

Adverse drug effects during the COVID-19 pandemic

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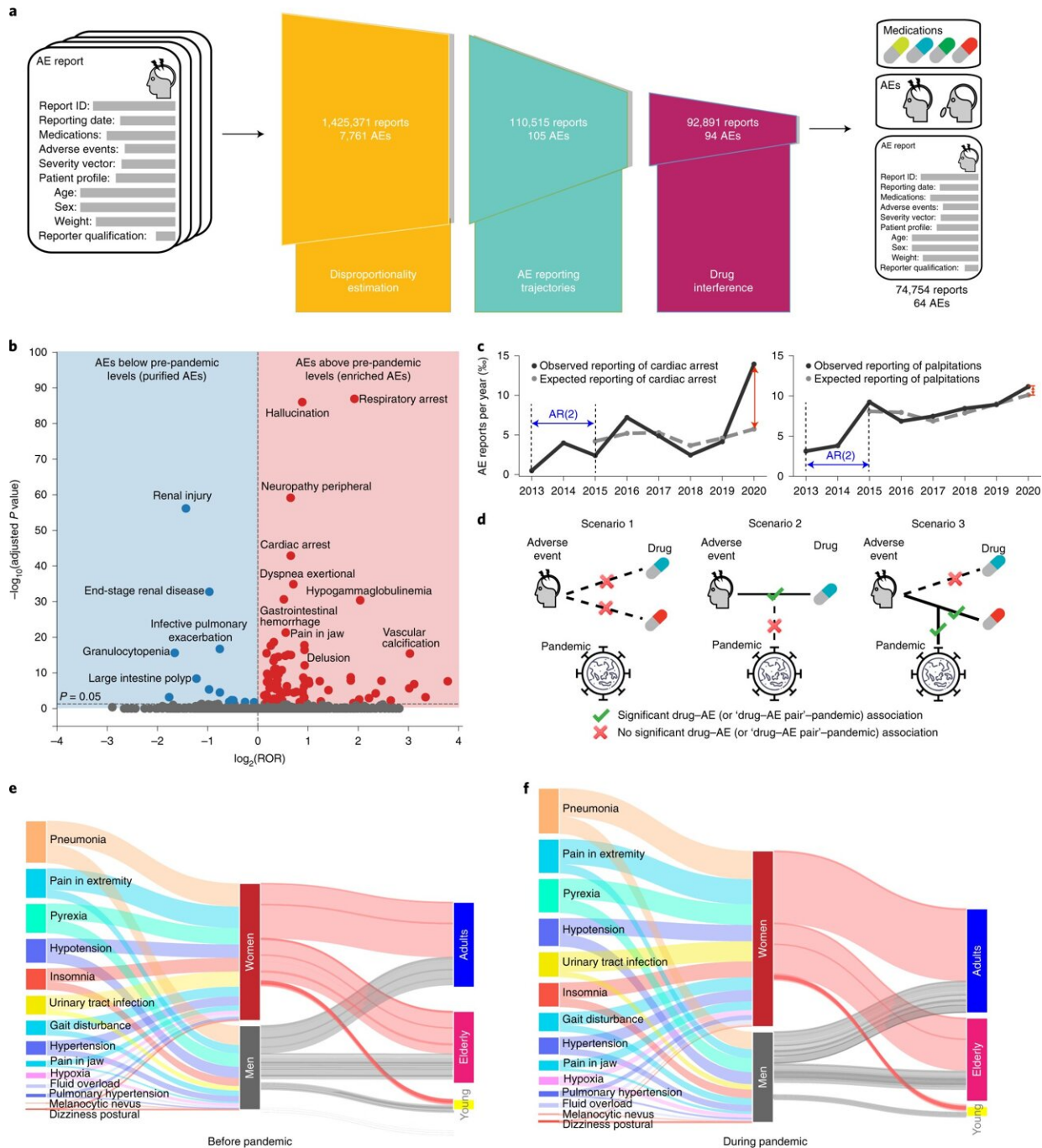


Fig. 1: Algorithms for the population-scale analysis of patient drug safety. a, Our algorithmic approach detects drug safety signals associated with the pandemic by leveraging a large-scale dataset of adverse event (AE) reports on drugs and their associated adverse reactions. In the overall patient population, it identifies 64 significant types of adverse event, out of 7,761. b, Disproportionality estimation. Adverse events with P 0.8 enriched in women. The total number of reports

during the pandemic increased by 28.1% relative to pre-pandemic in women and only by 7.7% in men, implying an increased gender disparity. The difference between lengths of input and output streams in women or men are due to reports with unknown age. AR(2), second-order autoregressive model (Methods).

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The COVID-19 pandemic has reshaped health and medicine in ways both dramatic and subtle. Some of the less obvious shifts can only emerge from analysis of millions of pieces of data—patient records, medical notes, clinical encounter reports.

Taken in isolation these [data points](#) may offer tantalizing anecdotes. Analyzed together, they can offer a bird's-eye view of interesting interplays and reveal important trends, giving clinicians and public [health](#) experts valuable clues that can inform both prevention and intervention.

Marinka Zitnik, assistant professor of biomedical informatics in the Blavatnik Institute at Harvard Medical School, uses data science and machine-learning methods to glean such insights—hiding in plain view—about disease development and progression, therapeutic outcomes and response to treatment.

Zitnik's latest research, a study published Oct. 5 in *Nature Computational Science*, analyzes patterns in adverse medication events before and during the [pandemic](#).

In the study, Zitnik and co-authors Xiang Zhang, a post-doctoral research fellow at HMS, and Marissa Sumathipala, a graduate researcher at Harvard University used more than 1.4 million medical reports involving 2,821 drugs.

The researchers found that 54 types of adverse events increased in frequency during the pandemic, even though overall, the number of adverse medication events went down somewhat. Furthermore, the analysis revealed telltale gender and age differences in the likelihood of adverse events.

The results, the researchers say, have important implications for safe medication use and can inform better ways to stratify patients by risk profile to prevent, or at least minimize, health care inequality during health emergencies.

Zitnik discussed her findings with Harvard Medicine News.

HMNews: What did you set out to accomplish with this study?

Zitnik: Adverse events from medication use and [prescription drugs](#) accounted for more than 110,000 deaths in the United States in 2019. The primary motivation behind our study was understanding to what extent the pandemic, and the resulting disruptions, might have challenged the ability of health care systems to ensure safe medication use. We wanted to know whether there were any inequalities across different patient groups that got exacerbated, whether there were any adverse events that went above or below what we would have expected had the pandemic not happened.

To answer these questions, we looked at patterns of adverse events from medications going back seven years before the pandemic. We looked at historical trends for each [drug](#) and each adverse event captured in our database to predict what would be expected in 2020. Then we compared that expectation with what we actually did see in 2020. The difference between what we would have expected and the occurrence gave us a clue

about the effect of the pandemic.

HMNews: What were some of the key findings?

Zitnik: First, we found substantial variation of drug adverse events before and during the pandemic. We identified 64 types of adverse events whose patterns had considerably changed relative to the pre-pandemic levels. What was surprising was that 54 of the 64 adverse events increased during the pandemic. Why is this surprising? Because your expectation might be that since access to health systems was limited and patients were unable to go to the hospital and report adverse events, one would expect that such reports would go down. That was, indeed, the case.

The total volume of reports of adverse drug events did go down by 4.4 percent, compared with pre-pandemic levels. The surprising part was that 54 adverse drug events increased in incidence rate during the pandemic. Number two, we found pre-pandemic gender difference in adverse drug defects got exacerbated during the pandemic. We found that women suffered from more adverse events than men, relative to pre-pandemic levels, and those gender differences persisted across all age groups.

That, to me, was surprising. I can only imagine what the differences would have been across ethnic and racial groups if we had access to such data. Number three, we found relevant clinical differences in drug side effects across age groups. Side effects such as anxiety and insomnia were disproportionately increased in women and in the elderly, suggesting these are at-risk patient groups.

Taken together, we can identify certain risk-altering adverse events—or adverse events the risk of which is altered by an external disruption, in this case COVID-19.

HMNews: What are the advantages of using big data and computational analysis to study changes during a public health emergency?

Zitnik: Many of the observations we made and the conclusions we reached were only possible because of the sheer amount of data we analyzed. We mined more than 10 million reports from a national adverse-events reporting database for the period between January of 2013 and September of 2020, and we looked at the entire range of approved drugs.

There is a large body of prior research on adverse drug events from laboratory environments focused on the molecular characterization of drugs during clinical trials before approval. Patient safety studies done during the pandemic were also very limited and restricted to a small number of drugs—those for the treatment of COVID-19 or related conditions—small number of reports, and narrow time ranges.

What this large data analysis enabled us to do was to disentangle these intricate dependencies between the effect of the pandemic, the effect of the drugs, and patient characteristics. It allowed us to identify changes in the landscape of adverse events during a public health emergency. It allowed us to see how these changes play out in different patient populations, defined by gender, age and other demographics.

Here is one example: The drug remdesevir, which had been on the market before the pandemic and was repurposed for the treatment of COVID-19, was associated with risk for hypoxia, or low oxygen levels. Hypoxia was reported as a novel adverse event in the clinical trials of remdesevir for COVID-19 treatment but was not known before. So, in this case, our analysis highlights how algorithmic models used at population scale can identify otherwise rare and subtle events that do not

emerge until large numbers of people begin taking a medication.

Such analysis can help pharmacological vigilance for treatments, including those that are granted emergency approvals or repurposed for COVID-19, as was the case with remdesivir. Clearly this type of population-scale analysis is not equipped to reveal the causes behind the observations and the why behind the what.

However, this approach is valuable because it's a system-wide study that allows us to zoom out and see the forest for the trees. We wanted to understand what happens when you looked at the scale of the entire country—the United States—and look at real-world patients that take a variety of different medications and have a variety of diseases to capture the intricate interdependencies across all of these variables, including non-medical factors, such as age, gender, and where they live.

HMNews: What are your next steps?

Zitnik: The part that I am most excited about is that this work provides a blueprint for how we can compare COVID-19 with other public health emergencies. We'd be very interested to compare the effects of COVID-19 on safe medication use with those of the opioid crisis or hurricanes and wildfire emergencies that may similarly disrupt access to health care.

Is there something we learn from COVID-19 that we can transfer to other public health emergencies? Can we, based on these, formulate anticipatory guidance for public health authorities? The hope is that such insights may help inform drug prescription practices and improve patient safety by flagging individuals or patient groups that might be at higher risk for adverse events during a public health emergency.

These insights can identify patients that might be disproportionately

affected by certain preventable inequities and provide guidelines to public health experts to identify communities they should reach out to and then maybe design tools that can automatically ask patients what kinds of adverse events they are experiencing, what kinds of drugs they are on—without patients necessarily coming to the hospital, which is a major challenge during a pandemic.

Long-term, this type of large-scale analysis may provide enough granular data to help us move away from the one-size-fits-all approach and allow us to stratify the risk of adverse drug effects by patient based on a wide range of characteristics.

More information: Xiang Zhang et al, Population-scale identification of differential adverse events before and during a pandemic, *Nature Computational Science* (2021). [DOI: 10.1038/s43588-021-00138-4](https://doi.org/10.1038/s43588-021-00138-4)

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