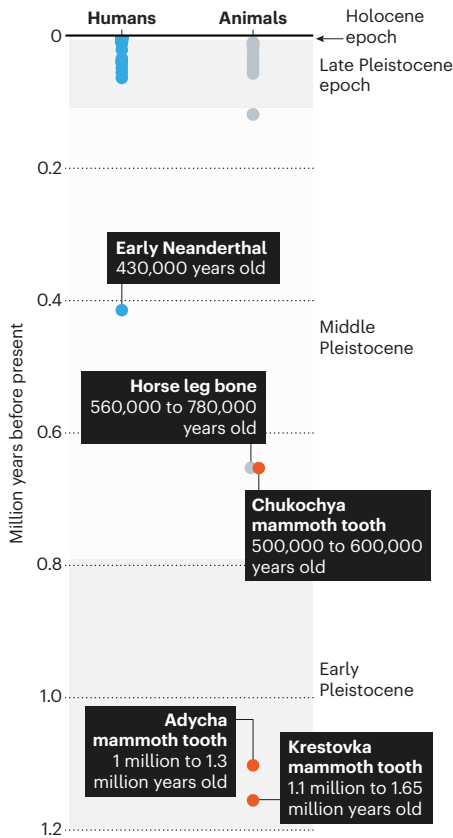


ANCIENT GENOMES

Scientists have for the first time sequenced DNA that is more than one million years old — from mammoths. The oldest DNA sequenced previously dates from between 560,000 and 780,000 years ago.



The upper age bound for the mammoth teeth is based on a genetic dating method; the lower bound is based on the age of the sediments in which the teeth were found.

permafrost always works,” he says.

And, indeed, two of the three molars from Sher’s excavations, retrieved from sediments more than one million years old, contained so little DNA that Dalén says he would have discarded them had they been younger.

But thanks to advances in sequencing technology and bioinformatics, his team managed to obtain 49 million base pairs of nuclear DNA from the oldest sample, found near a village called Krestovka, and 884 million base pairs from another tooth, called Adycha. Analysis of the DNA suggested that the Krestovka sample was 1.65 million years old, and the Adycha sample around 1.3 million (see ‘Ancient genomes’). The third sample, a 600,000-year-old woolly mammoth tooth dubbed Chukochya, produced nearly 3.7 billion base pairs of DNA, more than the length of its 3.1-billion-base-pair genome.

From their shape, the two oldest teeth looked as if they belonged to steppe mammoths, a European species that researchers think pre-dated woolly mammoths and Columbian mammoths (*Mammuthus columbi*), a North American species. But their genomes painted a more complicated picture. The Adycha specimen was part of the lineage

that gave rise to woolly mammoths, but the Krestovka specimen clearly was not.

Dalén’s team found that it belonged to an entirely new lineage. “We can’t say it’s a different species, but it sure looks like it,” he says. Although the Krestovka sample is from Russia, he suspects the lineage became isolated from other steppe mammoths in North America. The team found that Columbian mammoths trace half their ancestry to the Krestovka mammoth lineage, and the other half to woolly mammoths. Dalén estimates that the two lineages mixed more than 420,000 years ago.

The idea that new species can form through mixing — and not just splitting from a single parent species — is gaining currency. But this is the first evidence for ‘hybrid speciation’ from ancient DNA, says Orlando. “This is amazing.”

Hendrik Poinar, an ancient-DNA specialist at McMaster University in Hamilton, Canada, says different mammoth species probably routinely hybridized when glacial expansion brought them together. His team has found evidence that later woolly and Columbian mammoths occasionally interbred.

Even though researchers have long been expecting a million-year-old genome, crossing that threshold is important, says Viviane Slon, a palaeogeneticist at Tel Aviv University in Israel. “There’s a difference between what we think is possible and actually showing it.”

Tom van der Valk, a bioinformatician at the University of Uppsala in Sweden who led the tooth work with evolutionary biologists Patrícia Pečnerová and David Díez-del-Molino at the SMNH, hopes it will encourage other labs. “It is a symbolic barrier that I hope can inspire and motivate other groups that have ideas about really deep-time sequencing.”

By crossing the million-year threshold, ancient-DNA researchers might also access early histories of other mammals, says Dalén. Very old samples of musk oxen, moose and lemmings are now on his lab’s radar.

The mammoth DNA does not represent the oldest biomolecular information from fossils. In 2016, researchers reported protein sequences from 3.8-million-year-old ostrich eggshells from Tanzania³, and in 2019, another team decoded proteins from a 1.77-million-year-old rhinoceros tooth from Georgia⁴. Protein sequences tend to be much less informative about an organism’s ancestry than DNA. But protein molecules are much harder, so researchers can use them to glean insights from very old fossils found in places with no permafrost. The ostrich and rhino samples both come from archaeological sites famous for hominin remains.

The chances of finding million-year-old remains of ancient human relatives in the permafrost are very low, researchers say. But Dalén thinks the right environment, such as a deep cave, could yield samples that old. Neanderthal remains from a Spanish cave dated to 430,000 years ago represent the oldest DNA from an ancient human relative discovered so far⁵. “Finding a hominin in the sort of ideal context for preservation as permafrost would be a dream,” says Slon.

As for the likely age limit of ancient DNA, Dalén says 2.6 million years is the limit in permafrost. “Before that, it was too warm.”

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SOURCE: DAVID DÍEZ-DEL-MOLINO

COVID VACCINES AND SAFETY: WHAT THE RESEARCH SAYS

As the vaccines are rolled out, researchers are learning about the extent and nature of side effects.

By Ariana Rimmel

As people around the world receive COVID-19 vaccines, reports of temporary side effects such as headaches and fevers are rolling in. Much of this was expected — clinical-trial data for the vaccines authorized so far suggested as much. But now that millions of people have been vaccinated, compared with the thousands enrolled in early studies, reports of

some rare, allergic reactions are surfacing, and questions are arising about whether any deaths are linked to the shots.

There is no question that the current vaccines are effective and safe. The risk of severe reaction to a COVID-19 jab, say researchers, is outweighed by the protection it offers against the deadly coronavirus. *Nature* looks at what scientists are learning about the frequency and nature of side effects as huge numbers of people report their reactions to physicians and



Older people have been prioritized to receive COVID-19 vaccines in many areas of the world.

through safety-monitoring systems, such as smartphone apps.

How many people experience common side effects from COVID-19 vaccines?

For the two available messenger RNA (mRNA) vaccines – one made by Moderna in Cambridge, Massachusetts, and the other developed through a collaboration between Pfizer in New York City and BioNTech in Mainz, Germany – a significant proportion of people experience non-serious reactions, such as injection-site pain, headache and fatigue. These vaccines deliver bits of RNA that code for coronavirus proteins, which the body mounts a response against.

According to data from the US Vaccine Adverse Event Reporting System (VAERS), about 372 out of every million administered doses of the mRNA vaccines lead to a report of non-serious reactions. This number is lower than would be expected from clinical-trial data, which indicated that at least 80% of people would experience injection-site pain. Researchers running trials monitor vaccine recipients closely and record every reaction. VAERS, meanwhile, relies on health-care workers and vaccinated individuals to self-report side effects.

So far, reactions to the mRNA vaccines are similar. These vaccines are administered in a two-dose regimen: the first shot triggers an immune reaction, and the second is a ‘booster’ that strengthens the body’s ability to fight the coronavirus. For the Pfizer–BioNTech vaccine, which has been in use longer than the Moderna vaccine and therefore has generated more data, side effects increase with the second dose (see ‘Tracking side effects’).

In the United Kingdom, more than three million doses of another vaccine, developed by the University of Oxford and pharmaceutical firm AstraZeneca, have been doled out. This vaccine, which also requires a two-dose regimen, contains an inactivated cold-causing adenovirus with genetic instructions for making coronavirus proteins to trigger immunity. According to UK safety-monitoring system the Yellow Card Scheme, about 4,000 doses out of every million administered lead to adverse reactions. Again, clinical-trial data suggest that a higher frequency is more accurate: around 50% of participants had injection-site pain, headache or fatigue, according to data reported to the European Medicines Agency (EMA).

“I got the vaccine, and 6 hours later, I had chills, a high fever, muscle aches, and I went to bed for 24 hours.”

Safety data for vaccines rolling out outside Europe and North America, such as those in China, are harder to come by. Preliminary data from clinical trials of the adenovirus-based Sputnik V vaccine in Russia suggest that its most common side effects include influenza-like symptoms and injection-site reactions¹.

How does that compare with side effects from an annual flu shot?

At least for the mRNA vaccines, physicians are seeing more side effects than for flu shots, says Helen Chu, an infectious-disease specialist at the University of Washington School of Medicine in Seattle, who directs the Seattle Flu Study. In clinical trials for the Pfizer–BioNTech

vaccine, for instance, 75% of participants reported a ‘systemic reaction’, such as headache, fever or chills. In a clinical trial for the common flu vaccine Flubok Quadrivalent, around 34% of participants aged 18–49 had a systemic reaction. Side effects were even less frequent in study participants who were at least 50 years old.

Chu says the mRNA COVID-19 vaccines generate a particularly strong immune response that increases the risk of side effects, although this also means that the vaccines are working. She notes that her second dose of the Pfizer–BioNTech vaccine made her ill. “I got the vaccine, and 6 hours later, I had chills, a high fever, muscle aches and I went to bed for 24 hours,” she says. “Then by 36 hours later, it was totally over and I was back to normal.” But Chu would rather be temporarily ill from a vaccine than deal with COVID-19, “a potentially mortal disease that could kill me”, she says.

Have investigations linked any deaths to a COVID-19 vaccine?

Although some have questioned whether the vaccines have led to deaths, no deaths have been directly attributed to a COVID-19 jab. After 33 older residents in care homes in Norway died within 6 days of receiving the Pfizer–BioNTech vaccine, investigations by both the Norwegian Medicines Agency and the World Health Organization concluded that these deaths were in line with normal death rates in this age group and that the vaccine is still safe for older people. India’s Ministry of Health and Family Welfare reported 27 deaths in the country, but none of these has been linked directly to a COVID-19 vaccine, either.

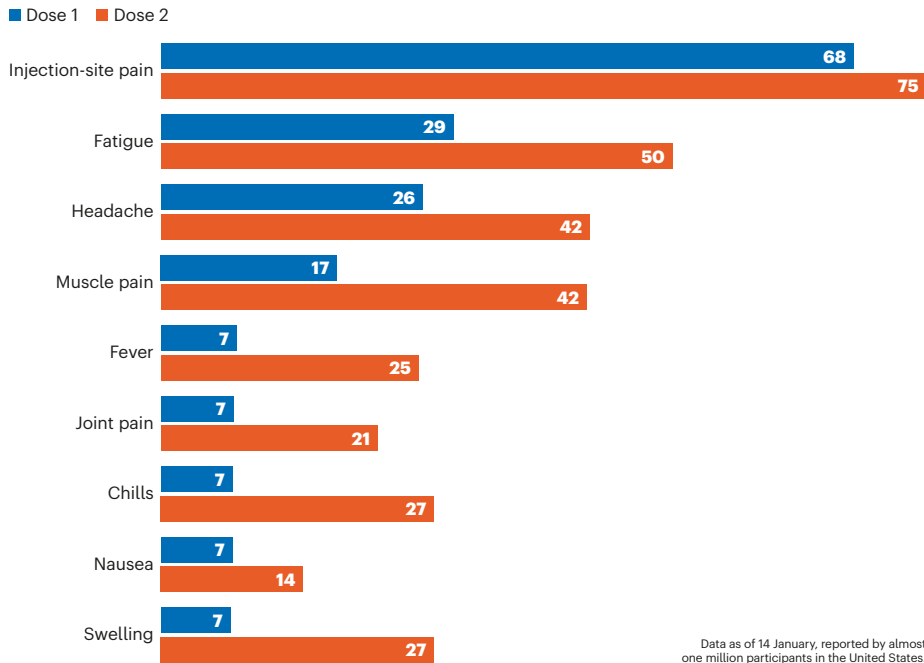
It is “extremely difficult” to link a death to the vaccine itself, says Hilda Bastian, a writer and scientist who specializes in validating evidence-based health claims. That is partially because the deaths reported so far have occurred days or weeks after an injection, making it hard to rule out other circumstances. Another reason is that clinicians have been prioritizing vaccines largely for a population of older people with underlying health conditions. Most of those who have died after vaccination have been in this group, according to reports from the United Kingdom and the United States.

What do researchers know about the rare, but severe, allergic reactions to the vaccines?

The Moderna vaccine elicits about three anaphylactic reactions per million doses administered, and the Pfizer–BioNTech vaccine triggers five reactions per million doses, according to VAERS data. This is a higher rate than for most other vaccines – including annual flu shots, which trigger anaphylaxis for only one out of every million doses administered². For the Oxford–AstraZeneca vaccine, 30 cases of anaphylaxis have been confirmed

TRACKING SIDE EFFECTS

According to data collected by the US Center for Disease Control and Prevention's smartphone app V-safe, a higher percentage of people reported side effects after receiving the second dose of the Pfizer-BioNTech vaccine than after receiving the first dose. Injection-site pain was most common.



overall so far, out of a little more than 3 million administered doses. Vaccine specialists expect that these rates might change as more shots are administered.

Although some people have required hospitalization, all have fully recovered. Public-health officials advise people with a history of allergies to any of the vaccines' ingredients not to get a COVID-19 jab.

Unlike COVID-19, anaphylaxis is treatable with drugs such as adrenaline (epinephrine) if caught quickly, says Paul Offit, a vaccine and infectious-disease specialist at the Children's Hospital of Philadelphia in Pennsylvania, who participated in the US Food and Drug Administration advisory-committee meetings that led the agency to authorize both mRNA vaccines. "I wish that SARS-CoV-2 could be immediately treated with a shot of epinephrine!" he says.

Most of the people who experienced anaphylaxis had reacted to other substances before: about 80% of people who reacted to the Pfizer-BioNTech vaccine, and 86% to the Moderna vaccine, had a history of allergies, according to the US Centers for Disease Control and Prevention.

The specific cause of the anaphylactic reactions remains unknown, but the US National Institute of Allergy and Infectious Diseases told *Nature* in an e-mail that the agency has designed a clinical trial to determine the underlying mechanism, but did not specify when the trial would begin.

What could be causing the allergic reactions?

Some researchers have had their eye on polyethylene glycol (PEG) as the anaphylaxis-causing

agent in the mRNA vaccines. The Moderna and Pfizer-BioNTech vaccines use hollow lipid nanoparticles to store and then deliver their mRNA payload to cells. PEG is linked to the lipids in these particles and, under normal circumstances, helps them to sneak by the immune system. Although PEG-linked molecules are found in a variety of products, such as

laxatives and gout medicines, they have been known to cause allergic reactions³.

Follow-up studies in people who experienced anaphylaxis could help to determine whether PEG is the culprit, says Samuel Lai, a pharmaco-engineer at the University of North Carolina at Chapel Hill. If blood samples from these people contain anti-PEG antibodies, it could be an indicator, says Lai, but it is as yet unclear how long these proteins remain in the bloodstream after anaphylaxis.

Vaccines that don't use PEG – such as the not-yet-authorized shot from Johnson & Johnson, which also uses an adenovirus to trigger immunity to the coronavirus – might be a way to vaccinate people with a sensitivity to the polymer, he adds.

Because mRNA vaccines have shown such promise, Ulrich Schubert, a polymer scientist at the University of Jena in Germany, thinks now is the time to invest in developing vaccine-compatible polymers that don't cause allergic reactions. At the German Research Foundation-funded collaborative research centre PolyTarget, where Schubert works, these studies are already in progress. "If we want to be ready for the next pandemic – which will come – we have to start now," he says.

Additional reporting by Smriti Mallapaty and Amy Maxmen.

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QUANTUM NETWORK IS STEP TOWARDS ULTRASECURE INTERNET

Experiment connects three devices, demonstrating a key technique that could enable a quantum internet.

By Davide Castelvecchi

Physicists have taken a major step towards a future quantum version of the Internet by linking three quantum devices in a network. A quantum internet would enable ultrasecure communications and unlock scientific applications such as new types of sensor for gravitational waves, and telescopes with unprecedented resolution. The results were reported on 8 February on the arXiv preprint repository (M. Pompili *et al.* Preprint at <https://arxiv.org/abs/2102.04471>; 2021).

"It's a big step forward," says Rodney Van Meter, a quantum-network engineer at Keio University in Tokyo. Although the network doesn't yet have the performance needed for practical applications, it demonstrates a key technique that will enable a quantum internet to connect nodes over long distances.

Quantum communications exploit phenomena that are unique to the quantum realm – such as the ability of elementary particles or atoms to exist in a 'superposition' of multiple simultaneous states, or to share an 'entangled' state with other particles. Researchers had demonstrated the principles