

# Drugs, Quarantine Might Stop A Pandemic Before It Starts

Thirty-six years after the last influenza pandemic, researchers wonder whether they can make these global disasters a thing of the past

It might just work. With military-style planning, a big stash of pills, and a lot of luck, the world might be able to stop a nascent influenza pandemic dead in its tracks, two new modeling studies conclude.

The models, published online this week in *Nature* and *Science* ([www.sciencemag.org/cgi/content/abstract/1115717](http://www.sciencemag.org/cgi/content/abstract/1115717)), are the first attempts to estimate the power of the antiviral drug oseltamivir to quash a pandemic—an unprecedented and audacious idea. If large numbers of people in the region first hit by a pandemic virus take the drug prophylactically and comply with some quite draconian measures to limit their movements and contacts, millions of lives might be saved, the authors of both papers say—and medical history would be rewritten in the process.

But just how likely is that scenario to succeed? As experts point out, the models, both of which chose Thailand as the presumptive ground zero, are based on several untested assumptions: that the runaway virus isn't highly infectious, for instance, and that large quantities of drugs can be distributed rapidly to the right people, even in remote villages. "The models make sense, and we should seriously consider this approach," says Harvard epidemiologist Marc Lipsitch, "but the take-home message is there's no way we can count on this."

The researchers—one team led by Ira Longini of Emory University in Atlanta, Georgia, the other by Neil Ferguson of Imperial College London—hope their work will lead to con-

crete actions because until now, there's been little if any official commitment to such a plan. The World Health Organization (WHO), which the researchers say would have to lead the effort, is "interested," says the agency's pandemic chief, Margaret Chan. Rich countries are stockpiling oseltamivir to protect their own populations, but they have no plans yet for shipping it to the cradle of a pandemic. Nor are the Asian countries affected by H5N1—the avian influenza strain most feared as the potential source of the next pandemic—on board or necessarily up to the logistics, although they were slated to discuss the idea at a meeting in Bangkok earlier this week.

**Drug of the day.** A global stockpile of up to 3 million treatment courses of oseltamivir might be needed.

Given influenza's history, most experts peg the chance that the world will be hit by another pandemic at 100%. The question is when it will occur and how bad it will be; there's widespread agreement that the death toll could be in the tens of millions. Vaccines offer by far the best chance to avert that danger—at least in countries that can afford them—but these would take months to produce after a pandemic begins (*Science*, 15 October 2004, p. 394).

A bold new idea is to use oseltamivir to battle a potentially pandemic virus at the source, before it becomes a global threat, using an internationally run stockpile. The strategy might be

the only way to prevent disaster in the majority of countries unable to afford vaccines or drugs at all, notes Arnold Monto of the University of Michigan, Ann Arbor. Oseltamivir would make those who get the flu less infectious to others, but by far its most important task would be to prevent infection in those exposed to the virus.

Now, that idea has been put to the test. Longini and his colleagues simulated an imaginary population of 500,000 people who live, work, and move about in rural Southeast Asia. Meanwhile, Ferguson and his colleagues built a model based on the 85 million people living in Thailand and a 100-kilometer-wide border zone in neighboring countries. Both then introduced a pandemic virus and looked at how well different containment strategies performed.

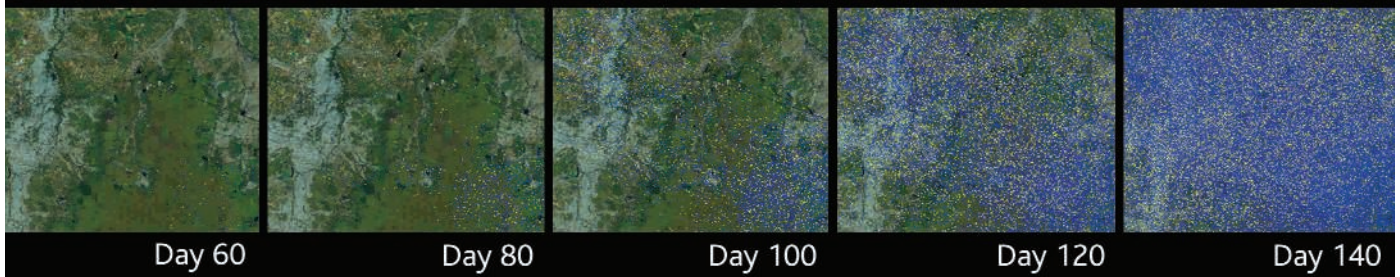
The cornerstone in each model was giving a 10-day prophylactic course of oseltamivir to the contacts of every suspected flu patient—either by treating everyone in their household, school, or workplace, or by simply giving it to anyone living within a certain radius. In both models, the drug regimens were supplemented by measures such as closing schools, "home quarantine," or "area quarantine," in which travel into and out of the hot zone is restricted.

And in both models, the more such measures were deployed, the higher the chances were that the pandemic petered out, with thousands or even millions of people taking an oseltamivir course, but only a few hundred actual flu cases. But success depended critically on a few factors.

One is the infectiousness of the pandemic virus. Epidemiologists characterize infectious agents by a factor called  $R_0$ , which denotes the number of secondary infections caused by a primary case. In both studies, viruses with an  $R_0$  between 1.0 and 1.8 could usually be contained, depending on the exact set of measures; with an  $R_0$  well above 2.0, the outbreak often spiraled out of control. Estimates for  $R_0$  during past pandemics have varied; in a paper published in December, Lipsitch concluded that it was between 2 and 4 in the United States during the 1918–19 pandemic. But Ferguson estimates it was about 1.8.



## Avian Flu Epidemic Without Intervention



**Stop right there.** A computer model shows how a new pandemic might spread in Thailand. With massive prophylaxis, the outbreak might end after just a few hundred cases.

CREDITS (TOP TO BOTTOM): ASSOCIATED PRESS; I. LONGINI ET AL.

## A Drug Makes It Big—But Can It Deliver?

The worldwide fears triggered by the Asian outbreak of H5N1 have created one clear winner: oseltamivir, the drug that, from a quartet of candidates, is considered the best one to fight a pandemic. More than two dozen governments have placed orders for a stockpile with the producer, Roche in Switzerland; 2005 sales are expected to exceed \$700 million—up from just \$110 million 3 years ago—and seem poised to grow further, says Bret Holley, an analyst at CIBC World Markets in New York City.

The procurement orders may be lucrative, but it remains to be seen just how effective oseltamivir, known commercially as Tamiflu, will be during an influenza pandemic. Nor is there agreement about how big a national stockpile should be, or who should receive the drugs to maximize their impact. And in the worst-case scenario, resistance in the flu virus might render stockpiles worthless.

As a remedy against nonpandemic flu, oseltamivir has certainly failed to win many supporters since its launch in 1999. The drug, which blocks a viral enzyme called neuraminidase, can make a bout with influenza more bearable and shorten the duration of symptoms by a day or more; it has also been shown to prevent complications and hospitalizations—but not mortality. The problem is that it needs to be given within 48 hours of infection to be fully effective. And even for patients who meet that deadline, most doctors don't think the benefits warrant the \$65 cost of a prescription. (Japan, where sales have soared, is the exception.)

How well oseltamivir will perform against human infection with H5N1 is unclear. It has shown anti-H5N1 activity in test-tube and animal studies, but human cases have been so rare that experience is extremely limited.

Who should get treatment is also in question. Pandemics may sicken between 25% and 50% of the population in 3 months, but many people with milder cases can probably recover by themselves. Still, countries such as France, the United Kingdom, and Finland are amassing enough oseltamivir to treat 20% to 30% of their populations; the United States,

on the other hand, currently has only 2.3 million doses for almost 300 million people. The Bush Administration was expected to announce a new order shortly—although nowhere near the 67 million to 124 million treatments that the Infectious Diseases Society of America has urged.

Recently, another potential role of oseltamivir has garnered a great deal of attention: that of preventing illness rather than treating it. Studies have shown that oseltamivir can reduce the risk of infection in people exposed to the virus by around 80%. That benefit is key in global plans to stamp out a pandemic early on (see main text); once a virus is on its worldwide rampage, national governments could similarly attempt to slow its spread within their own borders.

Last year, a study by Ira Longini's team at Emory University in Atlanta, Georgia, showed that using oseltamivir preventively could contain an outbreak in the United States, and a paper published this month by Ran Balicer of Ben Gurion University of the Negev in Be'er Sheva, Israel, suggests that stockpiling drugs for this purpose should be cost-effective if pandemics occur more often than once every 80 years. That may seem like a fairly safe bet, but it would require reserves for much more than 25% of the

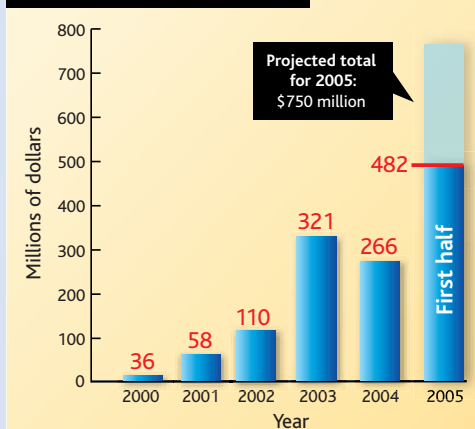
population—an amount few countries are considering at the moment.

For now, a more feasible and widely discussed approach may be to restrict prophylactic use to certain groups, such as health care workers, people performing "essential" jobs, or the elderly—although picking the beneficiaries might create wrenching ethical dilemmas.

Another worry is that once tens of millions of people start taking Tamiflu, the virus will become resistant. So far, resistance appears to be rare in other flu strains; during the 2003–04 flu season, when a whopping 6 million treatment courses were prescribed in Japan, only 4 of 1180 virus isolates tested there showed resistance, a group reported in April. And fortunately, mutations that confer resistance also appear to slow the virus's growth.

Tamiflu may soon face some competition, as other drugs are in the pipeline. And many researchers say they'd feel a lot better if the bullish market for flu drugs were split between a couple of rivals. —M.E.

Oseltamivir Global Sales



Another key condition in both models is that the operation starts within a couple of weeks of the first cases. Chances of containment drop dramatically if it takes more than 2 days to reach new patients' contacts. Both conditions may be challenges, to say the least, in rural areas with poor health care.

Some infectious-disease experts put little stock in models like these. "In 30 years in public health, I've never seen any statistical modeling that had any impact on public health. And this is no exception," says Michael Osterholm, director of the Center for Infectious Disease Research and Policy at the University of Minnesota, Twin Cities. A single SARS patient in a Hong Kong hotel triggered a worldwide outbreak in 2003, he notes; no model could have predicted that turn of events.

But to Anthony Fauci, director of the U.S. National Institute of Allergy and Infectious Diseases, the studies provide an "interesting

blueprint" of what might be possible. "Even if there's only a 20% or 30% chance of success, it's worthy of the effort," adds Frederick Hayden, an antiviral expert at the University of Virginia, Charlottesville, "given the enormous impact that a pandemic would have."

It wouldn't be all that expensive, Hayden notes. The amount of oseltamivir needed—some 3 million courses in Ferguson's most unfavorable scenario—isn't very much; the United Kingdom alone has ordered almost 15 million 5-day courses for its own citizens. WHO already has more than 100,000 treatment courses, donated by Roche, sitting in a stockpile. And Roche may soon make another, much larger donation to WHO, says David Reddy, the company's influenza pandemic task force leader.

But although WHO welcomes any oseltamivir it can get its hands on, more studies, as well as discussions with the affected

countries, are needed to find out whether the snuffing-out scenario is feasible, Chan says. The Thai government, for its part, is interested in exploring the option, says Supamit Chunsuttiwat, a senior expert for communicable diseases at the Ministry of Public Health. The two papers, he says, "give us some hope that we might be able to do this."

But Osterholm worries that the two papers might calm fears prematurely. Even if the scheme envisioned by Ferguson and Longini were successful once, he said, it would need to be repeated as long as H5N1 is rampant in the bird population. Longini agrees. But who knows, he says, researchers might get better at it after the first time. And in any case, only a small region would be affected in every budding pandemic. "It's not like we're exposing the entire world to a fire drill every time," Longini says.

—MARTIN ENSERINK