its pandemic vaccine is based on a more highly conserved—but less immunogenic—antigen, the extracellular domain of the M2 viral matrix protein (M2e). "The real hurdle here is M2 has never been shown to protect humans against disease—it works well in mice," says Shaw.

Universal vaccines, based on highly conserved viral antigens, such as M2e, could provide multi-year protection against multiple influenza strains (**Table 2**). They could be stockpiled in advance allowing vaccine makers to get off the annual reformulation treadmill needed to keep up with the HA and NA antigens' mutability. Other recent work has suggested that a concealed hydrophobic pocket in the conserved stem region of HA might also be a conserved epitope suitable for vaccine development (*Nat. Struct. Mol. Biol.* **16**, 265–273, 2009; *Science*, published online, doi: 10.1126/science.1171491, February 26, 2009).

Several universal vaccines have already entered the clinic, but progress has been slow. "I believe one of the reasons these things have not moved very quickly is the results have not been spectacular," says Dino Dina, CEO of Dynavax Technologies, of Berkeley, California. Next year, Dynavax aims to start a clinical trial of another candidate universal vaccine, a recombinant protein comprising two conserved viral antigens, nucleoprotein (NP) and M2e, fused to an immunostimulatory sequence that acts as a TLR9 agonist. "Nucleoprotein generates immunity during natural infection, but it's only present in trace amounts in conventional vaccines," says Dina. The protein, he says, elicits a cytotoxic T-cell response, which could help to reduce viral spread and transmission. "In a pandemic kind of setting that would be a very valuable feature."

But others see universal vaccines as a long-term bet. "Our biggest concern is that the regulatory pathway for universal vaccines is not clear," says Rahul Singhvi, CEO of Rockville, Maryland–based Novavax. The firm uses VLP technology to develop vaccines based on HA and NA and the structural protein M1. A baculovirus vector expressed in an insect cell culture system produces particles, which closely resembles the native virus. "To the immune system it appears like there's a natural infection at the site of immunization," says Singhvi. This approach, he says, would enable large-scale manufacturing within around 12 weeks of a pandemic strain being characterized.

The company is also offering, in conjunction with GE Healthcare, a subsidiary of Fairfield, Connecticut–based GE, a low-cost, portable, disposable manufacturing system for pandemic vaccines. "You can do this in low-infrastructure environments," Singhvi says.

Quebec-based Medicago is also harnessing VLP technology, but in a radically different setting. The company has developed a transient gene expression system in the plant species *Nicotiana benthamiana*, a close relative of the tobacco plant, which can produce VLPs comprising the viral HA antigen only. It relies on an *Agrobacterium* plasmid to deliver the construct to the plant cells. Frederic Ors, Medicago's vice president of business development, says the purified VLPs are highly immunogenic, and the production process is also relatively low cost. "All you need is a greenhouse," says Ors. "The biomass production is cheap, even in comparison to eggs."

It will be several years yet, however, before any of these innovations—and others in development at competitor firms—will be ready for commercial rollout. In the meantime, drug therapy will remain a vital frontline defense against a pandemic (**Box 1**).

At this point, it is not yet clear whether the current pandemic alert will escalate further or will peter out, as recent avian flu epidemics have done. What is certain is that a vaccine for swine-derived H1N1 lies several months away.

Cormac Sheridan *Dublin*

Profiting from pandemics

It's most likely that established vaccine developers, such as London-based GlaxoSmithKline and Sanofi Aventis of Paris, would pump out stockpiles of any pandemic flu vaccine, but it is the small biotechs that literally rise and fall with the world's pandemic concerns. Note Birmingham, Alabama–based BioCryst, developer of the clinical stage neuraminidase inhibitor peramivir, for influenza. The firm received a 90% stock boost to $3.29 on April 27, after the H1N1 influenza (swine flu) grabbed headlines. And in London, Lipoxen on April 30 announced positive preclinical results for the delivery of an enhanced influenza vaccine, adding that the technology should also work against the new swine flu strain. Investors boosted Lipoxen's share price from £6.62 ($10.11) to £21.75 ($33.23). Also consider Rockville, Maryland–based vaccine developer Novavax. The company's stock slowly lost ground this year, dropping from $2 per share to around 85 cents in mid-April. But when swine flu became the topic of conversation, Novavax's shares jumped more than 200% to $2.55 over two sessions. Similarly, in 2005, when the flu was avian rather than swine, Novavax's shares traded at less than a dollar for most of that summer. However, in the fall, when the company's avian flu vaccine, manufactured using their virus-like particle technology, performed well in animal models, Novavax's stock jumped to close as high as $5.53. ***Brady Huggett***