Large numbers of people working close together in a cold environment may make meatpacking plants fertile ground for the novel coronavirus.

PHOTO: KIYOSHI OTA/BLOOMBERG/GETTY IMAGES

COVID-19

Case clustering emerges as key pandemic puzzle

Why do some patients infect many others, whereas many don't spread the virus at all?

By **Kai Kupferschmidt**

When 61 people met for a choir practice in a church in Mount Vernon, Washington, on 10 March, everything seemed normal. For 2.5 hours the chorists sang, snacked on cookies and oranges, and sang some more. But one of them had been suffering for 3 days from what felt like a cold—and turned out to be COVID-19. In the following weeks, 53 choir members got sick, three were hospitalized, and two died, according to a 12 May report by the U.S. Centers for Disease Control and Prevention (CDC) that meticulously reconstructed the tragedy.

Many similar "superspreading events" have occurred in the COVID-19 pandemic. A database by Gwenan Knight and colleagues at the London School of Hygiene & Tropical Medicine (LSHTM) lists an outbreak in a dormitory for migrant workers in Singapore linked to almost 800 cases; 80 infections tied to live music venues in Osaka, Japan; and a cluster of 65 cases resulting from Zumba classes in South Korea. Clusters have also occurred aboard ships and at nursing homes, meatpacking plants, ski resorts, churches, restaurants, hospitals, and prisons. Sometimes a single person infects dozens of people, whereas other clusters unfold across several generations of spread, in multiple venues.

Other infectious diseases also spread in clusters. But COVID-19, like two of its cousins, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), seems especially prone to attacking groups of tightly connected people while sparing others. It's an encouraging finding, scientists say, because it suggests that restricting gatherings where superspreading is likely to occur will have a major impact on transmission and that other restrictions—on outdoor activity, for example—might be eased.

"If you can predict what circumstances are giving rise to these events, the math shows you can really, very quickly curtail the ability of the disease to spread," says Jamie Lloyd-Smith of the University of California, Los Angeles, who has studied the spread of many pathogens. But superspreading events are ill-understood and difficult to study, and the findings can lead to heartbreak and fear of stigma in patients who touch them off.

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Most of the discussion around the spread of SARS-CoV-2 has concentrated on the average number of new infections caused by each patient. Without social distancing, this reproduction number (R) is about three. But in real life, some people infect many others and others don't spread the disease at all. In fact, the latter is the norm, Lloyd-Smith says: "The consistent pattern is that the most common number is zero. Most people do not transmit."

That's why in addition to R, scientists use a value called the dispersion factor (k), which describes how much a disease clusters. The lower k is, the more transmission comes from a small number of people. In a seminal 2005 *Nature* paper, Lloyd-Smith and co-authors estimated that SARS—in which superspreading played a major role—had a k of 0.16. The estimated k for MERS, which emerged in 2012, is about 0.25. In the flu pandemic of 1918, in contrast, the value was about one, indicating that clusters played less of a role.

Estimates of k for SARS-CoV-2 vary. In January, researchers at the University of Bern simulated the epidemic in China for different combinations of R and k and com-

pared the outcomes with what had actually taken place. They concluded that k for COVID-19 is somewhat higher than for SARS and MERS. But in a March preprint, Adam Kucharski of LSHTM estimated it's only 0.1. "Probably about 10% of cases lead to 80% of the spread," Kucharski says.

If he is right, SARS-CoV-2 needs to be introduced undetected into a new country at least four times to have an even chance of establishing itself, Kucharski says. That may explain why the virus did not take off around the world sooner after it emerged in China, and why some very early cases elsewhere—such as one in France in late December 2019, reported on 3 May—apparently failed to ignite a wider outbreak. If the Chinese epidemic was a big fire that sent sparks flying around the world, most of the sparks simply fizzled out.

Why coronaviruses cluster so much more than other pathogens is "a really interesting open scientific question," says Christophe Fraser of the University of Oxford, who has studied superspreading in Ebola and HIV. Their mode of transmission may be one factor. SARS-CoV-2 appears to transmit mostly through droplets, but it does occasionally spread through finer aerosols that can stay suspended in the air, enabling one person to infect many. Most published large transmission clusters "seem to implicate aerosol transmission," Fraser says.

> **"Probably about 10% of cases lead to 80% of the spread."**
>
> **Adam Kucharski**, London School of Hygiene & Tropical Medicine

Individual patients' characteristics play a role as well. Some people shed far more virus, and for a longer period of time, than others, perhaps because of differences in their immune system or the distribution of virus receptors in their body. A 2019 study of healthy people showed some breathe out many more particles than others when they talk. (The volume at which they spoke explained some of the variation.) Singing may release more virus than speaking, which could help explain the choir outbreaks. People's behavior also plays a role. Having many social contacts or not washing your hands makes you more likely to pass on the virus.

Superspreading usually happens indoors. Researchers in China studying the spread of the coronavirus outside Hubei province—ground zero for the pandemic—identified 318 clusters of three or more cases between 4 January and 11 February, only one of which originated outdoors. A study in Japan found that the risk of infection indoors is almost 19 times higher than outdoors. Some situations may be particularly risky. Meatpacking plants are likely vulnerable because many people work closely together in spaces where low temperature helps the virus survive.

Countries that have beaten back the virus to low levels need to be especially vigilant for superspreading events, because they can easily undo hard-won gains. After South Korea relaxed social distancing rules in early May, a man who later tested positive for COVID-19 visited several clubs in Seoul; public health officials scrambled to identify thousands of potential contacts and have already found 170 new cases.

If public health workers knew where clusters are likely to happen, they could try to prevent them and avoid shutting down broad swaths of society, Kucharski says. "Shutdowns are an incredibly blunt tool," he says. "You're basically saying: We don't know enough about where transmission is happening to be able to target it, so we're just going to target all of it."

But studying large COVID-19 clusters is harder than it seems. Many countries have not collected the kind of detailed contact tracing data needed. And the shutdowns have been so effective that they also robbed researchers of a chance to study superspreading events. (Before the shutdowns, "there was probably a 2-week window of opportunity when a lot of these data could have been collected," Fraser says.)

The research is also prone to bias. People are more likely to remember attending a basketball game than, say, getting a haircut, a phenomenon called recall bias that may make clusters seem bigger than they are. Clusters that have an interesting social angle—such as prison outbreaks—may get more media coverage and thus jump out to researchers, while others remain hidden. Clusters of mostly asymptomatic infections may be missed altogether.

Privacy is another concern. Untangling the links between patients can reveal who was at the origin of a cluster or expose information about people's private lives. In its report about the chorus, CDC left out a seating map that could show who brought the virus to the practice. Some clubs involved in the new South Korean cluster were gay venues, which resulted in an antigay backlash and made contact tracing harder.

Fraser, who is tracking HIV transmission in Africa by sequencing virus isolates, says it is a difficult trade-off, but one that can be managed through good oversight and engagement with communities. Epidemiologists have "a duty" to study clusters, he says: "Understanding these processes is going to improve infection control, and that's going to improve all of our lives." ■

COVID-19

T cells found in coronavirus patients 'bode well' for long-term immunity

New findings suggest past infections may offer some protection against the novel coronavirus

By **Mitch Leslie**

T cells are among the immune system's most powerful weapons, but their importance for battling SARS-CoV-2, the virus that causes COVID-19, has been unclear. Now, two studies show infected people harbor T cells that target the virus—and may help them recover. Both studies also found that some people never infected with SARS-CoV-2 have these cellular defenses, most likely because they were previously infected with other coronaviruses that cause the common cold.

"This is encouraging data," says virologist Angela Rasmussen of Columbia University, who wasn't involved in the work. Although the studies don't clarify whether people who clear a SARS-CoV-2 infection can ward off the virus in the future, both identified strong T cell responses to it, which "bodes well for the development of long-term protective immunity," Rasmussen says. The findings could also help researchers create better vaccines.

The more than 100 COVID-19 vaccines in development mainly focus on triggering a different immune response: antibodies. Researchers know our B cells make antibodies against SARS-CoV-2, which vaccine developers hope can latch onto the virus and prevent it from entering cells. But T cells can also help thwart infections. Helper T cells spur B cells and other immune defenders into action, whereas killer T cells target and destroy infected cells. The severity of disease can depend on the strength of these T cell responses.

To determine whether the new coronavirus provokes T cells, a team led by Shane

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