Regulators face tough flu-jab choices

Rich countries' pandemic strategies may cause vaccine shortages elsewhere.

Imminent decisions on a strategy for H1N1 pandemic flu vaccination in the United States could leave other countries short of vital doses if it elects not to follow World Health Organization (WHO) advice on vaccine formulation.

The United States is the biggest buyer among a group of rich countries whose combined orders for vaccine against the H1N1 2009 virus could potentially tie up most of the world's pandemic vaccine production capacity for 6 months or longer, so depriving other countries of vaccine.

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A fistful of vaccines: but will there be enough to go round?

To counter this prospect, the WHO recommended on 13 July that countries use shots that contain adjuvants, chemicals that boost the immune system's response to a vaccine. This allows smaller amounts of antigen — the molecule that stimulates the immune response — to be used in each dose, boosting the overall amount of vaccine available from existing production capacity and allowing orders to be filled more quickly.

The United States' global responsibility to consider dose-sparing strategies is briefly alluded to in the minutes of a mid-June US National Biodefense Science Board meeting, released on 17 July: "Federal decision-making will affect not only the 300 million Americans who depend on the government to support the public health system but also people all around the world."

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The United States has certainly kept open the option of using adjuvants. It has already allocated almost US$2 billion for antigen and adjuvant to provide every American with up to two doses of vaccine. That sum includes orders of $483 million for Novartis's MF59 adjuvant, and $215 million for GlaxoSmithKline's AS03 adjuvant.

But although Canada and many European countries are set to use adjuvanted pandemic flu vaccines, the United States may do so only as a last resort. "All things being equal, an unadjuvanted vaccine is often just fine in terms of giving protection against influenza virus," Anne Schuchat, director of the National Center for Immunization and Respiratory Diseases at the Centers for Disease Control and Prevention in Atlanta, Georgia, told a media briefing on 17 July.

"Adjuvant use would be contingent upon showing that it was needed or clearly beneficial," added Jesse Goodman, acting chief scientist and deputy commissioner of the Food and Drug Administration (FDA). "But we want them on the table in case there are issues where they might be needed to protect people in this country." If there is significant genetic drift in the virus, for example, adjuvanted vaccines are better able to handle such strain variations. And early attempts at pandemic vaccine manufacture are so far producing two to four times less antigen than seasonal flu strains, raising the threat that the world's production capacity is actually much less than was hoped.

If each shot of pandemic flu vaccine contains 15 micrograms of antigen — the dose used in seasonal flu — and no adjuvant, annual global capacity stands at about 876 million doses, according to the WHO. But as virtually no one is immune to the virus, most experts say that each person will need two doses, immediately halving that capacity. Moreover, higher doses of antigen may be needed to get an adequate response, further reducing capacity. Using adjuvants would boost annual capacity — to more than two billion doses in some WHO projections.

Europe is well placed to quickly authorize adjuvanted pandemic vaccines. Since 2003, the European Medicines Agency (EMEA) has had a fast-track approval system in which manufacturers can prepare 'mock-up dossiers' — vaccine registration applications that use non-pandemic viral strains but for which pandemic strains can subsequently be substituted. GlaxoSmithKline and Novartis already have mock-up dossiers in place for the H5N1 avian flu virus, and plan to file H1N1 substitutions by the end of July.

Although the EMEA requires the companies to provide new clinical testing and data as they roll out their products, the product itself can be approved in five days if the agency is satisfied that the extrapolation to the new strain is valid, says Martin Harvey-Allchurch, a spokesman for the EMEA. In contrast, the United States has never licensed an adjuvanted flu vaccine, and has no fast-track system in place, although the FDA can give emergency authorization for new vaccines. The regulators are also mindful of political and public concerns about mass vaccination of the population, given that a vaccination programme in 1976 against a new strain of swine flu caused neurological side effects in about 1 in 100,000 people, and killed 25. Modern flu vaccines, however, have a very good safety record.

The WHO's Global Advisory Committee on Vaccine Safety says "no significant safety concern or barriers" exist to using adjuvanted pandemic H1N1 vaccines. But regulatory agencies may have to approve pandemic vaccines — both adjuvanted and non-adjuvanted — without all the data they would normally require, warns Marie-Paule Kieny, the WHO's vaccine research director. Some preliminary clinical and safety data may be available by September, when flu cases could surge in the Northern Hemisphere, but complete data for adults are unlikely to be available until the end of December, and not until February 2010 for children. Regulators would accompany pandemic vaccine rollouts with parallel clinical trials, and, as in any mass-vaccination campaign, extensive surveillance would monitor for any adverse side effects. ■

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