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WELCOME TO THE HOTEL INFLUENZA

A GROUNDBREAKING UMD RESEARCHER INVESTIGATING HOW RESPIRATORY INFECTIONS SPREAD ASKS VOLUNTEERS TO CHECK IN—AND GET SICK FOR SCIENCE.

PG. 18

BY CHRIS CARROLL ILLUSTRATIONS BY NOMA BAR

WELCOME TO THE Hotel Influenza

A GROUNDBREAKING UMD RESEARCHER INVESTIGATING HOW RESPIRATORY INFECTIONS SPREAD ASKS VOLUNTEERS TO CHECK IN—AND GET SICK FOR SCIENCE.

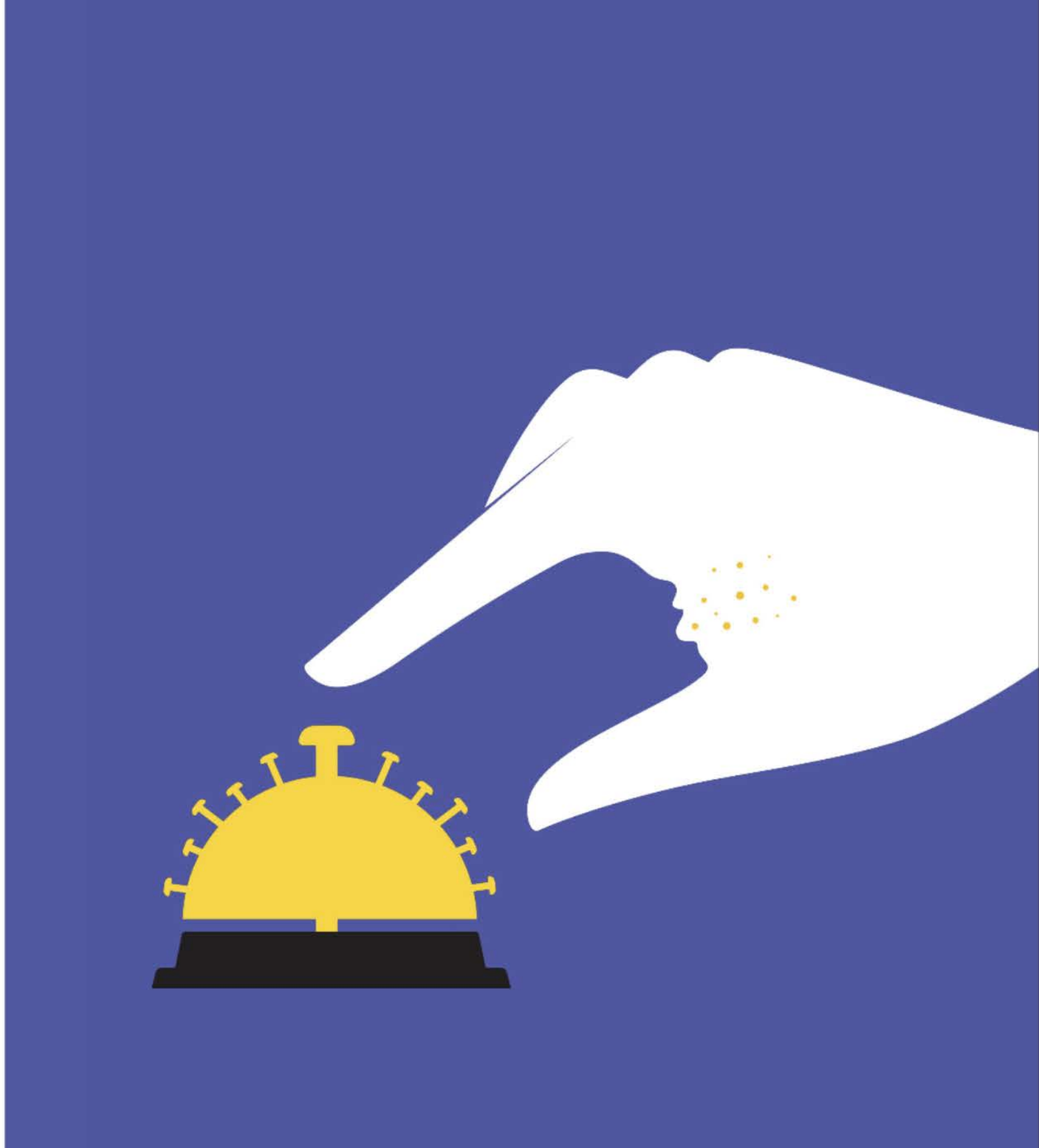
THE STATELY 23-STORY HOTEL OPENED AT the height of the Jazz Age, but less than a year later, Wall Street's 1929 crash snuffed out revelry in the opulent ballroom and secret speakeasy. That's when the property, then one of Baltimore's tallest buildings, supposedly began accumulating ghosts: failed businessmen, wiped-out tycoons, even a bankrupt couple reputed to have jumped to their deaths on a downtown street with their young daughter.

Today, as tour groups try to detect the spectral child bouncing her ball down the halls of the hotel, University of Maryland researchers and colleagues are using the location to track an unseen presence that's more substantial—and threatening.

Each year, according to the World Health Organization, seasonal influenza respiratory infections kill up to 650,000 people; while science has pinned down much of the biology of flu and other dangerous viruses, it hasn't yet provided a precise account of how they're passed from person to person to cause illness—or clear answers about preventing their spread. Did you get flu from a dirty doorknob or a sneeze in the face? Or as recent research from UMD and other sources suggests, do airborne viruses "haunt" indoor air around infected people, waiting to be breathed deep into the lungs?

As part of an audacious bid to put such questions to rest, paid volunteers have checked into a sealed-off floor of the hotel (which the managers asked *Terp* to avoid naming) over the past two winters, with more on the way this winter. During stays of up to two weeks, they're participating in a randomized, controlled trial with a surprising objective: to spread, or catch, the flu for science.

Supported by $20 million in grants from the National Institutes of Health and Balvi Filantropic Fund, the study could fundamentally alter how health authorities and the public fight respiratory infections. It brings together a multidisciplinary team from UMD's School of Public Health and A. James Clark School of Engineering, and the School of Medicine at the University of Maryland, Baltimore, led by UMD MPower Professor of Environmental and Occupational Health Donald K. Milton.



He has spent much of his 40-year career analyzing airborne pathogens and advocating, at times controversially, for society to take greater precautions. It took the COVID pandemic—when he played a pivotal role in overturning national and global health authorities' opposition to masking to stop airborne viruses—for his ideas to gain greater traction. But that was a little too late to avoid disastrous shutdowns of schools and other societal institutions.

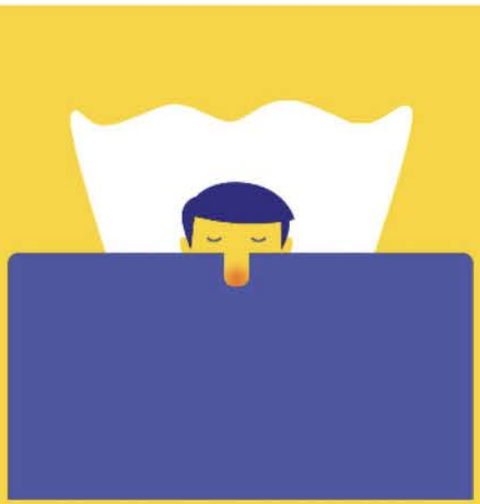
"I tried to find a way to avoid this calamity, but here we are," he told *Terp* in mid-2020. "Maybe this tragedy will get us past our fear of the idea of airborne transmission and prepare to control it, which could help us to avoid all this next time."

Midway through his flu study, Milton finds himself in the odd spot of rooting for a virus—within the walls of the hotel—that he's fought for decades.

INVISIBLE THREAT

Indoor air is about 90% of all the air most of us breathe, Milton says, so he frequently keeps track of what's in his. In his office in the School of Public Health Building, Milton reaches over and plops a device on his desk reminiscent of a small digital clock. At the beginning of our interview, the big number on its LCD screen reads a little over 400, but some 45 minutes later, the number has risen dramatically. Our breath as we spoke boosted carbon dioxide in the room to nearly 700 parts per million.

While the CO_2 concentration itself is not a health hazard—even at much higher concentrations, like at a 2022 Maryland Public Health Association meeting he attended that had levels well over 2,000 parts per million—it's a worrying sign. The amount of CO_2 in the air indicates the risk of infectious viruses floating around, according to a mathematical model Milton proposed with the late Stephen Rudnick of Harvard Medical School in an influential 2003 paper rejected by *Science* but published in *Indoor Air*.



Respiratory disease has shadowed Milton's life. He grew up in the Baltimore area in the 1950s and '60s, when factories and mills still crowded Sparrows Point and other parts of the city and belched pollution into the air far thicker than any hovering around Charm City today. As children, he and his two sisters watched their mother struggle with bronchiectasis, a condition that involves recurring, painful bouts of bronchitis and airway infection, and caused her death in 1995. "I think I may have gravitated toward studying respiratory issues from wondering as a child why my mother couldn't get out of bed, what we could do to help her."

He graduated from the University of Maryland, Baltimore County and Johns Hopkins University School of Medicine and later earned a doctorate in public health from Harvard. While serving as a practicing physician in environmental and occupational medicine, Milton began focusing on indoor air quality.

One tragedy in particular—the death of a woman who had been among several workers in a badly ventilated room who developed adult-onset asthma—galvanized his direction in medicine and public health. Her body was discovered in her home, clutching a rescue inhaler.

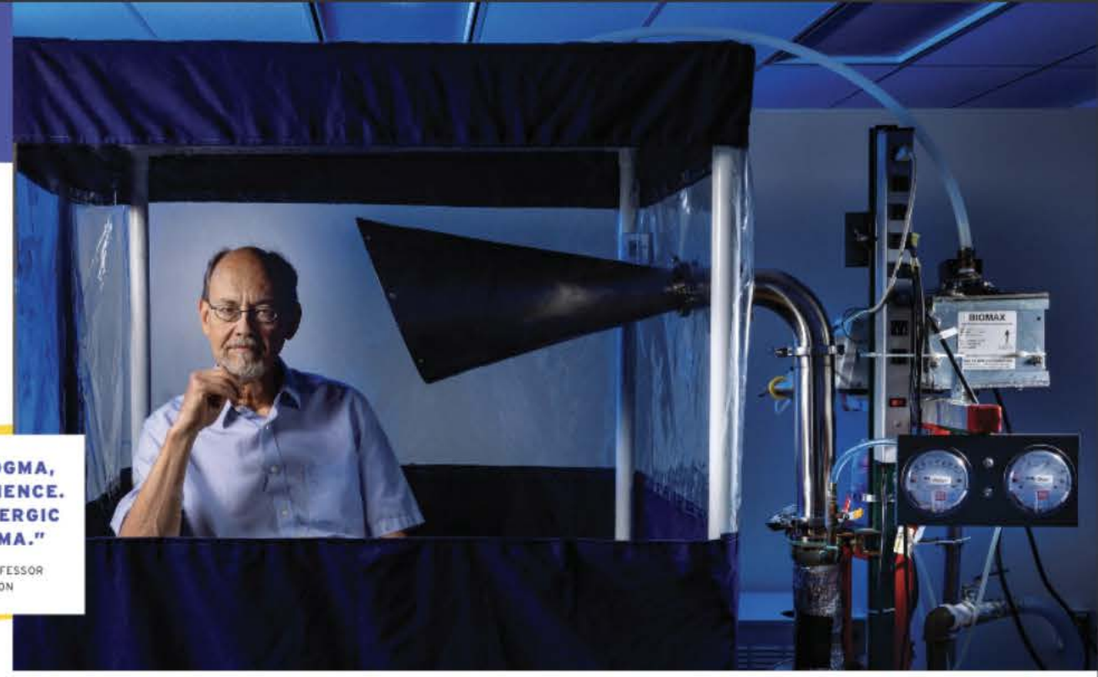
"That indelible image and the failure of medical treatments to save my patient keeps me focused on the importance of indoor air," he says.

CLEARING THE AIR

Many prominent physicians (not to mention the disinfecting wipe industry—"kills 99.9% of viruses and bacteria!") still hew to the idea that the primary routes of infection are through the spray of a sneeze or cough directly into the face, or onto a surface to be transferred by touch to the mouth, eyes or nose.

The developing idea that "aerosols," fine particles that can remain suspended in the air for considerable periods, can hold enough exhaled virus to cause infection was increasingly bringing Milton into conflict with the medical establishment.

One of Milton's papers, which examined the possibilities of airborne smallpox soon after the 2001 attacks with the deadly anthrax bacteria when there was concern about bioweapons in Iraq, was met with livid responses from reviewers, including charges he was a "quack and a charlatan," he says.



"IT'S DOGMA, NOT SCIENCE. I'M ALLERGIC TO DOGMA."

–MPOWER PROFESSOR DONALD MILTON

To prove his point about what's in the air, he developed a machine, which he named Gesundheit II (above); the vaguely steampunk assemblage of tubes and gauges leads to a Victrola-like horn into which visitors to his Public Health AeroBiology Laboratory stick their faces so the machine can capture their breaths and extract viruses. In a 2013 study published in *PloS Pathogens*, he used it to demonstrate flu virus could be captured from infected people's breath and cultivated. The paper also showed that surgical masks reduced the amount of influenza virus escaping into the air from an infected person by 70%.

A past collaborator of Milton's, Raymond Tellier, an associate professor and microbiologist at McGill University in Montreal, says the backlash against Milton in part stems from scientific disputes stretching back to the early 20th century, when doctors fought unscientific beliefs about "miasma," or unhealthy night air thought to cause everything from cholera to the bubonic plague. The idea led to measures that encouraged disease, such as buildings designed to prevent ventilation with outside air; while such thinking has been universally rejected, its echoes remain, he says.

"The idea of aerosols with virus particles was being lumped together with the old reaction against the miasma theory," says Tellier, who adds that today those who refuse to consider Milton's ideas are the ones ignoring science.

Milton also attributes some of the reaction to hospital administrators' unwillingness to swallow the cost of air cleaning or issuing masks that are more protective—and expensive—than surgical masks. But the resistance is underlain by the idea that "this is how we've always done it," he says.

"It's dogma, not science," he says. "I'm allergic to dogma."

As the COVID-19 pandemic began, Milton watched with dismay as his work seemed to have little effect on what medical and public health authorities were telling people; masking was initially widely dismissed, and social distancing, handwashing and even wiping down supermarket purchases were presented as the best means to stay COVID-free.

But in March 2020, Milton and several co-authors posted a paper online that was soon published in *Nature Medicine*. The study used Gesundheit II to confirm that surgical masks could stop coronaviruses as well as influenza when worn by infected people. Its impact was life-changing for much of the world: Mask use soon became widespread—even mandatory in many places—perhaps signaling a growing open-mindedness about the route of transmission Milton had been focused on for two decades. He quickly became a standby source for journalists covering COVID-19 and other respiratory infections, spoke to the White House and Congress, and served on an increasing number of global public health advisory boards.

"Although his contributions are now widely recognized, Don has not received the accolades that he has deserved," says Jonathan M. Samet, professor and former dean of the Colorado School of Public Health. "It took a pandemic ... for his work to finally receive an appropriate level of attention, given its implications."

PORTRAIT BY STEPHANIE S. CORDLE

"IT TOOK A PANDEMIC FOR HIS WORK TO FINALLY RECEIVE AN APPROPRIATE LEVEL OF ATTENTION, GIVEN ITS IMPLICATIONS."

–PROFESSOR JONATHAN M. SAMET, COLORADO SCHOOL OF PUBLIC HEALTH

Researchers and students from Milton's lab test technology used to track participants in the flu study's common room by playing a dancing video game.

HIGH-RISK, HIGH-REWARD

Milton's latest major study began in 2021 with $15 million in funding from the National Institutes for Health, although fieldwork at the hotel didn't kick off until late 2022. For the first time, it joins a full range of scientific elements and expertise to document in detail a flu transmission, says Professor Jelena Srebric, the Margaret G. and Frederick H. Kohloss Chair in Mechanical Engineering, an expert in indoor air quality and computational fluid dynamics, and one of Milton's co-principal investigators.

"Of course, you can't actually see individual viruses causing someone to be infected, but the design of this study will give more understanding of every step along the way than we have ever had before," Srebric says. "We'll know what made you sick and what didn't make you sick."

Unlike other controlled trials of virus transmission, the hotel-based one calls for flu recipients to quarantine in their rooms—reading, working remotely, watching TV—when they're not being intentionally exposed to infected flu "donors." Previous hospital-based studies that discount the importance of airborne transmission didn't take steps to ensure people weren't picking up the virus at home or elsewhere. As a result, they mean little, Milton contends.

In the Baltimore hotel study, participants are brought together in a common room at intervals throughout the day to play cards and board games, do yoga or belt out renditions of "Baby Got Back" and "I'll Make a Man Out of You" from Disney's "Mulan" in karaoke. Among other tightly controlled factors, Srebric and colleagues are testing different room ventilation rates to see if cleaner air results in fewer infections via the airborne route.

To examine other modes of infection, randomly chosen participants use hand sanitizer and wear face shields to prevent viruses from being propelled into their nose, eyes or mouth from coughs or sneezes, and to prevent them from touching their faces; others are unprotected. All participants are then instructed to pass digital devices and other common objects around to test touch as a route of infection.

Constant rapid PCR testing, using machines donated by the Balvi Filantropic Fund, keeps track of who has the flu and who doesn't, while the Gesundheit II allows researchers to measure how much virus donors put in the air; molecular sequencing at NIH tracks what strain virus donors bring in.

A team led by School of Medicine Professor Wilbur Chen, an infectious disease physician-scientist, oversees the medical testing while keeping constant tabs on the well-being of participants; another led by mechanical engineering Professor Don Devoe focuses on creating novel testing devices and technology for analyzing airborne viruses.

In another element of the experiment funded by the Balvi gift, which invests widely in respiratory infectious disease research, the researchers will test whether a new type of germicidal ultraviolet light devices prevents infections. That would support the theory that the flu virus is transmitted in room air and provide a silent and energy-efficient way to sanitize indoor air.

All told, the extremely complex project could change how the world thinks about infection, or it could go off the rails. In the experiment's first year, an unusually early flu season struck before the team was ready to quarantine participants; last year saw several flu donors, but with a dearth of recipients—just 11 in total, despite room for nearly 50—the illness hung back in the shadows like a shy ghost.

PHOTO BY STEPHANIE S. CORDLE

No volunteer recipients tested positive for the flu virus during quarantine, although one later showed chemical markers of an infection in a blood test. And in an illustration of the challenges of human studies, another participant who developed mild symptoms despite testing negative never returned to confirm whether they had been infected.

Ironically, to better fight the flu, the research team needs the flu to do better this winter.

"We are going to do everything we can, so all those hotel rooms are filled," Milton says. "The point is to get more people exposed for more time."

A former colleague at Harvard Medical School uninvolved with the current study says Milton's scientific reputation and administrative abilities helped him secure funding for a type of study that is rare in the world of science.

"It says something about Don that he's able to launch these human-to-human transmission clinical trials," says Edward Nardell, a physician who specializes in tuberculosis research. "These are high-risk studies—and high-reward if they succeed."

"LIKE SUMMER CAMP"

Soon-to-graduate UMD student Priscila Terry was entertaining competing thoughts when she arrived in the sumptuous hotel lobby in February: The information science major was unhappy that her sick roommate had coughed freely around their apartment—including directly into a fan as she slept—the likely source of Terry's flu. On the other hand, the payment involved—donor participants in the trial receive up to $1,900, while recipients can receive $2,500—would allow her to repay her parents for the fee they'd covered when she canceled a semester abroad to graduate early.

And she was wrestling with the complex ethics of medical trials, particularly those meant to induce illness: "I was always taught you should try avoiding coughing on people—it's gross. It's inconsiderate. But now I was supposed to make people sick."

Qualms like Terry's were unnecessary, says Lehua Gray, who also participated in a February quarantine. The 36-year-old digital user experience designer from Baltimore County first signed up for so-called "challenge trials"—where scientists manually infect participants—to help develop a COVID-19 vaccine, but was not chosen. While Milton's airborne transmission hypothesis lacks the electricity of the high-stakes fight against the pandemic, the deep scientific and policy questions involved quickly grabbed her.

One of the most surprising aspects of the experience to Gray was the bond that the recipients developed during their activities over their two weeks—"like summer camp." Several have since stayed in touch, even meeting for drinks and lobbying with administrators to check back in as a group this winter.

"I could randomly catch the flu going to the grocery store, and it wouldn't help anything," Gray says. "If I get it as part of this study at the hotel, maybe it will help science understand something we don't understand as well as we thought we did."

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Interested in sharing your flu or borrowing someone else's as a paid volunteer to help researchers learn how to conquer the illness? Visit ***cvdtrials.org/baltimoreflu*** to get started.