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Restaurants and other crowded indoor spaces are prime spots for superspreading events, in which one person passes the virus to many others.

THE SUPERSPREADING PROBLEM

Uneven transmission of the SARS-CoV-2 coronavirus has had tragic consequences — but also offers clues for how best to target control measures. **By Dyani Lewis**

On 5 December last year — the eve of traditional Christmas gift-giving in Belgium — residents of the Hemelrijck care home near Antwerp were treated to a visit by *Sinterklaas*, or Santa. But the festive event, intended to spread cheer, turned tragic. Forty staff members and more than 100 residents — at least 26 of whom have since died — were unintentionally infected with the coronavirus SARS-CoV-2 by the costumed volunteer, who also subsequently tested positive.

Superspreading events like this, in which many people are infected at once, typically by a single individual, are a now-familiar feature of the COVID-19 pandemic. Choir practices, funerals, family gatherings and gym classes have all spawned dangerous outbreaks.

Akira Endo, an infectious-diseases modeller at the London School of Hygiene & Tropical Medicine, noticed the telltale signs of superspreading before such events became a staple of COVID-19 news coverage. One clue came from early investigations of cases in which a single person infected up to ten others[1]. Another curious fact was that outside Wuhan, China, home to the first big outbreak, infected individuals weren't immediately causing exponential local outbreaks, says Endo, who was one of the earliest to quantify the phenomenon.

This uneven, sputtering form of transmission, in which some individuals infect many people but most infect only a few, if any, is shared by the coronavirus's cousins — SARS-CoV, which caused the deadly epidemic of severe acute respiratory syndrome (SARS) in 2003, and MERS-CoV, the source of Middle East respiratory syndrome. A similar mode of transmission occurs with the pathogens that cause Ebola, smallpox and tuberculosis.

As the pandemic enters its second year — a time marked by news of fast-spreading variants of the virus — researchers are now more convinced than ever of the importance of superspreading in how the COVID-19 pandemic has played out, and how it will do so in the future. They have found that superspreading events are one of the main ways in which SARS-CoV-2 has gained a foothold in communities around the world, so far infecting more than 100 million people and killing more than 2.4 million. Without effective control measures, superspreading events might even become larger and more frequent as more-transmissible variants first

identified in the United Kingdom, South Africa and Brazil push out other strains of the virus.

With a year's worth of data, researchers have amassed ample evidence of some chief ingredients of superspreading events: prolonged indoor gatherings with poor ventilation. Activities such as singing and aerobic exercise, which produce many of the tiny infectious droplets that can be inhaled by others, are also common components.

But key questions remain. "We have some ideas of what factors are involved, but we still don't know what is the main driver of the superspreading," says Endo. Foremost are uncertainties about how much individual differences in people's behaviour and biology matter — or can be controlled — and how best to target high-risk settings while keeping the cogs of society turning. Understanding the underlying factors that drive superspreading is crucial, says Lucy Li, an infectious-diseases modeller at the Chan Zuckerberg Biohub in San Francisco, California.

Experts say that we already know enough about the main factors of superspreading to use this phenomenon to our advantage. They are calling on policymakers to harness this knowledge to target control measures that will slow — or even stamp out — the pandemic. One of the most basic steps is closing crowded, indoor hotspots to prevent superspreading events. Researchers also recommend following Japan's lead, by using backwards contact tracing to uncover superspreading events.

Explosive transmission

On average, each person who contracts SARS-CoV-2 will pass it on to between two and three others. But that tidy population-level estimate — known as the basic reproduction number (R_0) — hides immense variation at the individual level. In reality, most infections arise from just a handful of people (see 'Infection connections'). Endo's early analysis estimated that around 10% of cases in countries outside China accounted for 80% of secondary infections up to the end of February[2].

Estimates from places such as Israel, India, Hong Kong and other parts of China back up this observation. And although this pattern occurs in other infectious diseases, it is especially pronounced in COVID-19. Influenza, by contrast, has less individual variation, says Endo, and tends to spread more evenly.

The upshot of superspreading is that a few infections can rapidly blossom into a raging outbreak, says Li, who has studied the phenomenon in locations across the United States, Europe and China. "If you have a chain of superspreaders, then the cases could explode in a really short period of time," she says.

New variants of SARS-CoV-2 that first attracted attention in the United Kingdom, South Africa and Brazil could make superspreading worse, says Li. On the basis of a reported 50% higher transmission rate in a variant called B.1.1.7 (ref. 3), "there will likely be an increase in both the frequency and size of superspreading events", she says.

A team led by Bronwyn MacInnis, a geneticist at the Broad Institute of MIT and Harvard in Cambridge, Massachusetts, traced the impact of superspreading events using viral genome sequences. One superspreading event — a two-day international business conference held in Boston in late February 2020 — seeded more than 90 cases in attendees and their close contacts[4]. But the true impact was much greater, says MacInnis. She estimates that roughly 20,000 infections in Boston and its surrounding areas could be traced back to the conference.

Are there superspreaders?

Although a few people account for the lion's share of transmission, researchers are still teasing out whether some people have biological factors that cause them to pass the virus to many others. For instance, some individuals naturally speak louder or expel more air when they exhale. So they would naturally emit more aerosols — the tiny virus-laden particles that travel through the air, says Christian Kähler, a physicist who studies aerosol production and dynamics at the University of the Federal Armed Forces in Munich, Germany. Also, children and women tend to emit less than men owing to their smaller lung capacities, says Kähler.

But he and other researchers are sceptical about biological differences beyond that. "The belief in the super-emitter, that's too simple," he says.

> **"If you have a chain of superspreaders, then the cases could explode in a really short period of time."**

Kähler thinks that a person's behaviour — whether they fail to keep a safe distance from others during conversations, say, or refuse to wear a mask — is much more likely to heighten transmission risk than is the amount of aerosol they emit. Actions such as singing and shouting also boost that amount, he says. Estimates suggest that speaking loudly can increase the number of particles emitted by up to 50 times compared with normal speaking[5], and singing can produce up to 99 times more, according to a study that has not been peer reviewed[6].

Individual variation in immune responses could affect how much virus a person produces, says virologist Dominic Dwyer at NSW Health Pathology, the state's public pathology service, in Sydney, Australia. Differences in how young children's immune systems respond to infection are thought to be why they catch and pass on the coronavirus less frequently than adults do[7]. It's possible that a spectrum of immune responses exists in adults, too, says Dwyer. At the far end of the spectrum, "if somebody is immune-suppressed, then generally they're more likely to shed more virus for longer", he says.

A study of aerosol emissions from nearly 200 healthy people, published this month[8], lends weight to the idea that biological differences could affect transmission of the virus. The measurements showed that 20% of the study participants accounted for 80% of the aerosol particles emitted, and that people who were older or overweight produced more aerosols than others.

But researchers using mathematical modelling to chart outbreaks say they don't need to invoke biological differences to explain superspreading events. In a study[9] that is yet to be peer reviewed, physicist Mara Prentiss at Harvard University in Cambridge, Massachusetts, and her colleagues calculated how many viral particles were emitted by a single infected person at each of five superspreading events.

Despite the events differing drastically — one took place in a spacious call centre, one in an exercise class, two others in buses and another in a choir rehearsal — the amount of virus emitted by the infected person was remarkably similar. "We were kind of surprised," says Prentiss, because it suggests that individual differences are minimal when superspreading occurs.

In all of the cases Prentiss and her team looked at, the person most likely to have infected others was either mildly symptomatic or hadn't yet developed symptoms. This is a key similarity between the events and is probably shared by other occurrences of superspreading. "It's transmission in young, healthy, mobile populations that actually does the most damage," says MacInnis. "Just because you feel well doesn't mean that you're not infected and potentially spreading," she says.

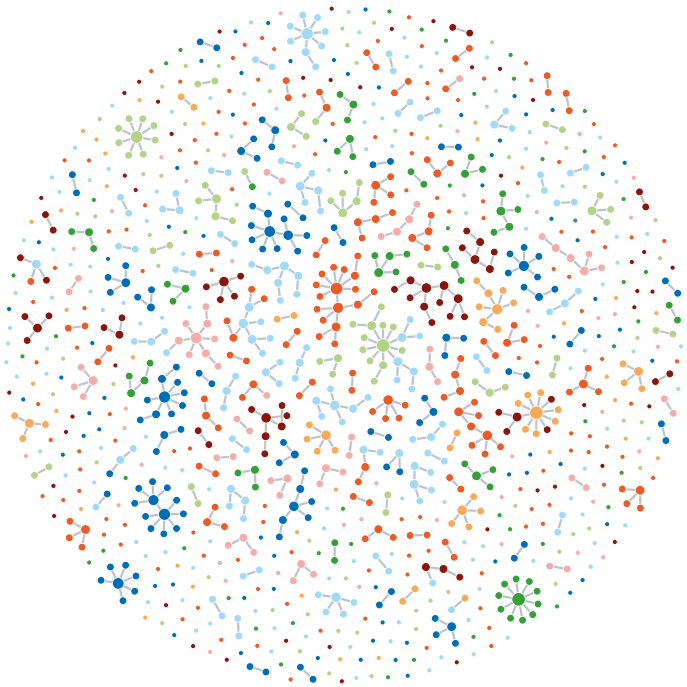
Although transmission patterns might not depend much on biological differences between people, the same can't be said for their behaviour. A person whose job or lifestyle brings them into contact with numerous people or who is more gregarious during social gatherings might be more likely to be a superspreader than someone who is a wallflower, according to Kähler.

Problem places

One of the most important lessons to have emerged over the past year is that the spaces where people congregate matter when it comes to infection risk. Numerous superspreading events have occurred in crowded indoor spaces with poor ventilation. This aligns with other pieces of evidence that airborne transmission through aerosols is an important — if not the main — mode by which SARS-CoV-2 passes from one person to the next.

INFECTION CONNECTIONS

Coloured dots represent people infected with SARS-CoV-2 in early 2020 in Hunan province, China. Researchers reconstructed chains of transmission for 1,178 people, represented by lines connecting the dots. Most individuals did not infect anybody else, but 15% of people accounted for 80% of secondary infections — an indication that superspreading played a major part in transmissions.



SOURCE: K. SUN *ET AL. SCIENCE* **371**, EABE2424 (2021)

Japan recognized this issue early, and in February 2020 promoted awareness of 'the 3Cs' that put people at risk of infection — closed spaces, crowded places and close-contact settings. The World Health Organization's Western Pacific Region adopted the 3Cs public-health message in July. Limits on the number of people allowed to gather indoors have been a staple of worldwide public-health measures designed to curb the spread of the virus.

But researchers are working to improve their understanding of precisely what makes for a risky indoor environment, so that restrictions can be better targeted and less disruptive. Jure Leskovec, a computer scientist at Stanford University in California, and his team used human-mobility data to see which venues are particularly risky. The group used anonymized mobile-phone location data to model the hour-by-hour movements of around 100 million people in the United States over a 2-month period from March to May last year. By making the simple assumption that venues carry a greater risk if they are smaller, more densely occupied and visited for longer, he found that restaurants, cafes and gyms are transmission hotspots[10]. Ten per cent of the locations accounted for 80% of predicted infections, he says.

Leskovec's model also provides clues as to why lower-income communities are disproportionately affected by the pandemic. People from low-income neighbourhoods reduced their movements less in response to lockdowns — perhaps owing to work obligations — than did people in wealthy areas. But venues were also more risky in low-income areas. Grocery stores were more densely occupied, and people stayed there for longer. "A single trip to a grocery store was about twice as risky for a low-income individual" due to differences in mobility alone, says Leskovec. These differences could explain the observed higher infection rates in these neighbourhoods, he says, and indicate that resources — education or masks, say — could help to stem transmission in such communities.

Max Lau, a disease modeller at Emory University in Atlanta, Georgia, also used mobile-phone data to track transmission dynamics[11]. By calculating the variation in individual transmission in parts of Georgia — a value known as the dispersion parameter, k — he was able to compare rates of superspreading in different populations. A small k corresponds to clumpier transmission, or more superspreading.

Lau found that superspreading was particularly prominent in people younger than 60 — the working, socializing portion of the population. It was also an important driver of transmission in rural areas, perhaps because there was less adherence to shelter-in-place orders, he says.

Superspreading as an advantage

The growing understanding of superspreading — and its role in driving transmission — has pointed to ways to squash outbreaks when they emerge. One of these is intensive contact tracing to find and alert everyone who might have been exposed to a superspreading event.

In February last year, Japan successfully implemented this type of strategy, called cluster-focused backwards contact tracing. Instead of working forwards and finding close contacts who might have been exposed to a particular individual, backwards contact tracing follows the transmission chain back in time to locate the individual who infected the person in question. Each newly infected person is more likely to have been infected in a superspreading event than by someone who passed the virus only to them. So contact tracers have a good chance of uncovering such events in this way. Endo's modelling shows that backwards contact tracing has an oversized effect on controlling transmission[12].

But this type of contact tracing is labour-intensive, and can usually be adopted only when case numbers are already coming down. At this point, "backwards tracing can work pretty well as the final hammer to finish the outbreak", says Endo.

Ideally, public-health measures should prevent superspreading events from happening in the first place. But, says MacInnis, pinning down some of the finer points of superspreading becomes harder as case numbers surge — as they have recently in the United States, the United Kingdom and large parts of Europe.

Leskovec's work suggests a way to limit transmission. By simulating various scenarios, he found that restaurants account for 20% of the future month's transmissions if all businesses reopen. That implies that restaurants are particularly risky, and could be targeted for restrictions, rather than requiring all businesses to close. Leskovec is currently in discussions with policymakers to use his model to fine-tune reopening measures that maximize disease control and minimize disruption to businesses.

But not all risks can be addressed easily, says Li. Essential workers who spend time in close proximity to others, such as meat processors, will continue to be exposed to high-risk environments. "There will always be an underlying risk of superspreading events just because of the way that society is structured," she says.

Many nations started off this year with some of the worst outbreaks of the pandemic. And, as more-infectious variants spread worldwide, an end to the pandemic seems distant. But when outbreaks do start to peter out — whether as a result of lockdowns or of mass vaccination — superspreading will account for an even greater share of the case load, says Lau. That makes it especially important to stay the course with prevention measures, even when case numbers are low. "If we see the decline of cases, we have to be even more careful about avoiding these superspreading events," he says.

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