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MORBIDITY

A personal response

Some people get horribly sick from the flu, and even die. Others just rest for a few days. What's behind this fateful variation?

BY CHRISTINE JUNGE

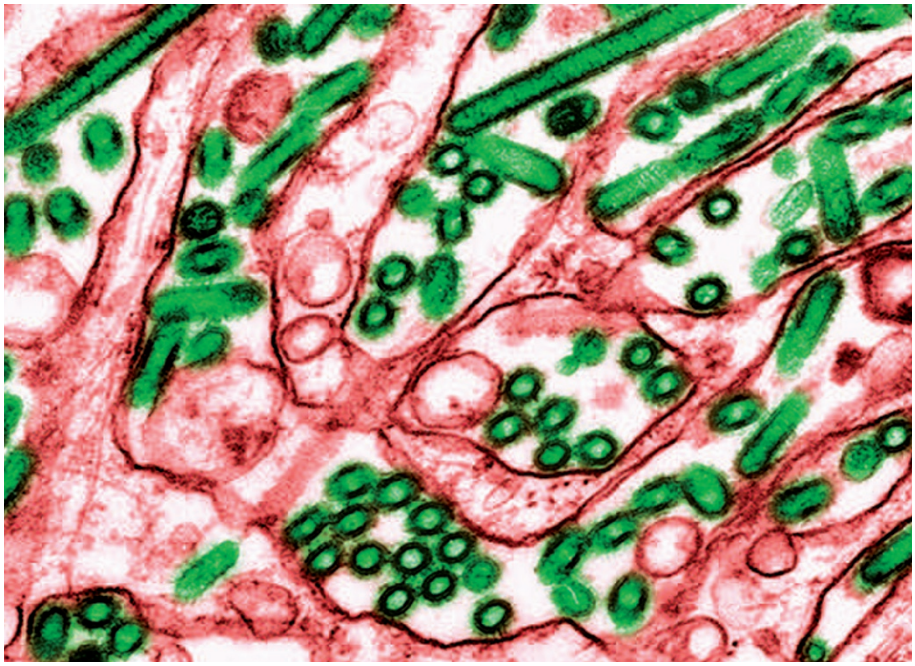
Your spouse had the flu last week and could barely get out of bed for five full days — she was feverish and her aching body exhausted. Then your four-year-old became sick and you had to rush her to the hospital when her fever spiked. Now that you've come down with the virus, you're tired, a bit achy, but that only lasts for two or three days. How is it that the flu virus can have such a variable impact on people?

In order for the flu to pose a danger to any individual, two major factors must align: the host person has to be a clean slate — someone who hasn't been exposed to an influenza virus related to the one circulating; and the virus itself has to be especially potent. The range and severity of symptoms the host experiences depend on the answers to a few other questions, such as whether the person's immune system is compromised, and whether some genetic vulnerability exists.

The first question to delve into when asking about why a particular person gets very sick is: what makes a particular strain of flu more likely to take hold in a human host? The answer lies in the basic structure of the pathogen. The influenza virus always consists of two types of major proteins: one hemagglutinin (H) and one neuraminidase (N). There are at least 16 types of neuraminidase and 9 of hemagglutinin, in principle, capable of forming more than 100 strains of flu virus. In reality, however, the flu viruses that commonly infect humans have been limited to only three types of hemagglutinin and two types of neuraminidase[1], giving six possible flu strains. Each season, there's a chance that, through mutations and recombinations, a novel virus will emerge — one that few, or no, humans have encountered before. Rolling this viral game of dice leads to deadly consequences. 1957 saw the emergence of the H2N2 strain. This represented a major structural shift for the virus; for the previous 40 years, all the flu cases had been caused by H1N1 viruses. This new virus killed 70,000 people in the United States alone[2].

A more recent example of a novel virus was the H5N1 swine flu that circulated in 2009. Unlike seasonal flus, which are most severe in the elderly and those with other health problems, this virus killed a large number of young people — about a quarter of the deaths were in people younger than 24 years (many of them without pre-existing illness), and more than 60% were in people aged 25–64 years — again, many of them otherwise healthy. The reason for this reversal of fortunes was that the virus was similar to ones that had circulated many years ago. Many elderly people, therefore, had some immunity to it, but their children and grandchildren had never been exposed to any influenza like this one and so lacked any resistance to it[3].

Another issue that sets flu apart from some other infectious diseases is that antibodies against influenza don't have a very long shelf



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Up close and personal: H5N1 (green) in cell culture.

life. In certain groups of people, there are additional concerns: after peaking, antibody levels decline faster in older people than in younger people. In people with compromised immune systems, such as someone with HIV/AIDS or someone taking certain cancer drugs, it's double trouble — antibody levels don't rise as high after exposure to the virus in the first place, nor do they last as long. "It's difficult to say whether any individual is still protected after a year or not, which is why we recommend getting the flu shot each year," says Lisa Grohskopf an infectious disease specialist who works in the influenza division of the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia. She adds that protection can wane from the beginning of one flu season to its end, since the season can stretch for seven or eight months.

Infants or young children who haven't come into contact with the flu virus before — either by getting infected or from vaccination — don't have antibodies specific to the viruses circulating in a given year, putting them at risk for getting the flu.

For reasons that aren't always clear, according to microbiologist Peter Palese at the Mount Sinai School of Medicine in New York, people with certain chronic illnesses also have a harder time resisting flu or fighting it once they do get it. Flu is more dangerous for people with heart disease, diabetes, asthma, chronic obstructive pulmonary disease (COPD) and morbid obesity. Palese explains that some of those diseases, such as asthma and COPD, cause persistent lung problems, so any illness that causes fluid to accumulate in the lungs, as flu does, would be more problematic for these people. For the obese, he says, breathing can be difficult, so the act of clearing mucus from the lungs might also be difficult, and the virus would linger in the lungs longer. Grohskopf adds that various health problems can create a vicious cycle. For instance, she says, "diabetes affects the immune system and so may affect the body's ability to fight influenza; in turn, being ill with the flu can cause difficulty with keeping blood sugar under control," an outcome that can complicate diabetes.

Flu's effects can be amplified not only by illness but by our genes. Indeed, just as the genetics of the flu virus itself (which determines which H and N type it is) can make it stronger or weaker, the genetics of the person who encounters the influenza virus can make that person more or less likely to become ill. One thing that has become clear in recent years is that single nucleotide polymorphisms in one of a number of genes governing immunity affects a person's susceptibility to infectious diseases, and how sick he or she becomes from those infections. A 2008 study by Ute Vollmer-Conna, a geneticist at the University of New South Wales in Australia, who studies the genetic response to infection, advanced that idea. Vollmer-Conna's research looked at 300 people infected with one of three viruses: Epstein-Barr, *Coxiella burnetii* (which causes Q fever) and the Ross River virus[4]. Her conclusion: those who had the most severe symptoms, and those who were ill for the longest, had polymorphisms that significantly influenced pro- and anti-inflammatory cytokine production. Vollmer-Conna explains that these genetic predispositions intensify the inflammatory response to an acute infection, as well as prolonging recovery time. Although the scope of her study did not include influenza, she hypothesizes that "the same principles apply across a much broader range of common infections, including flu".

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Another, more recent study looked at the changes in gene expression caused by the flu virus specifically. Researchers exposed 17 healthy subjects to flu virus type H3N2. Nine came down with flu symptoms and eight did not. When the scientists looked at blood from each subject, they noticed that different genes were up-regulated, depending on whether the person fell ill or not. "Individuals who became symptomatic had up-regulation of genes involved in the inflammatory response," says Geoffrey Ginsburg, director of the center for genomic medicine at the Duke Institute for Genome Sciences and Policy in Durham, North Carolina, and one of the authors of the study. "The exuberance of the inflammatory response is likely at the root of why we have symptoms of infection," he says. In those who did not become ill, he explains, the genes that were up-regulated were those involved in protein synthesis and oxidative stress. "Asymptomatic subjects may have mechanisms at work that prevent active infection and therefore reduce the inflammatory response."

Aside from more research into the human genes that control the immune response to flu, there are plenty of other lines of investigation that would help explain why different people respond to flu so differently. Vollmer-Conna argues for more research to tease out which genes and biological processes are responsible for recovery after an infection. This knowledge, she writes, could let doctors identify those at risk for severe illness following infection with common diseases, and therefore set them up with special prevention and treatment programmes.

In a 2004 research paper, Palese posed several questions, including what makes it possible for some influenza viruses to hop from one animal species to another; questions that he hoped researchers would have answered by now. He concedes that seven years later, the questions on his list are still pertinent. One in particular that still remains an important area of research, says Palese, are the viral genes that determine transmission versus the host or environmental factors that promote its spread.

Clearly researchers have made some progress, but as the poet Robert Frost once wrote, there are miles to go before we sleep. Frost was writing about stopping in the woods on a snowy evening in winter — which, of course, is flu season. ■

Christine Junge *is a science writer in North Easton, Massachusetts.*

1. Palese, P. *Nature Medicine* **10**, S82–S87 (2004).
2. Dolin, R. *How to understand your risk and protect your health (Harvard Health Publications*, 2009).
3. Vollmer-Conna, U. *et al. Clinical Infect. Dis.* **47**, 1418–1425 (2008).
4. Huang, Y. *et al. PLoS Genet.* **7**, e1002234 (2011).