

Influenza

Suryaprakash Sambhara of CDC, senior author on the *Lancet* study.

Both universities are seeking funding for clinical tests from NIAID and companies. Sambhara plans to give the Purdue team an adenovirus-based vaccine containing genes for NP and M, which codes for M2 and an inner protein, as well as H5HA; and Andrea Gambotto of Pittsburgh hopes his vaccine, which also worked in chickens, may be picked up as a bird vaccine. A company called PowderMed avoids using adenoviruses to

deliver the DNA, which have some drawbacks, instead using gold-coated particles and high-speed injection to get HA-based DNA vaccines into a person's skin cells.

Although the variety of approaches to broader flu vaccines can be dizzying, "having all of those efforts moving forward gives us more weapons in the arsenal and makes us more likely to find the best platform," NIAID's Nabel says. Even if one approach rises to the top, there are many obstacles ahead, such as

persuading regulatory agencies—who now approve flu vaccines based only on HA antibody responses—to use CTL responses as a measure of efficacy instead, notes virologist Albert Osterhaus of Erasmus University in Rotterdam, the Netherlands. Still, if universal—or at least broader—flu vaccines can make it to the market, they could save lives during regular flu season and stave off disaster when the next pandemic strikes.

—JOCELYN KAISER



NEWS

Oseltamivir Becomes Plentiful—But Still Not Cheap

The shortage of oseltamivir may soon be a thing of the past. But whether the drug will become cheap enough for developing countries and how well it will work against a pandemic remain to be seen

For more than 6 months, German physician Tido von Schoen-Angerer has "desperately" tried to order oseltamivir from Roche, the Swiss company that produces the anti-influenza drug. "But I've given up," he says. Von Schoen-Angerer, research and development director of the Campaign for Access to Essential Medicines at Médecins sans Frontières in Berlin, wanted 100,000 treatment courses to protect MSF personnel and to treat patients, should the organization ever find itself at the cradle of a pandemic. But Roche kept saying it simply didn't have enough of the drug, Von Schoen-Angerer says. He eventually picked up 500 treatments from a Dutch wholesaler last month, at a price he says was too high.

As global demand for oseltamivir, better known by Roche's brand name Tamiflu, reached the stratosphere, many clients found themselves at the end of a long queue. But their frustrating wait should soon be over. Last month,

Roche announced a series of deals with other companies to dramatically ramp up production of oseltamivir; in 2007, it says it will be capable of producing 400 million treatment courses (each consisting of 10 capsules) yearly. That's up from just 6 million 3 years ago and much more than the expected demand. Supply will be boosted further because a handful of generic drug makers have started producing their own versions of oseltamivir—some with a sublicense from Roche, others without.

Although production may finally meet worldwide demand, several questions remain. It's unclear whether oseltamivir's price will drop enough for poor countries to stockpile the drug; many fear that they will be left behind (*Science*, 18 November 2005, p. 1103). That's why it's essential to find simpler ways to produce the drug, some say. One such method may be a revolu-



Drug of choice. More than 65 countries are stockpiling oseltamivir, better known as Tamiflu.

tionary, easy, and cheap synthetic pathway that Harvard University chemist and Nobel laureate Elias Corey and his team are now reporting.

Also unanswered is the question of how well oseltamivir will work against a pandemic virus. The drug is effective against seasonal flu strains, but there aren't solid data about its efficacy against H5N1, the avian influenza strain that some suspect is a prime candidate to evolve into the next flu pandemic. "We think it's effective" against H5N1, says Nikki Shindo, a medical officer at the World Health Organization (WHO) in Geneva, Switzerland, "but that's a feeling. We would like to have more evidence." Some studies on the drawing board aim to get just that.

Change of heart

Until less than a year ago, Roche routinely dismissed suggestions that it sublicense oseltamivir, saying it needed tight control over the complex production process, which includes a risky step involving an explosive intermediate compound called an azide. It also refused to say how much oseltamivir it produced or how much it was charging governments for it.

But the company did an about-face last fall. In the past 6 months, it has signed deals with more than 15 companies, each of which will help carry out a step in Tamiflu's production process. In addition, Roche has sublicensed Shanghai Pharmaceuticals and HEC, both in China, and Hetero in India, to make oseltamivir from beginning to end. Those companies will produce generic versions for local use; they won't be named Tamiflu, and Roche will not control quality, production volume, or pricing policy, says David Reddy, Roche's pandemic task force leader.

Two Indian generic drug makers—Ranbaxy and Cipla—have started making oseltamivir without a deal with Roche; they can sell it in India and other places where Tamiflu is not covered by a patent, Roche says, such as Thailand, Vietnam, Indonesia, and sub-Saharan Africa. Cipla—which has dubbed its drug Antiflu—can currently produce about half a million treatments

per month and plans to double capacity soon, says the company's joint managing director, Amar Lulla; the production process is "difficult but not impossible," he adds. Ranbaxy also hopes to double its current production, to over half a million treatments per month. Generic drug makers in Taiwan, Bangladesh, and Algeria also make oseltamivir.

For now, the generic companies aren't offering much of a discount. Roche charges governments in developing countries roughly \$15 for a treatment course (rich nations pay \$18); Cipla will sell Antiflu for about \$12, says Lulla, and other generic drug makers have quoted prices in the same ballpark. "We're not seeing generic [drug] prices that are vastly dissimilar to ours," says Reddy. But Von Schoen-Angerer is confident that competition from the generics will cause prices to plummet, as happened with HIV drugs. At \$12, he says, "developing countries still cannot stockpile in any meaningful way."

Innovation could further drive down prices. The Achilles' heel of oseltamivir production is its starting point, a compound called shikimic acid. It was originally derived from star anise, an herb grown in China and Vietnam that quickly became scarce as oseltamivir demand surged. However, Roche says it now gets roughly one-third of its shikimic acid through fermentation by genetically engineered *Escherichia coli* bacteria, developed by John Frost of Michigan State University in East Lansing; it would like to increase that proportion further to two-thirds.

New chemistry could do away with the need for shikimic acid altogether, some scientists say. Harvard's Corey says his synthesis route, described in a paper accepted for publication by the *Journal of the American Chemical Society* (JACS), starts with butadiene and acrylic acid, "two of the cheapest chemicals you can buy." As an added bonus, the synthesis route is easy to scale up and avoids the explosive



But does it work? Exactly how effective oseltamivir is against H5N1 infection in humans is unclear.

intermediate, says Corey. Organic chemist K. C. Nicolaou of the University of California, San Diego, and the Scripps Research Institute, who is familiar with the work, says, "The synthesis is strikingly short and efficient." Corey, who serves on Roche's bioscience scientific advisory board, says he has told Roche about the findings, which he did not patent in hope

that they will become widely used. "My hope is that this work will save lives, especially in poor countries," he says.

If it holds up, Corey's production method would have to garner regulatory approval and would need to be scaled up. What's more, other companies couldn't simply start using it, because patents for oseltamivir cover the compound itself, not just the way it is made, says Vid Mohan-Ram, a patent agent with Foley & Lardner in Chicago. But generic drug makers could adopt the process, he says, which could drive their prices down. And an easier production route could also encourage Roche to lower its price. Reddy says that Roche is "always looking at new types of technologies" but declined to discuss Corey's work or that of chemist Masakatsu Shibasaki of the University of Tokyo, who, in another paper accepted by JACS, claims to have found a second new route to oseltamivir. (Shibasaki says that "Roche chemists are examining the details" of his findings.)

Clinical study

As oseltamivir stashes begin to grow, several international efforts are under way to answer basic questions about the drugs' effects on avian influenza in humans. Animal studies have suggested, for instance, that H5N1's virulence may call for a higher dose than the 150 milligrams used daily to treat ordinary flu. Now, 11 hospitals in Indonesia, Thailand, and Vietnam have teamed up with the U.S. National Institutes of Health for a randomized trial to test whether patients with serious influenza—either from H5N1 or a human strain—fare better when they receive 300 milligrams per day. The logistics are complex, says Menno de Jong of the Hospital for Tropical Diseases in Ho Chi Minh City, but the study could start in a few months.

WHO, too, is working on study protocols, says Shindo, and on agreements with countries to implement them when new human cases show up. They're looking into the efficacy of prophylactic use in health care workers and other high-risk groups as well as the usefulness of combining an older influenza drug, amantadine, with oseltamivir.

But with human cases so rare—so far there have been fewer than 200, scattered across nine countries—any such trial will be extremely difficult to conduct. In Turkey, for instance, where WHO had relatively good access when human cases popped up in January, Shindo says there wasn't really an opportunity to study prophylaxis; communication problems and practical concerns got in the way. "Our primary objective during an outbreak is not doing science," she says. "It's to save people's lives and stop the outbreak."

—MARTIN ENSERINK



Supply surge. With help from other companies, Roche says it can produce 400 million treatment courses of oseltamivir next year. Generic drug makers plan to make millions more.