For our sixth annual Articles of the Year roundup, we considered all Original Investigations, Special Communications, and Brief Reports published across the JAMA Network from October 1, 2021, through September 30, 2022, and ranked them based on online views. Editors from each journal then provided insight into why these articles caught readers’ attention.

COVID-19 dominated the list for the third year in a row.

“The most viewed articles in 2022 reflect the continued interest in the effects of SARS-CoV-2 infection and vaccines and treatments for COVID-19, as well as other science important for human health,” said Kirsten Bibbins-Domingo, PhD, MD, MAS, editor in chief of JAMA and the JAMA Network.

Other popular topics ranged from the amount of exercise needed to combat depression to how worldwide cancer rates have changed since 2010.

Here, we present the top-viewed article of each JAMA Network journal in order of the most online views.

**US Reports of Myocarditis Following mRNA-Based COVID-19 Vaccination**

JAMA

Original Investigation

Published January 25, 2022

The top-viewed article in our flagship journal was about a hotly debated issue surrounding COVID-19: the risk of heart inflammation associated with messenger RNA (mRNA)-based vaccines. Although vaccinated adolescent males and young men were most at risk of developing myocarditis, the chances were slim.

“This risk should be considered in the context of the benefits of COVID-19 vaccination,” the research team concluded.

In an analysis of about 192 million people in the US who received mRNA-based COVID-19 vaccines from December 2020 through August 2021, 1626 probable or confirmed myocarditis cases were reported within a week of vaccination. Most cases occurred among male patients aged 12 to 24 years after receiving a second dose. Even in this group, however, the risk of developing myocarditis was rare. Those at highest risk were male adolescents aged 16 to 17 years, whose myocarditis rate after a second dose was 105.9 per million doses of the BNT162b2 vaccine.

There were no confirmed myocarditis-related deaths among patients aged 30 years or younger who did not have another identifiable cause of death.

“The introduction of new vaccines should be accompanied by strong scientific evaluation of potential adverse health reports that may be associated with vaccination and, importantly, such reports should be placed in context with the benefits of effective vaccines,” Bibbins-Domingo said.

**Ivermectin for COVID-19 Disease Progression in High-risk Adults**

JAMA Internal Medicine

Original Investigation

Published February 18, 2022

This randomized clinical trial carried out in Malaysia put another nail in the coffin for ivermectin treatment against COVID-19. Taking 0.4 mg of ivermectin per kilogram of body weight for 5 days within the first week of developing COVID-19 did not prevent the disease from progressing into a severe case. In fact, the anti-parasitic drug was associated with a...
higher—albeit statistically insignificant—risk of severe disease.

Participants were high-risk adults being treated for mild to moderate COVID-19. The cohorts included 249 patients in a control group who were treated only with standard care, such as laboratory tests and chest imaging, and 241 patients who were treated with both standard care and ivermectin. Overall, 21.6% of patients treated with ivermectin and 17.3% of patients in the control group developed a severe case of COVID-19 that required supplemental oxygen. And there were no significant differences between the groups when it came down to intensive care unit (ICU) admission, mechanical ventilation, or death.

The trial helped to inform the National Institutes of Health’s COVID-19 treatment guidelines, which recommend against using ivermectin for the disease outside of clinical trials.

“There have been multiple randomized controlled trials that do not support the use of ivermectin for patients with COVID-19,” noted Robert Steinbrook, MD, editor at large of JAMA Internal Medicine. “Nonetheless, the interest in the drug as a potential treatment for COVID-19 has remained strong.”

**SARS-CoV-2 Vaccination and Myocarditis in Nordic Countries**

**JAMA Cardiology**

**Original Investigation**

**Published April 20, 2022**

Similar to JAMA’s top-viewed article, this year’s most popular article in JAMA Cardiology also investigated heart inflammation and COVID-19 vaccination, but this time in Nordic countries. (A study of vaccine-associated myocarditis also nabbed the top spot in JAMA’s cardiology journal last year.) The Nordic study confirmed the small odds of developing inflammatory heart disease, such as myocarditis and pericarditis, after receiving mRNA-based vaccines.

“The low risk of myocarditis following vaccination needs to be balanced against the known benefits of protecting against severe COVID-19 disease,” emphasized the journal’s Editor Robert O. Bonow, MD, MS.

To evaluate the risk of heart inflammation after SARS-CoV-2 vaccination, the authors conducted a meta-analysis that included national health care records from millions of patients residing in Denmark, Finland, Norway, or Sweden; 81% of individuals had been vaccinated by the end of the study.

Receiving 2 doses of the same vaccine was associated with an increased risk of myocarditis and pericarditis within 28 days of the second jab—especially among male patients aged 16 to 24 years. But in their study of 23.1 million patients’ records, the authors only identified 1077 myocarditis cases and 1149 pericarditis cases.

**Reported Adverse Events From Placebos in COVID-19 Vaccine Trials**

**JAMA Network Open**

**Original Investigation**

**Published January 18, 2022**

This study found that about one-third of individuals who received a placebo in a COVID-19 vaccine trial reported adverse events, mostly headaches and fatigue. Also known as nocebo responses, these effects often result from expecting adverse reactions to a treatment.
Olfactory Tissue Damage in Patients With COVID-19

JAMA Neurology

Original Investigation

Published April 11, 2022

A common symptom of COVID-19 is loss of smell, so a team of researchers set out to determine whether SARS-CoV-2 infection can injure the olfactory system. Autopsies revealed that patients who died with COVID-19 were more likely to have injured olfactory blubs and tracts than a control group of deceased individuals who were matched for age and disease severity. Among the 23 patients with COVID-19, olfactory axon damage and microvascular pathology were worse in individuals whose medical records noted an altered sense of smell.

The virus was only detected in olfactory tissue from 3 patients with confirmed SARS-CoV-2 infections, which suggests that direct viral infection didn’t cause the axon and microvascular damage.

“The article also provides a window into COVID-19-related injury to the nervous system at large,” remarked JAMA Neurology Editor S. Andrew Josephson, MD. “Since direct viral invasion was not the main cause, treatment and prevention can focus on secondary injury and the inflammatory and other cascades that follow viral infection rather than viral suppression alone.”

Birth During the COVID-19 Pandemic and Neurodevelopmental Delays

JAMA Pediatrics

Original Investigation

Published January 4, 2022

Last year, the top-viewed article in JAMA Pediatrics was about maternal and neonatal risks of developing COVID-19 during pregnancy. In the study that made the list this year, researchers investigated whether prenatal exposure to SARS-CoV-2 is linked to neurodevelopmental delays by age 6 months.

“The effects of COVID on children extend far beyond direct medical effects,” explained JAMA Pediatrics Editor Dimitri A. Christakis, MD, MPH. “COVID infection did not appear to directly impact child development;” he said of the study, “but the pandemic may have.”

The authors compared neurodevelopmental differences among 2 cohorts of infants born at the same hospital in New York City. One group was born before the pandemic, between November 2017 and January 2020, and the other was born during the pandemic, between March and December 2020. On questionnaires completed by their mothers, infants born during the pandemic had significantly lower scores for motor and social skills than infants born before the pandemic hit, irrespective of in utero exposure to SARS-CoV-2 infection. Maternal stress related to the pandemic could be a potential underlying mechanism, according to the authors.

Still, the study had limitations. “Although a true experimental design would not be possible, the findings need to be put in a broader context and we need to see if they are replicated,” Christakis pointed out. “Regardless, the need to focus on the developmental and mental health impacts of the pandemic remain.”

How the Global Burden of Cancer Changed From 2010 to 2019

JAMA Oncology

Original Investigation

Published December 30, 2021

For this systematic analysis, researchers quantified incidence and mortality for 29 cancers across 204 countries and territories. The authors estimated that 23.6 million new cancer cases and 10 million cancer deaths occurred in 2019—representing a 26.3% increase in incidence and a 20.9% increase in mortality since 2010.

Mary L. Disis, MD, editor of JAMA Oncology, emphasized that the largest increase of cancer burden was observed in “countries with lower social and economic development, highlighting the global disparities in cancer treatment and prevention.”

According to Disis, the comprehensiveness of the analysis is a notable aspect of the study. “The reader has the opportunity to see at a glance which cancers are decreasing in incidence and which are increasing depending on location,” she said. “This provides a great guide for highlighting new research questions—but more importantly—identifying locations where specific interventions to limit the development of cancer should be deployed.”
practitioners encouraging any increase in physical activity.”

**How Weight Loss Surgery Is Associated With COVID-19 Risk and Severity**

**JAMA Surgery**

Original Investigation

Published December 29, 2021

Obesity increases the risk of developing a severe COVID-19 case that requires ICU care or mechanical ventilation. The authors of this cohort study investigated whether successful weight loss achieved with surgery lowered the risk and severity of COVID-19 infection in patients with obesity. Weight loss surgery did not reduce the chances of SARS-CoV-2 infection, but it was associated with less severe COVID-19.

The study consisted of 2958 patients who had undergone weight loss surgery between January 1, 2004, and December 31, 2017, and 8851 patients in a control group who did not receive a surgical intervention. Although the rates of SARS-CoV-2 infection were similar among both cohorts, patients who had undergone the surgery lost 18.6% more weight and experienced a 49% lower risk of hospitalization, a 63% lower risk of needing supplemental oxygen, and a 60% lower risk of developing severe COVID-19.

“This paper demonstrated an additional benefit of weight loss surgery that some may not have predicted,” said Melina R. Kibbe, MD, editor of *JAMA Surgery*. “While the benefits of weight loss surgery have been demonstrated and are undeniable with respect to reducing comorbidities and improving overall health, widespread adoption of weight loss surgery remains to be achieved.”

**Theophylline as Treatment for COVID-19-Related Olfactory Dysfunction**

**JAMA Otolaryngology–Head & Neck Surgery**

Original Investigation

Published July 7, 2022

Another popular article about COVID-19-related loss of smell discussed the use of theophylline for olfactory dysfunction.

Unsurprisingly, “this article was popular with physician readers and the public because of the large number of people who experienced olfactory dysfunction after COVID-19,” said corresponding author Jay F. Piccirillo, MD, who is also editor of *JAMA Otolaryngology–Head & Neck Surgery*. While most individuals recover their sense of smell, not all are so lucky, he added: “For those who experienced chronic loss of smell, there are no known effective treatments.”

Enter theophylline, a phosphodiesterase inhibitor that, according to the study’s authors, “has been theorized to promote neural olfactory signaling and sensory axonal regeneration.”

In a small, phase 2 randomized clinical trial involving adults diagnosed with chronic COVID-19-related olfactory dysfunction, adding 400 mg of theophylline to saline nasal irrigation twice a day for 6 weeks appeared to be safe. Ten of 23 participants (43%) in the placebo group—who received 500 mg of lactose powder for their saline rinse—reported an improvement in olfactory function, compared with 13 of 22 participants (59%) who used the theophylline treatment.

The authors acknowledged that evidence of theophylline’s efficacy remains inconclusive and that larger studies are needed before using theophylline as an outpatient treatment for COVID-19-related olfactory dysfunction.

**Factors Associated With Health Care Overuse in the US**

**JAMA Health Forum**

Original Investigation

Published January 14, 2022

A cross-sectional analysis of 676 US health systems using Medicare claims from 2016 to 2018 concluded that higher bed counts, more physician practice groups, and fewer primary care physicians in hospitals and their affiliated outpatient clinics were linked to overuse of health care. Systems owned by investors or that didn’t include a major teaching hospital were also more likely to overuse care.

“Overuse of low-value services is a growing concern for patients and for public and private insurers that bear the costs of these services,” said John Z. Ayanian, MD, MPP, editor of *JAMA Health Forum*. “This study presented a measurement tool, the Overuse Index, and key findings that insurers and health systems can use to track rates of overuse, thereby supporting efforts to limit overuse of these low-value services, reduce excess costs, and promote higher-value care.”

The authors had previously created the Overuse Index. Updated for this study, the publicly available tool may also inform clinical practice and future research.

**Controlling Childhood Myopia With Aspherical Lenslet Spectacles**

**JAMA Ophthalmology**

Original Investigation

Published March 31, 2022

Both this year and in 2021, the top-viewed study in *JAMA Ophthalmology* examined myopia among children.

“Myopia is a silent epidemic, growing throughout the world,” said Neil M. Bressler, MD, the journal’s editor. “Myopia control interventions are a major public health need, and randomized clinical trials evaluating new treatments in this field could have profound influence on vision health and blindness.”

The 2-year results of this randomized clinical trial of 157 children in China diagnosed with mild to moderate myopia showed that those assigned to wear aspherical lenslet spectacles had 55% less myopic progression and 51% less axial length growth than children who wore single-vision spectacle lenses. Whereas single-vision spherical spectacle lenses are curved and have the same focus distribution across each lens, aspherical lenslet spectacles have flatter and thinner lenses. (The latter were originally designed to combat spherical aberration, when light rays do not focus evenly across the lens.)

The findings are good news for kids with myopia, assuming they regularly wear their eyeglasses. Scientists aren’t sure whether myopia would rebound if aspheric spectacle use were discontinued, according to Bressler.

“Since these lenslets can cause glare at their edges and degrade vision through the aspheric portion of the lens when the child’s gaze wanders away from looking straight ahead, it’s unknown how compliance with wearing these spectacles would be,” he explained. “Furthermore, the mean age at enrollment for the children in this randomized clinical trial was 10 years, when much of the rapid myopic progression has occurred. It is unknown if there would be different effects in younger children or if compliance would change.”
Using Upadacitinib for Moderate to Severe Atopic Dermatitis
JAMA Dermatology
Original Investigation
Published March 9, 2022

Long-term oral treatments for moderate to severe atopic dermatitis are limited, but upadacitinib—a selective Janus kinase (JAK) inhibitor that’s often prescribed for rheumatoid and psoriatic arthritis—could become an option.

“Previous data published in JAMA Dermatology showed that upadacitinib is superior to what was previously considered first-line, the IL4-receptor inhibitor dupilumab,” the journal’s Editor Kanade Shinkai, MD, PhD, said. However, she pointed out, most of these studies examined drug safety over the course of just a few months and under half a year at best.

In this follow-up analysis of 2 ongoing phase 3 clinical trials involving 1609 adults and adolescents, researchers found that taking 15 mg to 30 mg of upadacitinib once a day was safe and effective for at least 52 weeks. The treatment discontinuation rate was low as well.

This wasn’t the journal’s only study published in 2022 that supports the drug’s use. A network meta-analysis “was updated earlier this year to put upadacitinib at the forefront of atopic dermatitis systemic immunosuppression,” Shinkai said. “Because the JAK-inhibitor class is a newer treatment for atopic dermatitis, having data showing its safety and durable clinical benefit at 52 weeks is both important and reassuring.”

Note: Source references are available through embedded hyperlinks in the article text online.