In linking the inflammatory syndrome to COVID-19, “We’re going on more than just a hunch,” says Jesse Papenburg, a pediatric infectious disease specialist at Montreal Children’s Hospital, in a city that’s seen about 25 children with the condition. Kawasaki disease is rare, ordinarily affecting just one to three in every 10,000 children in Western countries, though it’s more common in children with Asian ancestry. The spikes recorded so far, in COVID-19 hot spots like northern Italy and New York City, track the novel coronavirus’ march around the world. And although a minority of these children test positive for SARS-CoV-2, a study published in The Lancet by a team in Bergamo, Italy, reported that eight of 10 children with the Kawasaki-like illness had antibodies to the virus, indicating they had been infected. Positive antibody tests have been reported in sick children elsewhere, too.

“It was obvious that there was a link,” says Lorenzo D’Antiga, a pediatrician at the Papa Giovanni XXIII Hospital who led the study. The new coronavirus can elicit a powerful immune response, which he thinks may explain why shock and a massive immune reaction called a cytokine storm are more common in the COVID-19–linked cases than in textbook Kawasaki disease. And a time lag between infection and the Kawasaki-like illness could explain why many of the affected children show no evidence of the virus. The immune system’s overreaction may unfold over weeks, though virus could also be hiding somewhere in the body.

“There’s clearly some underlying genetic component” that puts a small number of children at risk, says Tom Maniatis, founding director of Columbia University’s Precision Medicine Initiative. New York state is investigating at least 157 cases, and Maniatis is also CEO of the New York Genome Center, which is pursuing whole-genome sequencing of affected children and their parents, as well as sequencing the virus found in children, with family consent. Finding genes that heighten risk of the illness or of developing a severe case could point to better treatments or help identify children who may take a sudden turn for the worse.

Genetics may also help explain a puzzle: why the illness hasn’t been reported in Asian countries, even though Kawasaki disease is far more common in children with Asian ancestry. The virus’ own genetics may be important; an analysis last month indicated that the predominant viral variant in New York was brought by travelers from Europe. It’s also possible that the Kawasaki-like illness is so rare that it only shows up in COVID-19 hotspots. “The areas that have been hardest hit by coronavirus are the areas reporting this syndrome now,” says Alan Schroeder, a critical care physician at Lucile Packard Children’s Hospital at Stanford University, which has seen one potentially affected child, a 6-month-old baby, who recovered quickly.

Yeung is also pursuing ways to flag children with COVID-19 who are at risk of this complication. She co-leads an international consortium that’s banking blood from affected children, both before and after treatment, and screening for various markers, including the cytokine molecules that indicate a revved-up immune system. The group is also searching for gene variants known to predict poor outcomes in Kawasaki disease. “There’s also core COVID stuff that needs to be measured,” Yeung says, such as markers of heart function and levels of D-dimer, a protein fragment in the blood that indicates a tendency toward clotting and that surges in many sick adults.

A European Union Horizon 2020 project called DIAMONDS, originally designed to improve diagnosis of pathogens in children with fevers, is recruiting children across Europe with the Kawasaki-like complication, along with those who have run of the mill COVID-19 symptoms. Scientists will study blood for pathogens—not just SARS-CoV-2—and the behavior of immune cells such as T cells and B cells.

“We have to do a deep dive into the immunology of those patients,” says Elie Haddad, a pediatric immunologist and scientist at Sainte-Justine University Hospital Center who, with Yeung and Susanne Benseler at Alberta Children’s Hospital, is leading a Canadian research effort on the new syndrome. These deep dives may also clarify the immune system chaos seen in many sick adults. Children are “cleaner,” Haddad points out—they’re less likely to have other health burdens, such as diabetes or high blood pressure, that can make it harder to tease out the virus’ impact on the immune system.

Last week, young adults with possible cases of the condition were identified, suggesting it may not be limited to children. A global effort studying COVID-19 in adults, called the International Severe Acute Respiratory and Emerging Infection Consortium, will look at adults’ clinical data and blood samples, Whittaker says, “to see, is this a uniquely pediatric problem?”

Eager as they are to understand this new face of the pandemic, doctors want to avoid overstating the hazards. “We need to identify early and we need to intervene early” in treating these children, Yeung says. But she also urges calm. “The kids we’re seeing so far,” she stresses, “they respond to the treatments we’re giving.”
New tools aim to tame pandemic paper tsunami

Researchers harness AI and old-fashioned expertise to glean findings, but face challenges

Despite a global effort to persuade publishers to make all papers relevant to COVID-19 immediately free, as many as 20% of new papers are still behind paywalls, a recent study found, off-limits to some readers and AI analysis. Some of the new search tools, meanwhile, aren’t very user-friendly or are little known. And many researchers are skeptical that the tools will tell them what they really want to know: What is the work’s quality? “People tend to oversell and put up papers with data that do not support their conclusions,” Sheahan says. “It’s a mess.”

One line of work got a boost on 16 March, when the White House Office of Science and Technology Policy announced the launch of the COVID-19 Open Research Dataset (CORD-19), a trove that now includes more than 128,000 peer-reviewed articles and preprints, including studies of virology and coronaviruses dating back decades. To create the archive, some of the largest groups active in machine learning—including Google, the Chan Zuckerberg Initiative, and the Allen Institute for AI—collaborated with the National Institutes of Health and others to use search methods, such as natural language processing, to scan the scientific literature for relevant terms. The team also converted PDF files into a form readable by machine learning algorithms so other researchers could analyze the papers.

CORD-19’s creation was “amazing work,” says Giovanni Colavizza, a bibliometrics researcher at the University of Amsterdam. But analyses he and colleagues conducted have found potential shortcomings. For example, as of 17 April, about 75% of the papers don’t mention search terms used by CORD-19’s creators, such as “coronavirus,” in their titles, abstracts, or keywords, the researchers reported in a preprint posted on bioRxiv. That means these articles might only be tangentially related to COVID-19, he says. What’s more, fewer than half the papers provided full text, necessary for comprehensive data mining by AI programs.

A growing number of papers are also not freely available to human readers. In response to calls from major science funders, including some governments, most major publishers have pledged to make free their COVID-19-related papers. But the number of paywalled publications is growing faster than the free ones, according to a study led by Nicolas Robinson-Garcia of the Delft University of Technology and posted as a preprint on 26 April on bioRxiv. By 1 June, nearly half of all COVID-19 papers could be behind paywalls, the researchers estimate, which also limits data mining and AI-enhanced searching.

Despite these limitations, many teams are turning to advanced computational tools to mine databases such as CORD-19. Data scientists, for example, have launched more than 1500 projects in response to a White House call to build tools that use CORD-19 to help answer 10 high-priority, pandemic-related research questions identified by the U.S. National Academy of Sciences and the World Health Organization.

One fruit of these efforts, which are listed on the Kaggle online hub, is an “AI-powered literature review.” It used algorithms to harvest data points from more than 830 papers in CORD-19 on 17 topics, and presents a web page for each topic that displays data tables and links to more information. But the algorithms don’t always extract the data correctly, so medical students and other volunteers idled by the pandemic have been manually checking the tool’s accuracy.

Another challenge is making some tools user friendly. A team at the Allen Institute for AI recently unveiled SciSight, which helps those searching the CORD-19 database by automatically suggesting similar papers and drawing browsable maps of related papers.

Grabowski’s team at Johns Hopkins decided to emphasize human judgment over automated approaches. To create their 2019 Novel Coronavirus Research Compendium, which debuted on 17 April, more than 50 are combing through the literature. So far, they have selected and summarized more than 120 papers on eight topics, including vaccines and treatments. The team excluded most of the articles it examined because they only contained commentaries, protocols, poor-quality models, or no original findings, Grabowski says. The effort is focused on studies in humans, and the intended readers include health care workers and policymakers, Grabowski says. “We are trying to fill a void that we saw ... [T]here is just so much information, but a lot of the studies are not conducted very well.”

It’s too soon to measure the quality of pandemic papers based on citations or retractions, specialists say. But if quality is suffering, it’s not because, as often feared, large numbers of studies are bypassing peer review and appearing only as preprints. Preprints only make up a minority of the COVID-19 gusher, according to Robinson-Garcia’s team. As of 14 April, some 80% of the more than 11,000 COVID-19 manuscripts it examined had appeared in refereed journals. (Some were preprints originally.)

Despite the many efforts to help them navigate the literature, Sheahan and other scientists say they have not heard of new tools released in recent weeks or have had little time to try them. And persuading researchers to adopt them could be difficult, says Jevin West, a data scientist at the University of Washington, Seattle. “It’s going to take some time to get people to change their habits,” he says. Making that pitch during a pandemic is “like going into an emergency room and giving the doctors a different scalpel and saying: ‘This is actually better.’”

In the meantime, many researchers say they are falling back on time-tested ways to keep up with new results, including reading bulletins from scientific societies and a few leading journals, as well as relying on word of mouth—including tweets—from trusted colleagues.
New tools aim to tame pandemic paper tsunami
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