Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Science in crisis

Amid the pandemic, a second epidemic of preliminary, unverified and misinterpreted research has broken out, reports Graham Lawton

SOME people describe it as “havoc”, others as “a recipe for disaster”. Not the effect of the coronavirus on healthcare or the economy, but on something even more fundamental to defeating it: science.

Since the pandemic began, thousands of studies related to it have been published. “The research community has mobilised in the face of the pandemic in an unprecedented way,” says John Inglis at academic publisher Cold Spring Harbor Laboratory Press in New York.

But in the race to understand the coronavirus, and amid the cacophony of political messages, inexpert journalists and viral social media messages, a parallel pandemic has emerged – one of rumours, unverified claims and malicious falsehoods. The World Health Organization has described this confusion as an “infodemic”.

In particular, the role of preprint servers has been raising alarm. These are online repositories of preliminary findings that haven’t yet been independently reviewed. They were invented because of dissatisfaction with the conventional peer-review model, and to take advantage of new opportunities afforded by the internet.

Free-flowing information

This alternative system of academic publishing has increased in importance and credibility in recent years. It means findings can be shared widely much faster – a useful tool in an unprecedented health crisis. But the pandemic has also exposed the practice’s weakness: anyone can publish anything, with little or no quality control.

Preprint servers enable information to “flow directly from people who are making scientific claims to users who don’t have the savvy to evaluate those claims”, says Jonathan Kimmelman, a biomedical ethicist at McGill University in Canada.

Life science research was slower to adopt preprint servers than the physical sciences, in part because the research often has health implications, says John Ioannidis at Stanford University in California. But in 2013, Inglis and his colleagues created a biosciences server, bioRxiv, and last year they set up another for the health sciences, medRxiv.

In medRxiv’s first eight months, people posted 1100 papers to it. Then the pandemic hit. A further 3700 have been added in the two months since, mostly about the SARS-CoV-2 virus and the covid-19 disease that it causes. A combined medRxiv/bioRxiv site dedicated to the virus contains more than 2700 articles.

The protocol of a preprint server is that scientists post their preliminary findings for others in their field to comment on and criticise. The paper is typically then revised and submitted to a journal, or retracted. About 70 per cent of preprints eventually get published in conventional journals, says Inglis.

Under normal circumstances, this can greatly improve the research process, says Stuart Ritchie at King’s College London, author of the forthcoming book Science Fictions: Exposing fraud, bias, negligence and hype in science. “In general, I think preprints are a brilliant innovation, speeding up science, allowing open discussion of findings and letting people see others’ criticisms.”

But these aren’t normal circumstances. All of a sudden, says Ritchie, people who wouldn’t normally be interested in biomedical preprints, and don’t necessarily understand or care about their limitations, have started reading and sharing them. That includes politicians, policy-makers, journalists, bloggers, social media influencers, armchair pandemic warriors, political agitators and conspiracy theorists. “When you mix the science with all that social and media reverberation, you get an explosive mix,” says Ioannidis.

Another problem is that people with little or no biomedical expertise are making scientific claims to users who don’t have the savvy to evaluate those claims. Journalists must shoulder some of the blame for confusion on coronavirus.
from submission to publication," typical time for a scientific paper wait six months, which is the area in China that helped us begin from Wuhan and the surrounding insights into preliminary data preprint servers hosted valuable the coronavirus first emerged, data and hypotheses. When studies are published 

But some think the rapid dissemination of hastily done research can be too risky. "Under certain circumstances, a little bit of information is worse than no information at all," says Kimmelman. "I would say these are circumstances under which that would apply."

"Game-changing" drugs

The much-touted antimalaria drug hydroxychloroquine is a good example of the system going badly wrong. A preprint about the drug's efficacy against covid-19 in a small clinical trial appeared on 20 March (medRxiv, doi.org/dp7d). The trial was poorly conducted, says Alfred Kim at Washington University School of Medicine in St Louis, Missouri, who wrote a critique of it in the Annals of Internal Medicine (doi.org/gqg8b4). Among other issues, the trial had a sample size of just 20 people (see "Seven signs that science may be suspect", right).

A second preprint by different researchers detailing methodological flaws in the trial appeared three days later (Zenodo, doi.org/dtsn).

Nonetheless, says Kim, the trial's findings were picked up and amplified by the press, social media and many government and institutional leaders, including US president Donald Trump, who knowledge are posting and commenting on preprints. "You have lots of preprints that are by people who are not properly trained in science at all, and others from people who work in scientific fields that are completely different," says Ioannidis. "You have lots of people who have suddenly become epidemiologists overnight. It's a recipe for disaster."

There are, of course, benefits to the rapid dissemination of data and hypotheses. When the coronavirus first emerged, preprint servers hosted valuable insights into preliminary data from Wuhan and the surrounding area in China that helped us begin to understand the virus. "You can't wait six months, which is the typical time for a scientific paper from submission to publication," says Ioannidis. "That is double the time of the entire epidemic wave."

"We have learned an extraordinary amount extraordinarily quickly about the pandemic and the infectious agent," says Inglis. "Preprint servers were there for [researchers] to use for sharing the latest research almost immediately, at no cost, with minimal obstacles, and in an entirely open way."

Seven signs that science may be suspect

With researchers, journals, politicians, journalists and social media influencers all capable of espousing misleading or unverified scientific findings, it pays to be able to recognise the telltale signs of a study that might be poor. Here are seven potential warning flags:

Study is published on a blog, preprint server or social media

Such science can still be valid, but exercise caution because it is unlikely to have been reviewed by independent experts or undergone much vetting.

Study has only one author

This can sometimes be a warning sign that a paper or report is an early exploration of an idea or a tentative new hypothesis that shouldn't necessarily be taken too seriously.

The researchers are from a surprising field of study

All fields of research require specialist training and knowledge, but that doesn't stop some people applying themselves to subjects they know little about.

The analysis is very fast

When studies are published within days or weeks of an event, or report results from a clinical trial that hasn't finished yet, these first impressions should be treated with caution until researchers have had more time to validate their work.

The study is very small

Medical studies that look at small numbers of people are less likely to have results that will stand up in further trials. There are no strict rules, but anything under 50 participants is highly tentative, and studies involving at least hundreds of patients or volunteers are preferable.

The trial has no placebo group

It isn't always possible to design experiments to include a placebo group, but without one, it can be difficult to know for sure if the observed effects are meaningful.

The study reports a correlation or association

Many factors can be linked without one causing the other. In observational studies, factors such as age, wealth or sex may also have an effect on the issue in question. Even when studies say they have accounted for such confounding factors, it is possible that their effects haven't been completely removed from the analysis.

"Any medical study with fewer than 50 participants should be treated as highly tentative"
famously called the drug a "game changer". Public interest exploded.

It got worse. On 30 March, a preprint appeared on medRxiv reporting the results of another small clinical trial on 62 patients in a hospital in Wuhan with mild-to-moderate covid-19 (doi.org/gqqm4v). It found that those given the drug recovered faster.

The New York Times reported on these results the day after. The article, written by a specialist science reporter, was careful to say that the study was small and not peer-reviewed, and that more research was needed, but it did feature boosterish expert quotes. “The physicians interviewed in the story made it sound like it was a credible report,” says Kimmelman.

But this study was beset with methodological problems, says Kimmelman. “There was striking dissimilarity between what they said they were going to do in that study and what was actually reported.” A diligent peer reviewer might have picked this up, he says, but somebody who isn’t an expert in the methodology of clinical trials has little chance of doing so.

This shows just how difficult it is for even skilled journalists to pick up pretty glaring errors in research reports, says Kimmelman, who adds that even trained doctors are rarely equipped to do so.

These infodemic failures have real-world consequences. Hospital doctors started giving hydroxychloroquine to covid-19 patients, and some people began self-medicating with it. There were shortages of the drug for people with rheumatoid arthritis who really need it, and scarce scientific resources pivoted to research the drug when they could perhaps have been spent better elsewhere.

The blame for such confusion can’t all be placed on the preprint servers. The dedicated covid-19 preprint site features a prominent disclaimer, reminding visitors that the reports posted there shouldn’t guide clinical practice or health-related behaviour, or be reported in the media as established information.

5700

An inexpert study predicted there would be this many UK deaths

Preliminary hydroxychloroquine results have diverted scientific resources and left many confused

Fixing the problem

Preprint servers aren’t the font of all bad knowledge. Peer-reviewed journals have also been criticised for publishing hasty, poor quality papers during the pandemic.

We also know that the process of academic publishing has many issues, including a bias towards positive results. Peer review is no guarantee that a study’s findings will stand the test of time and be successfully replicated.

But given the benefits of preprint servers, what can be done to reduce their negatives? Inglis says the science community is already taking action to rapidly vet the content of preprints. These efforts include dedicated projects to provide informal peer review and expert commentary at Mount Sinai Hospital in New York, and at the University of Cambridge. A consortium of journal publishers is exploring how to speed up the peer review of preprint papers without compromising on quality.

Ritchie suggests that preprints should be electronically watermarked with a disclaimer to avoid any doubt about the provisional status of the research.

And while the medRxiv site says all manuscripts undergo a basic screening process for non-scientific content and material that might pose a health risk, arguably more could be done to vet research before it is posted to servers around the world.

But scientists should shoulder some of the blame, says Ritchie. One problem is the volume of low-quality studies that researchers are posting.

Many scientists are unwilling to discuss their research with journalists until it has been peer reviewed. This doesn’t necessarily help, because journalists may report on preprint studies anyway. Some of those researchers who do speak to the media could be clearer about the preliminary nature and limitations of their work, says Ritchie.

Another issue is experts in one field turning their hand to another. In March, for example, an electrical engineer and a cardiologist posted a preprint estimating that the UK could experience just 5700 covid-19 deaths (medRxiv, doi.org/dtss). Several UK newspapers gave the estimate prominent coverage. The UK’s confirmed death toll currently stands at over 28,000.

Kimmelman believes there is a wider societal issue. “I think this is part of a much broader problem of how information flows in contemporary societies, particularly around expertise. We’ve seen parallel issues in politics and democracy – fake news, false claims, etc.,” he says.

“If we want good research and effective healthcare, we need to get on top of this problem”