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Benefit and Doubt in Vaccine Additive

By [ANDREW POLLACK](#)

Are Americans obligated to use an unproven vaccine to help protect people in other countries from [the flu](#) pandemic?

That is the crux of a debate over adjuvants — a class of substances that somewhat mysteriously increase the potency of vaccines. Early studies suggest that adjuvants (pronounced AD-joo-vants) could allow four times as many people to be immunized against the H1N1 pandemic influenza with a given amount of vaccine. So with the world facing possibly severe shortages of vaccine, the [World Health Organization](#) and some health experts have been calling for the use of adjuvants to stretch the vaccine supply.

“We have always argued that using adjuvanted vaccine would leave more vaccine for poor people,” said Marie-Paule Kieny, director of the World Health Organization’s initiative for vaccine research.

Wealthy nations have contracted for much of the expected pandemic vaccine production, leaving little for poorer countries. But while Canada and some European nations will use vaccines containing adjuvants, American officials have decided against it for now. They say that they have enough vaccine and that the safety of the additives has not been proved.

“These are products that potentially can be given to millions of healthy people,” said Dr. Jesse Goodman, chief scientist at the [Food and Drug Administration](#). “There is not a known, specific safety danger or issue” with the adjuvants, Dr. Goodman acknowledged. “There’s just more uncertainty.”

Officials also fear that using an adjuvant would raise public fears about vaccine safety at a time when their challenge might be about to shift from procuring enough vaccine to persuading people to use it.

“If you add what the public would perceive as another unknown there, there’s a concern that people would be reluctant to get vaccinated,” said Dr. [Anthony S. Fauci](#), director of the [National Institute of Allergy and Infectious Diseases](#).

Furthermore, officials say, one reason to use adjuvants is that they can increase a vaccine’s potency against a virus to which it is poorly matched. But the [swine flu vaccine](#) is well matched to the virus, which has not mutated.

In the last two weeks, new data has lifted some of the pressure on the government to use adjuvants. Early studies suggest that even without an adjuvant, a single injection of swine flu vaccine — rather than the two anticipated — will confer adequate protection on adults and children at least 10 years old. That effectively doubles the number of people who can be immunized, and last week the government said it would make 10 percent of its roughly 200 million vaccine doses available to other countries. Eight other nations are also releasing some vaccine.

Still, Dr. Tadataka Yamada, president of the global health program at the [Bill and Melinda Gates Foundation](#), said that most of the world’s population of six billion people, mostly in poorer countries, would still be without vaccine, especially early in the pandemic.

Less vaccine than expected has been produced so far because of manufacturing problems. “Over all, there is still clearly a shortage of vaccine supplies,” said Dr. Andrin Oswald, chief executive of the vaccine business at Novartis. Except for the United States, Dr. Oswald said, most countries ordering from Novartis have taken vaccine with

adjuvant.

Dr. Kieny, of the W.H.O., said as many as three billion doses of vaccine could be produced in a year. But she said governments that had ordered adjuvant vaccines should not abandon them. "There's no reason to think these vaccines will not be safe," she said.

Even if adjuvants do not save the day in this pandemic, experts say they will become increasingly important for vaccines against all manner of diseases.

That is because many vaccines now being developed "simply don't work that well without an adjuvant," said Dr. Thomas Monath, acting chief medical officer of Juvaris BioTherapeutics, a company developing adjuvants.

Vaccines once typically contained a weakened or killed pathogen to spur an [immune response](#). Some newer vaccines consist of only proteins or protein fragments from a pathogen, which makes them purer, safer and quicker to produce. But it turns out that the missing parts of the pathogens help to jolt the immune system; without them, an adjuvant is needed. Companies and academic laboratories are racing to develop adjuvants, "mainly because everyone recognizes the adjuvant could be the make-or-break component of a vaccine," Dr. Monath said.

Intercell, an Austrian company, is developing an adjuvant for [flu](#) shots in a patch worn on top of the injection site for a few hours.

Scientists are also learning how adjuvants work and how to devise them rationally rather than by trial and error.

"For the longest time, adjuvants were sort of a witch's brew of substances, empirically designed," said Bali Pulendran, a professor of pathology at [Emory University](#). "What was once a black box is now being illuminated at the mechanistic level by new advances in immunology."

The term adjuvant, from a Latin word meaning "to help," was coined in the 1920s by Gaston Ramon, a veterinarian at the Pasteur Institute in France, who observed that horses given [diphtheria](#) toxin had a stronger immune response if they had some inflammation at the injection site. Among his first adjuvants were bread crumbs and tapioca.

Within a few years, scientists discovered that aluminum salts could prompt an immune response. Alum, as this adjuvant is often called, is now used in various vaccines, including those for [tetanus](#) and [hepatitis B](#). It is a relatively weak adjuvant. But about 80 years after its discovery, it is still the only one used in vaccines the United States.

That could soon change. An advisory committee to the F.D.A. recently recommended approval of Cervarix, a vaccine against the virus that causes [cervical cancer](#). The vaccine, made by GlaxoSmithKline, uses an adjuvant containing a bacterial lipid. ([Gardasil](#), the Merck cervical cancer vaccine already in use, has an aluminum adjuvant.)

Alum is not used in flu shots because it has little effect. But Novartis and GlaxoSmithKline are selling pandemic flu vaccines containing newer adjuvants they have developed. They are oil-in-water emulsions of squalene, a lipid that is found in the body. Glaxo's also contains vitamin E.

A seasonal [flu vaccine](#) containing Novartis's MF59 adjuvant has been used in Europe since 1997. Glaxo's adjuvant, called AS03, is in a vaccine approved in Europe for use against the H5N1 [bird flu](#), which spurred fears of a pandemic a few years ago.

For the bird flu, an adjuvant was crucial because vaccines without adjuvants did not work well in tests and required huge doses. Glaxo's vaccine required only one twenty-fourth as much antigen, the viral component of the vaccine, as another company's vaccine that did not contain an adjuvant.

Thinking the swine flu might pose the same problem, federal officials ordered \$700 million worth of adjuvant from Novartis and Glaxo.

If the adjuvants were used, they would have to be combined with the vaccine before the injection was given. And because the adjuvants have not been approved by the F.D.A., they would fall under a so-called emergency use authorization.

But in the last two weeks it has been learned that the vaccines against the H1N1 virus stimulate a strong response on their own. A single shot containing 15 micrograms of antigen — the same amount used for each strain in a seasonal flu vaccine — should confer adequate protection for most people.

Preliminary data from GlaxoSmithKline show that a vaccine with an adjuvant might use only one-fourth as much antigen. But federal officials say the savings are not large enough to offset the possible risks and extra complexity of using the adjuvants.

While adjuvants tend to increase the temporary pain, [swelling](#) or fatigue caused by a vaccine, the main concern is whether they might cause an autoimmune disease, like [rheumatoid arthritis](#), in which the immune system attacks the body's own tissues. Some animal studies have suggested that possibility.

Last year, the F.D.A. halted a clinical trial of a [hepatitis B](#) vaccine containing a novel adjuvant after one participant developed a type of blood-vessel inflammation that is considered an autoimmune disease. But the agency lifted its hold this month, apparently satisfied that the vaccine, made by Dynavax Technologies, was not the cause.

Adjuvant makers say there is no cause for concern with the flu vaccines. Dr. Bruce Innis, head of the clinical flu vaccine team at GlaxoSmithKline, said the immune response spurred by his company's adjuvant was directed only at the antigen in the vaccine. "There is not a general upregulation of immune responses across the body," which would be needed for an autoimmune disease, Dr. Innis said.

Novartis says more than 40 million doses of vaccine with its adjuvant have been used in Europe, with no signs of problems. But Dr. Fauci, of the National Institute of Allergy and Infectious Diseases, said Novartis's adjuvant had been used mainly among the elderly, who tended to have weaker immune systems. There is less data, he said, on its use among children, younger adults and pregnant women.

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