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FLU FIGHTERS

Drug firms help battle the **NOVEL H1N1 VIRUS** in response to calls from health agencies and governments

ANN M. THAYER, C&EN HOUSTON

ALTHOUGH THE WORLD'S been tracking the novel H1N1 influenza virus since April, the course of the flu pandemic it's causing can't be predicted. The winter flu season in the Northern Hemisphere is beginning, and the unpredictable virus and its unexpected epidemiology have public health agencies hoping for the best but preparing for the worst.

"We can't stop the tide of flu any more than we can turn a hurricane in its course or stop the earth shaking during an earthquake, but we can mitigate the effect, and we can help prevent people from becoming severely ill by preparing well and acting effectively," warned Jay Butler, director of the H1N1 Vaccine Task Force at the U.S. Centers for Disease Control & Prevention (CDC), in a late August telephone briefing.

Health officials hope that rapid action coming after years of pandemic preparedness planning will blunt the new flu's most extreme effects. Manufacturers are ramp-

ing up production of antiviral drugs that can lessen the severity and spread of illness while vaccines are being readied to prevent infection (see page 27). But until the flu plays out, the world won't know whether the scale and timing of the response is adequate.

The 2009 H1N1 virus isn't the everyday flu, which doesn't necessarily mean it makes you feel sicker. Most cases are mild and resolve in about a week without treatment, according to CDC. Still, alarmingly, the new virus causes more healthy young people to get sick and even die, compared with seasonal flu. Pregnant women and individuals with preexisting medical conditions are at risk for more severe disease as well.

This novel H1N1 virus has knocked the usual seasonal varieties out of contention and now accounts for about 60% of flu viruses circulating worldwide. Flu virus subtypes are designated by their surface proteins: one of 16 possible hemagglutinins (H1-H16) and one of nine neuraminidases (N1-N9). Despite

the large number of possible permutations, human flu is generally caused by H1, H2, and H3 subtypes in combination with N1 or N2.

H1N1 subtypes are quite common among seasonal influenzas. The 2009 H1N1, however, is a unique hodgepodge of reassorted genetic elements from avian, human, and swine sources. Its mixed heritage initially made it unidentifiable when it cropped up during routine tests in April. After CDC received samples, its researchers quickly sequenced the strains and developed real-time reverse transcriptase polymerase chain reaction assays to detect them.

With the help of diagnostics, it became clear that the 2009 H1N1 virus was spreading rapidly. On June 11, the World Health Organization director general declared a level 6 pandemic, indicating that a new

STOCKING UP Roche has increased production of its antiviral drug Tamiflu by 15-fold.

virus not previously circulating in humans was being rapidly transmitted. Six weeks later, WHO stopped trying to count the illnesses and deaths, finding it nearly impossible to confirm them.

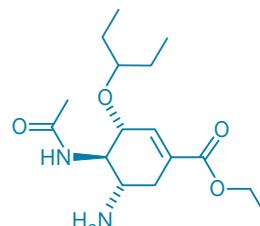
Because few people are immune to the new virus, WHO has predicted that as many as 2 billion people, or about 30% of the world's population, could become

infected over the next two years. In a typical flu season, about 5–15% of the world's population gets the flu, 3 million to 5 million people get severely sick, and 250,000 to 500,000 die. WHO anticipates that the percentage of deaths from H1N1 2009 will be small but disproportionately higher in countries with limited medical resources.

Wherever the flu hits, doctors will need

to know their opponent, and diagnostic tools will be critical. Current rapid tests often fail, and more sensitive methods are time-consuming. To act quickly to treat patients, many doctors will likely make decisions on the basis of clinical signs and symptoms rather than confirmed test results. Surveillance is also needed to know when, and whether, the virus becomes resistant to drugs. Fortunately, while testing tries to catch up with H1N1's rapid spread, the virus remains susceptible to drug treatment.

In principle, four antiviral flu drugs are available. But like many seasonal flu viruses and the H5N1 avian flu strain, novel H1N1 is resistant to amantadine and rimantadine, two older adamantane drugs that block the virus's M2 ion channel protein (C&EN, Feb. 11, 2008, page 53). GlaxoSmithKline's (GSK) Relenza (zanamivir) and Roche's Tamiflu (oseltamivir), both neuraminidase inhibitors, are still effective.



Oseltamivir (Tamiflu)

ANTIVIRALS CAN BE used for treatment and prophylaxis. WHO, CDC, and other agencies recommend them primarily for hospitalized patients or those at high risk for complications. Officials caution against prophylactic use and suggest antivirals only for high-risk groups or health care workers who could be exposed to the virus. "Most children, adolescents, and adults who have influenza-like illness do not need antiviral medicine," said Anne Schuchat, director of CDC's National Center for Immunization & Respiratory Diseases, when she updated the treatment guidelines on Sept. 8.

Limiting use helps conserve supplies and avoid the development of resistance in the virus. Treatment works best within 48 hours of the start of symptoms because the drugs target viral replication under way at that time. Once the virus gets knocked down, the body can usually clear the infection.

At best, the available drugs reduce the duration of the illness by a day or so, points out Holger Rovini, head of infectious and respiratory diseases at the market research firm Datamonitor. As a result, he says, Relenza and Tamiflu haven't had great con-

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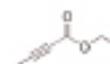
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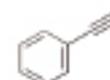
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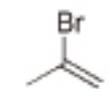
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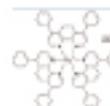
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ability to prevent infection about 90% of the time and to decrease the severity of illness by 40% and hospitalizations by 61%.

To further extend efficacy, Roche has also worked with Novartis to study Tamiflu in combination with amantadine and with GSK to look at a Tamiflu-Relenza pairing. Emeryville, Calif.-based Adamas Pharmaceuticals, working with the Naval Health Research Center and academic collaborators, recently presented results from a Phase II trial. The firm showed the high potency of a triple combination of existing flu drugs—amantadine, ribavirin, and oseltamivir—that act at different stages of

the virus life cycle, even in drug-resistant strains.

Meanwhile, GSK has contracts to supply 195 million doses of Relenza to more than 60 countries. The company expects to triple its production capacity by the end of 2009, which would allow it to make 190 million treatments per year. Government orders have increased Relenza sales 10-fold, to nearly \$470 million in the first half of 2009. GSK has allocated 10% of its new capacity for developing countries, including a donation of 2 million doses to WHO.

If broad-based resistance to Tamiflu did develop, Relenza would be the only ap-

DIAGNOSTICS

Reliable, Easy-To-Use Tests Could Aid Treatment

Not surprisingly, most of the detected cases of the newly emerged 2009 H1N1 virus have been in well-off countries that can afford diagnostic tools. “What we and many other diagnostic companies

are trying to do is develop technology that is less expensive and easy to use so that it can be placed in parts of the world that really need to do more surveillance,” says Kathy Rowlen, chief executive officer of InDevR, a small biotechnology firm in Boulder, Colo.

More expensive real-time reverse transcriptase polymerase chain reaction (rRT-PCR) methods, which measure influenza-specific RNA, are very sensitive when the properly designed panel of primers and probes is in hand, Rowlen explains. Once the U.S. Centers for Disease Control & Prevention created a relevant panel in April, the Food & Drug Administration issued an Emergency Use Authorization (EUA) allowing qualified labs to use the CDC assay. Soon after, FDA granted an EUA to Focus Diagnostics for its rRT-PCR test.

According to evaluations by CDC and other research groups, however, test-

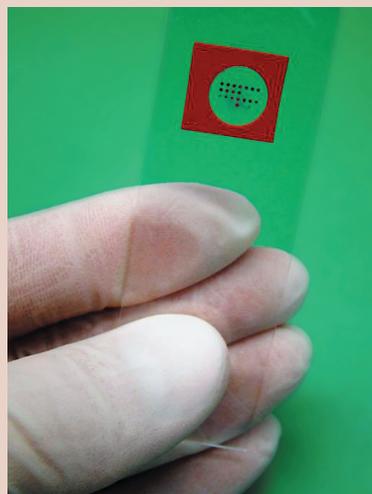
ing falls short with another test class: rapid antigen-detection immunoassays. Although such tests can give an answer within 30 minutes, many can determine only whether a person has influenza

and cannot distinguish between subtypes or detect the novel H1N1 virus. Because of the unacceptably low sensitivity of rapid tests to rule out novel H1N1 infections, CDC offers guidance on how to interpret results and proceed with treatment.

In the meantime, CDC has been working with Meso Scale Diagnostics to advance a rapid point-of-care test that can identify subtypes. Likewise, with support from

the National Institute of Allergy & Infectious Diseases, InDevR researchers, while still at the University of Colorado, Boulder, collaborated with CDC to develop low-density DNA microarray technology.

With support from a National Institutes of Health grant, “we are looking to place this technology in 20 or so public health labs, at no cost to the labs, by the end of October or early November,”



GOTCHA A pattern on InDevR's FluChip microarray identifies the novel H1N1 influenza virus.

proved option. But because it is an inhaled powder, Relenza isn't recommended for anyone with a pulmonary condition. GSK is testing intravenous forms of the drug.

Beyond Relenza, the near-term flu drug pipeline doesn't hold many candidates because until recently the lackluster market offered few incentives for developers. "It's mostly more of the same," Rovini says, referring to new indications for existing drugs or related compounds with similar modes of action.

Nevertheless, a few candidates look promising. Biota is developing long-acting neuraminidase inhibitors, the most ad-

Rowlen says. The system includes the microarrays and a reader that costs under \$4,000, which is several times less than the cost of an rRT-PCR setup.

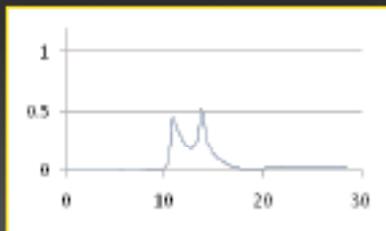
Rather than targeting the virus's mutable hemagglutinin or neuraminidase genes as other methods do, InDevR's FluChip uses the more stable *M* gene that encodes for an internal matrix protein. "We discovered that the *M* gene alone told us something about the subtype," Rowlen says. The company has shown that its test can distinguish novel H1N1 viruses, seasonal H1N1 and H3N2 viruses, and the deadly avian H5N1 virus.

InDevR's FluChip assay can identify an influenza A virus when its genetic sequences bind to complementary segments on the microarray. These segments are labeled with a photoinitiator, rather than an expensive fluorescence label. Exposure of a monomer solution on the microarray to light produces a visible pattern of polymeric dots that acts as a fingerprint for the virus subtype. "With a low-density microarray, we can address more gene targets than you can in a typical rRT-PCR assay, which is usually limited to one or two," Rowlen explains.

InDevR is developing two versions of its FluChip, one that requires about three-and-a-half hours to complete and one that takes about twice as long but provides more information. That the *M* gene can be used to identify different viruses and is highly reliable in testing could become important if the novel H1N1 virus were to mutate and become harder to detect. "We're not replacing rRT-PCR, but our technology is complementary to others and can stand in place if those assays should fail," Rowlen says.

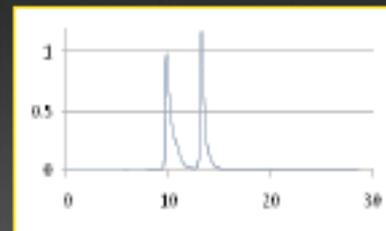
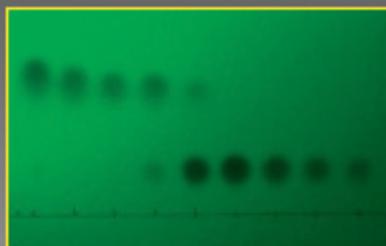
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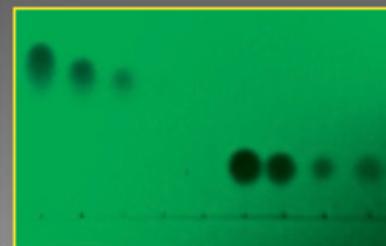
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“We can help prevent people from becoming severely ill by preparing well and acting effectively.”

vanced of which is laninamivir. The Australian drug firm was the original developer of zanamivir, the active ingredient in Relenza. Biota is jointly developing laninamivir with Japan's Daiichi Sankyo, which recently completed Phase III trials in Japan, Taiwan, Hong Kong, and South Korea.

Like zanamivir, laninamivir has been designed to fit snugly in the active site of the neuraminidase surface protein, explains Simon Tucker, Biota's vice president for research. Neuraminidase is involved in the release of new viral particles from infected cells. Inhibiting the enzyme should decrease the amount of virus that makes a person feel sick as well as the amount that can be spread to others.

“The compound is delivered as a pro-drug and then cleaved into the active species,” Tucker says. “Through that process it appears to be retained in the respiratory tract and is available for a considerable

length of time to inhibit the virus.” Clinical studies have found that a single dose, which is inhaled through the mouth, is as effective as Tamiflu given twice daily for five days. Laninamivir might also work as a preventive measure.

THE RESEMBLANCE of laninamivir and Relenza to their target enzyme's natural substrate means it is hard for the virus to evade them, and the two drugs have similar resistance profiles. “The antivirals target a very highly conserved region of neuraminidase that has a specific function,” Tucker says. “If the virus loses that function, it loses the ability to support replication, so there is a very strong pressure to retain that function.”

As a result, he adds, “there's also a reasonable expectation that the emergence of a new subtype won't drastically change the sensitivity to these agents.” On top of

this benefit, laninamivir's low required dosage, which should aid in patient compliance, and its effectiveness against seasonal, avian H₅N₁, and 2009 H₁N₁ viruses make laninamivir a candidate for pandemic stockpiling, Biota believes.

With funding from the National Institutes of Health, Biota is conducting Phase I and II trials outside Asia. Daiichi is preparing to file for Japanese regulatory approval by March 2010, but if the authorities there move quickly or allow an EUA, laninamivir could be used or stockpiled sooner.

BioCryst Pharmaceuticals has also been in discussions with regulators about getting an EUA for its neuraminidase inhibitor, peramivir. The Birmingham, Ala.-based company is preparing for Phase III studies to support a traditional U.S. approval. Its Japanese partner, Shionogi, has completed two Phase III clinical studies for seasonal influenza. In these trials, one dose of perami-

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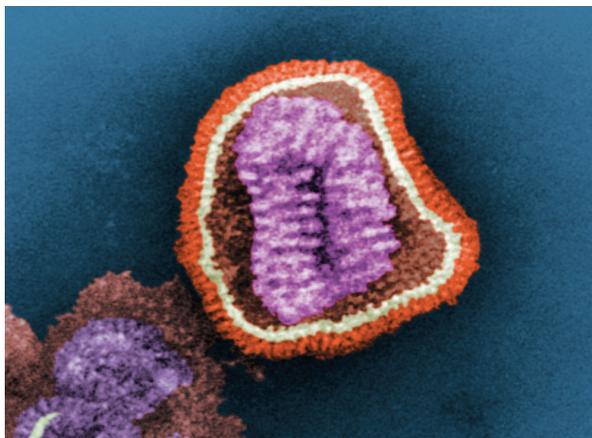
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vir was found to be as effective as a week's supply of Tamiflu. According to BioCryst, Shionogi is pushing to file for approval in Japan soon.

Peramivir is delivered intravenously and thus could hold promise in the niche market for hospitalized patients and for those who can't take an inhaled drug. BioCryst also just recently signed up partners in Mexico, Brazil, China, and Israel to help it look for opportunities to get peramivir into stockpiles and to market it for seasonal flu.

BioCryst has been working on injectable forms of peramivir since 2005, having halted earlier work on oral dosages. Last week, the Department of Health & Human Services awarded the firm another \$77 million, on top of the \$103 million, four-year contract signed in 2007, to support full development. In 2007, Shionogi also agreed to pay up to \$130 million to develop the drug in Japan.

Instead of drugs that are more of the same, next-generation therapies with differ-



CYNTHIA GOLDSMITH/CDC

VIRAL FOE The protein-studded surface of an influenza virus particle (about 100 nm in diameter) can be seen via TEM.

ent mechanisms of action—still in early clinical development—might be called for during future pandemics.

One of the greatest uncertainties and fears about the current pandemic is what future flu seasons will bring.

Earlier pandemics have had “herald,” or introductory, waves in one season, followed by more deadly waves. Whether the 2009 H1N1 virus will mutate or reassort with other flu viruses and take on a more virulent form isn't known.

Earlier this month, WHO reported on the nature of the outbreak in the Southern Hemisphere. In general, events there mirrored what had been seen previously in the North in terms of who got sick and how sick they became. Among other major findings, virologic data showed that the H1N1 strains were unchanged, meaning that the virus remains stable and sensitive to the neuraminidase inhibitors.

During the Southern Hemisphere's winter flu season, the 2009 H1N1 virus lingered in the North—a highly unusual phenomenon for the summer. Influenza activity in temperate southern countries such as Chile, Argentina, Australia, New Zealand, and South Africa is now declining, WHO reports, but activity persists in tropical regions of the Americas and Asia. Temperate regions in the Northern Hemisphere are seeing variable disease activity as winter approaches, with increases in the U.S.

“The good news is that so far everything that we've seen, both in this country

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and abroad, shows that the virus has not changed to become more deadly," CDC Director Thomas R. Frieden said at a press briefing earlier this month. "That means that although it may affect lots of people, most will not be severely ill." Nevertheless, the influenza virus is generally unpredictable and will require vigorous monitoring to see whether it's changing and whom it's affecting, Frieden warned. Officials must be prepared to change approaches depending on what the virus does.

Several small companies want to be the ones to offer such new approaches. San Diego-based NexBio is developing DAS181, an inhaled viral entry blocker that prevents respiratory viruses from infecting cells. "It is a fusion protein that contains both a sialidase enzyme and a cell-surface-anchoring domain that attaches the enzyme to respiratory epithelial cells to ensure retention and increase potency," says Ronald B. Moss, NexBio's executive vice president for clinical development and medical affairs.

Unlike existing drugs that attack the virus, DAS181 specifically cleaves a human host cell's sialic acid receptors, to which

viruses must bind in order to invade. Sialic acid receptors turn over every few days, "so we don't think there are any ill effects in temporarily knocking out the receptors in the upper airway," Moss says. Like other drugs, DAS181 could be used therapeutically and prophylactically. "A short course of treatment of up to three to five days with DAS181 should be sufficient to have a significant impact on both decreasing viral shedding and symptoms," he adds.

Because DAS181 acts on human cells and not the virus, it's expected to be a broad-spectrum drug. "DAS181 has been shown to be active against roughly 50 influenza strains, including 2009 H1N1, in animal and in vitro models" and is a potent inhibitor of drug-resistant strains, Moss says. "We feel very confident that this drug is going to play an important role in current and future pandemics, despite the fact that there may be ongoing evolution of the virus and drug resistance," he adds.

With a \$50 million National Institute of Allergy & Infectious Diseases (NIAID) contract, NexBio is preparing for large-scale studies. Further along, the company intends to study DAS181 in high-risk populations

such as individuals with pulmonary disease or transplant patients with suppressed immune systems for whom drug resistance could be more likely to occur.

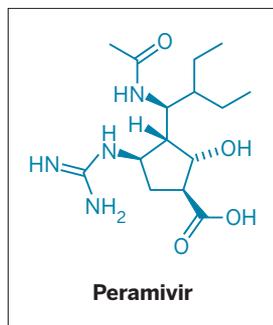
In Japan, Toyama Chemical is developing T-705, or favipiravir, which inhibits flu virus RNA polymerase, a viral-replication target identified by other groups as well (C&EN, Aug. 4, 2008,

page 9). Although the drug's half-life might need to be improved, it offers the benefit of working even if given several days after infection. The drug has potent and broad-spectrum activity against multiple flu strains, according to Toyama, and will soon be in Phase III studies in Japan.

TARGETING ANOTHER part of the virus, Crucell, in the Netherlands, has generated monoclonal antibodies (mAbs) that bind to the relatively invariant stalk of the hemagglutinin surface protein (C&EN, March 2, page 11). In preclinical studies, a Crucell mAb called CR6261 has been shown to neutralize a broad range of H5N1 and H1N1 strains. Although not a vaccine, the mAb not only can treat the disease but also has prevented H5N1 infection and even death in preclinical animal models. Last month, the company received an NIAID contract, potentially worth up to \$69 million, to advance development.

Relative to other drug development areas, the antiviral field is new and one that has been dominated by research on diseases such as HIV, executives at influenza drug development firms tell C&EN. With only one of two classes of flu drugs showing any efficacy, there's clearly a need for options that are more potent, less prone to resistance, and broadly active.

Roche's Burns has pointed out that the current flu pandemic is challenging conventional wisdom. The good news so far is that the novel H1N1 strain has not been as deadly as was once feared. Calling the pandemic "probably the largest fire drill the planet's ever had," Burns suggests that the many lessons to be learned will be important to all stakeholders as they deal with the flu virus. ■



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