

## WHO supports fair access to influenza A (H1N1) vaccine



WHO/L. Solberg

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Dr Marie-Paule Kieny is director of the Initiative for Vaccine Research at the World Health Organization (WHO). She received a degree in Economics in 1977, followed by a PhD in microbiology in 1980, both from the University of Montpellier in France. Her research career began with the development of a recombinant rabies vaccine. Since then, she has worked on the design of AIDS vaccine candidates and done research on cancer immuno-gene therapy, targeting mainly breast and cervical cancers. She has also served on several expert committees on vaccine discovery, AIDS and cancer research.

The vast majority of cases of pandemic influenza A (H1N1) have been mild so far with few deaths. It remains to be seen whether the virus will mutate into a more virulent strain. Marie-Paule Kieny explains how WHO is supporting countries' efforts to protect their populations with vaccines that should become available as of this month.

*Q: When will the first doses of vaccine for the pandemic influenza A (H1N1) be ready?*

A: Some manufacturers announced in July that vaccine is available, but that doesn't mean it's ready for use, as it needs regulatory approval. Regulatory authorities are considering the best way to register these vaccines as quickly as possible. The consensus is that the first doses will be available to governments for use in September.

*Q: Who will get vaccinated first? Who decides this?*

A: Vaccine will not be available on the private market and governments will decide who gets vaccinated first. WHO recommends that health workers be the first, to protect the health system and allow them to care for influenza and other patients. The strategy a country takes will depend on its policy objectives and the availability of vaccine. For example, if a country decides to concentrate on protecting essential infrastructure, it may target different people, such as truck drivers, if they are critical for food delivery. Others may try to reduce transmission of the virus. For example, the United States of America decided to immunize children before or at school entry who are in closer physical contact than adults and can amplify infection rates. Countries may also try to reduce morbidity and mortality and target specific groups, such as pregnant women.

Some high-income countries have ordered enough vaccine for the whole population. Nevertheless, no countries will have vaccine for everyone from the first day it is available for use, so that each country will need to prioritize. Some middle-income countries have also placed contracts with pharmaceutical companies and have been purchasing vaccine for between 1% and 10–20% of the population. WHO is working hard with manufacturers, governments and donors to ensure that developing countries can access vaccine as soon as possible to immunize their health workers, and when more vaccine becomes available, other groups will be immunized.

*Q: How are influenza vaccines produced?*

A: The main method is by injecting seed virus into embryonic chicken eggs and harvesting the fluid after several days and purifying it. There are two technologies. More than 90% of influenza vaccines available are known as "inactivated vaccines", which means you kill the virus to produce the vaccine. Less common are "live attenuated vaccines", which are derived from a weakened form of the virus that is not killed.

*Q: How many different vaccine candidates will be available for A (H1N1)?*

A: About 30. Most will be inactivated virus vaccines made in eggs, some will

be killed virus vaccines made in cell cultures and a few will be live attenuated virus vaccines. Then you have a lot of variation in the way vaccine is purified and in whether or not it is mixed with an additive, called an adjuvant, which is a booster of immunogenicity (which is the capacity of a vaccine to evoke an immune response) and which is used with killed virus vaccine. All vaccines create antibodies to fight the virus; some will produce a local response, such as attenuated vaccine administered in the nose to give more immunity at the port of entry of the virus. The industry will use tiered pricing, so high-income countries might pay between US\$ 10–20 per dose, middle-income countries may pay about half that and low-income half that price again. These are ballpark figures but this is the order of magnitude.

*Q: Isn't it too early to produce vaccines because the pandemic virus could mutate?*

A: Although the virus can mutate, we hope that there will be enough cross-protection through recognition of the new virus. But if the virus changes too much, we will need new vaccines.

*Q: WHO has recommended the use of adjuvant in pandemic vaccines, but some countries don't plan to follow this guidance.*

A: Many countries, including the USA, have not licensed vaccines with adjuvants of any kind yet. Other vaccines with the same type of adjuvant as planned for pandemic influenza A (H1N1) vaccines have, however, been licensed in European countries. Countries that intend to use vaccine with adjuvant will find that there is a large body of safety data for adults and some for children. In any case, all countries will need to carry out good post-marketing surveillance to make sure that they pick up any early sign of a safety problem with a particular vaccine.

*Q: These must be the fastest vaccines ever produced. Given their fast-tracking, what is the guarantee of safety and efficacy?*

A: The testing of influenza vaccines is different from that of other vaccines, because the rabies and measles vaccines for example do not change. Since

influenza viruses evolve constantly, it is impossible to carry out a complete clinical analysis of seasonal influenza vaccines yearly because the composition changes each year to adapt to the virus and so you are always a year behind. A complete clinical evaluation is not needed also because manufacturers produce seasonal influenza vaccines using the same procedure and equipment, but for a different virus each year. In the USA, vaccines for seasonal influenza are licensed without clinical trials on the basis of a “strain change”. The US regulatory authorities consider the change from seasonal to pandemic H1N1 influenza vaccine production (using the same procedure) as a change in the strain and therefore will not request clinical trials before registration. Having said that, all manufacturers will perform clinical trials to find out whether one or two doses are necessary, to test it in special populations and to administer it jointly with other vaccines. In Europe, a strain change is accompanied by a small clinical trial requested by the European Medicines Agency. In the last couple of years, manufacturers in the European Union registered “mock-up” or prototype H5N1 bird flu vaccines as nobody knows which H5N1 strain might become a pandemic strain. Manufacturers made clinical batches of an H5N1 vaccine with virus stocks from China, Indonesia and Viet Nam. They carried

out clinical trials and submitted the results to the regulatory authorities who said the vaccines were fine. They are not allowed to sell H5N1 vaccines, since there is no H5N1 pandemic, but they can use the same procedure to make H1N1 pandemic vaccine. That way they can get a licence in a few days. This is another way vaccines can be licensed without clinical trials, while still ensuring safety on the basis of what is known about influenza vaccines. Based on the extensive knowledge available on seasonal vaccines and the results obtained through evaluation of H5N1 avian influenza vaccines, there is no doubt that it will be possible to make effective H1N1 pandemic vaccines.

*Q: What's been done to ensure that developing countries get enough vaccine?*

A: It depends on what we mean by “enough”. Some countries want to vaccinate every member of the population, but there is no way we can do this for the whole world. WHO has a cross-organizational operation that is in place to secure vaccines for developing countries. This is spearheaded by the Director-General's Office and the legal and vaccine departments. We are engaged in three types of activities. The first is to negotiate donations with manufacturers. Two have been announced: 100 million doses by sanofi-aventis and 50 million doses from GlaxoSmithKline. Second, we

are working with other manufacturers to reserve a portion of their vaccine production for WHO at a reduced price. Third, we are working with governments to raise funds to purchase vaccines. We are also working with 11 vaccine manufacturers based in developing countries, providing them with seed financing and technical expertise to help them produce influenza vaccine domestically. We have also helped them access technology and given them sub-licences to use technology for producing live attenuated vaccine. These 11 companies will be manufacturing some of the 30 different expected vaccines.

*Q: What happens if developing countries have only partial coverage?*

A: Coverage will be partial and not only in developing countries. But we should not be “hypnotized” by vaccines. There are other measures, such as social distancing, school closure, avoidance of large gatherings, antibiotics and personal hygiene. This is not like rabies, which is 100% fatal: we are talking about a disease from which most people recover very well. We will try to help countries to gain access to as much vaccine as possible, at least to preserve their health systems functioning, but there is just not enough vaccine for every country in the world to vaccinate every member of the population twice. ■