Flu virus lapses shows quantum leap in technologies needed

Developing treatments that would calm pandemic fears need more funding and resources.

Cormac Sheridan

Recent extraordinary lapses in the monitoring of the influenza virus has revealed how vulnerable we are to the threat of a pandemic.

Regular disruptions in flu vaccine supply, the lapse that led to the recent worldwide distribution of a pandemic-like H2N2 strain, and fears that affected countries are failing to inform the World Health Organization of any changes in avian virus strains, have shown how current production methods for annual vaccines would be woefully inadequate in an emergency.

Classical approaches to flu virus prophylaxis and therapy have held sway for more than 50 years, and represent a key defence system against an outbreak.

But developing these vaccines — by growing the three most prevalent pathogenic strains recommended by the WHO in embryonated chicken eggs — is cumbersome and inflexible, requiring lead times of more than 6 months in advance of the flu season to enable manufacturers to produce sufficient volumes. Also, any pandemic strain of avian origin would be lethal for chicken eggs.

Initiatives are underway to improve the status quo. The UK's National Institute for Biological Standards and Control (NIBSC) is trying to build a 'seed reference library' of 10–15 strains corresponding to high-risk pandemic-like subtypes.

Should a pandemic emerge, says the NIBSC's John Wood, the library would allow rapid genetic comparison with the real pandemic strain. A close match could then be used to seed vaccine production during the early stages of a pandemic outbreak, buying around two-and-a-half months of time to ramp up production volumes.

One alternative is to remove the element of guesswork, by focusing on antigens that are conserved among influenza strains. Attempts to develop such universal vaccines have been underway for more than a decade, but supporters of the concept say progress has consistently been hampered.

"People are reluctant to accept the idea that perhaps there may be a way to use a more classical type of vaccine that is valid for many years against influenza," says Walter Fiers of the University of Ghent, Belgium, who is developing a prototype vaccine based on the extracellular domain of the M2 protein.

The Meriden, Connecticut-based biotechnology company Protein Sciences aims to launch its FluBl0k vaccine — based on purified recombinant hemagglutinin antigen produced in insect cell culture — in 2007, but the company's COO, Manon Cox, says it could have been on the market ten years ago.

"What has been in our way is [lack of] money," says Cox. The big players have been unwilling to embrace innovation. "These guys have no incentive whatsoever to do anything other than what they are doing," says Cox.

Klaus Stohr, head of the WHO's influenza programme, believes that the best way out of the current impasse is to launch a major, long-term global initiative to develop a cross-subtype-specific universal vaccine. Current spending on influenza vaccines, he estimates, is running at US$3 billion annually. If health authorities channelled 5% of this into a ten-year cooperative research programme, this would produce substantial improvements.

The WHO is encouraging the European Commission to consider this issue in its Priority Medicines sub-programme within its forthcoming Seventh Framework Program of research spending, although industry's response to the idea remains to be seen, says Stohr.

Meanwhile, other companies are pursuing alternatives to existing antiviral drugs. Treatments that can be stockpiled in advance offer an immediate means of fighting a pandemic infection and, potentially, limiting its spread. But the current best-sellers — neuraminidase inhibitors, including oseltamivir (Tamiflu; Roche) and zanamivir (Relenza; GlaxoSmithKline) — block viral entry and spread, yet offer limited efficacy and serve only to shorten the duration of illness.

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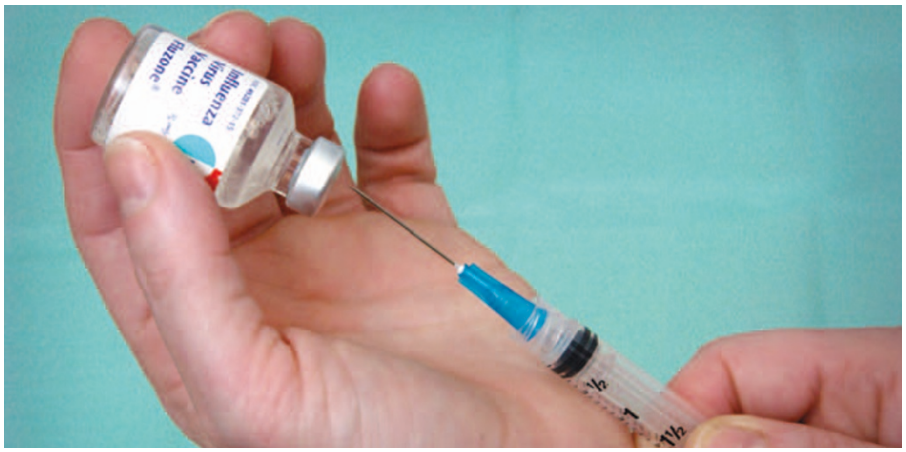
Alternatives, however, are at the early stage. NexBio, a San Diego-based biotechnology company, is developing a recombinant protein called Fludase containing the enzyme sialidase, which blocks viral entry to the epithelial cells lining the respiratory tract. "Our plan is to file an Investigational New Drug application by the end of this year and start a clinical trial during the first quarter of next year," says NexBio's Chief Scientific and Medical Officer, Fang Fang.

RNA interference (RNAi) is also being examined as a potential prophylactic and therapeutic option. Jianzhu Chen, Professor of Immunology at Massachusetts Institute of Technology showed that short interfering (si)RNAs specific for conserved regions of the influenza virus genome could both prevent and treat virus infection in mice. A team led by Suzanne Epstein at the FDA showed a similar effect with the same siRNAs in mice exposed to pandemic-like H5 and H7 subtypes.

Alnylam Pharmaceuticals is also interested in developing RNAi-based treatments to combat a pandemic threat. "The early work we are doing is examining how many different siRNAs we would need," says COO, Barry Greene. "It is likely you would need more than one."

A big step would be to target siRNA delivery to the lungs. Last month, Chen reported improved delivery of DNA and siRNA to mice lung tissue by full deacylation of a commercially available polyethylenimine vector. (Thomas, M. *et al.* PNAS 102, 5679–5684; 2005). "If an inhalable formulation can be developed that would be very, very significant," he says.



Centers for Disease Control and Prevention

Current flu vaccine production methods would be inadequate if a pandemic strikes.