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Giving it their best shot: vaccine producers are focusing their efforts on tackling flu viruses.

Race is on for flu vaccine

Drug companies are using adjuvants to boost their vaccines in a bid to be ready for a flu pandemic, as Meredith Wadman reports.

Not so long ago, vaccine manufacture was a neglected backwater of the drug industry. The threat of a global flu pandemic has changed that. Leading vaccine producers are now engaged in a furious race to be ready to tackle such a pandemic.

They face a considerable challenge. The cell-surface proteins of flu viruses change, or 'drift,' over time, so vaccine makers can't develop a vaccine in advance that they know will work if bird flu acquires the ability to pass between humans, triggering a pandemic. What's more, there aren't many companies in the race, after low profits drove many to stop producing vaccines at all.

It has been estimated that today's combined global manufacturing capacity could provide a vaccine for 450 million people at most (D. S. Fedson *J. Public Health Policy* 26, 4–29; 2005). And that calculation might be optimistic: it assumes that two vaccinations of 15 micrograms each would confer protection, whereas one recent trial suggested that two doses of 90 micrograms would be required.

"The biggest challenge unequivocally is vaccine production capacity," says Anthony Fauci, director of the US National Institute of Allergy and Infectious Diseases (NIAID).

Because of this capacity issue, vaccine producers are looking hard at ingredients known as adjuvants, which render vaccines more effective at low doses. France's Sanofi-Pasteur and CSL in Melbourne, Australia, are already conducting trials of candidate pandemic vaccines that use adjuvants made of alum, an aluminium salt — the only kind already approved for use in humans in the United States.

Sanofi-Pasteur's results from a trial of 300 subjects comparing vaccine alone with a vaccine containing an alum adjuvant, at a dose as low as 7.5 micrograms, are expected by the end of the year. And GlaxoSmithKline is planning to launch its own trials of a vaccine containing an alum adjuvant early next year.

But it is California-based Chiron — which is currently being taken over by Novartis — that may have the most promising adjuvant. Called MF59, it consists of emulsified squalene with influenza virus in the centre of each droplet. In clinical trials of an early candidate vaccine aiming to confer protection against H5N1 — the virus that has been killing birds by the million in Asia and Europe — vaccine containing the MF59 adjuvant was significantly better than vaccine alone at spurring the production of antibodies to H5N1 (K. G. Nicholson *et al. Lancet* 357, 1937–1943; 2001).

Coping with change

Perhaps the most exciting thing about MF59 is its apparent ability to confer protection against H5N1 even if the virus's cell-surface proteins change. The antibodies induced in the blood of volunteers immunized against the H5N1 virus that infected Hong Kong in 1997 were later found to neutralize versions of the virus that appeared in southeast Asia in 2003 and 2004 — even though they had different cell-surface proteins (I. Stephenson *et al. J. Infect. Dis.* 191, 1210–1215; 2005).

"We at Chiron believe we have the only practical answer to vaccination against pandemic flu," says Rino Rappuoli, the company's chief scientific officer. "The adjuvant allows you to vaccinate and to cover strains that may be drifting," he says. "So you can actually go from a strategy of containing a pandemic to preventing a pandemic completely by vaccinating people before it comes."

But the ability of MF59 to protect against a drifted strain of H5N1 cannot be proven until a pandemic strain actually emerges. "It depends on how great the drift is," says Jerald Sadoff, president of the Aeras Global TB Vaccine Foundation in Bethesda, Maryland. "And since we don't know that, it's not clear whether it would work."

The mechanism that allows adjuvants to prompt a more vigorous immune response isn't well understood. But they are thought to act by recruiting and activating the immune-system cells that respond to vaccine proteins, and by prolonging the time that a vaccine's active ingredient is exposed to the immune system.

Seeking approval

Alum adjuvants have a good safety record, and MF59 has been used in flu vaccines in Europe since 1997. But new combinations of adjuvants and vaccines can raise fresh safety issues — and it isn't clear how quickly MF59 will be approved in the United States.

Geoffrey Porges, an analyst at Sanford Bernstein, a New York investment bank, thinks that Chiron could face significant regulatory hurdles in bringing a flu vaccine containing the MF59 adjuvant to the US market: "It stands a better shot of getting to market quickly in Europe," he says. "In the United States, regulators might be wary of the new vaccine and new adjuvant combination, and more traditional vaccine approaches could have an advantage."

MF59 has also yet to be proven against H5N1 in large clinical trials. NIAID will shortly test Chiron's H5N1 vaccine in some 400 subjects, Fauci says, with another trial of Sanofi-Pasteur's alum-adjuvant vaccine to follow next year. Both trials will test vaccines formulated with adjuvant at the time of manufacture against vaccines in which adjuvant is added just before injection. If the latter is effective, existing vaccine stockpiles could be made to go further with the adjuvant's help.

Much is likely to depend on the results of the upcoming trial of Chiron's vaccine. "We'll have to work with the Food and Drug Administration to get enough data to see if we can get it licensed," Fauci says. "And that's going to depend purely on the data." ■