FACT SHEET
New technologies using genetic sequence data

Background
Surveillance and response to influenza requires state-of-the-art technological capacities, particularly with regard to genetic analysis. New technologies are starting to allow genetic sequence data (GSD) derived from influenza viruses to be used for an expanding range of purposes, including, in some cases, substituting for physical samples during pandemic risk assessment and the development of commercial products. With such advances, the implications of current technological developments – as well as those that are in progress and those that can be reasonably anticipated – need to be considered in a discussion about approaches to seasonal influenza viruses and to GSD in the context of the Pandemic Influenza Preparedness (PIP) Framework.

Influenza vaccines for disease prevention and control
Vaccination is the most effective way to prevent infection and severe outcomes caused by influenza viruses. For more than 50 years, WHO has been collaborating with scientists and policy makers on a global scale to develop a unified approach to identify and develop new vaccine viruses, testing and regulatory oversight of influenza vaccine development, as well as the efficient use and distribution of the vaccines.

The process of making influenza vaccines is uniquely complicated and difficult. The constantly evolving nature of influenza viruses requires continuous global monitoring and frequent reformulation of influenza vaccines, which is accomplished through the Global Influenza Surveillance and Response System (GISRS). In addition, the rapid spread of influenza viruses during seasonal epidemics, as well as the occasional pandemic, means that each step in the vaccine process must be completed within a compact timeframe if vaccines are to be manufactured and delivered in time. In response to the difficulties imposed by the nature of the influenza virus, a highly functional process has evolved over decades, in which the public and private sectors work together to develop and produce influenza vaccine.

Development of new influenza vaccine technologies
The ability to use genetic sequence data (GSD) has resulted in the emergence of new approaches to vaccine development that do not require live influenza viruses. An increasing number of vaccine manufacturers are using GSD as an alternative to conventional whole virus approaches. That is, manufacturers can – in some cases – now use specialized machines (similar to ink-jet printers) that transform genetic sequence information in digital form into molecules such as DNA, RNA and proteins, or even whole viruses. Those molecules and viruses can then be used in different ways to make vaccines. (See the ‘Genetic sequence data and databases Fact Sheet’ for more information on GSD.) These approaches are expected to lead to the development of better vaccines and to significantly decrease the time required to manufacture pandemic vaccines.

Influenza vaccine technologies
The section below provides information about 1) currently licensed vaccine technologies; 2) vaccine technologies in use but not yet licensed; 3) research on future vaccine technologies that could rely on GSD.

1) Technologies currently used for licensed vaccines
Four types of technologies are currently used for the development of licensed influenza vaccines: a) egg- and cell-based inactivated influenza vaccines; c) live attenuated influenza vaccine (LAIV); and d) recombinant vaccines.

Egg- and cell-based influenza vaccines
Every year, the 144 National Influenza Centres – laboratories belonging to the WHO GISRS located in 114 countries – collect and process millions of clinical specimens from patients with influenza-like illness. Some of these clinical specimens are shipped to WHO Collaborating Centres for further analysis and to reflect the proportions of each influenza virus type/subtype circulating in a given period of time. Based on influenza virus surveillance data provided by GISRS, WHO, in consultation with a group of experts, issues recommendations for the composition of
influenza vaccines. This is done biannually through the vaccine composition process.\(^2\)

On the basis of the vaccine composition recommendations, a few of the viruses isolated from shared clinical specimens are used to develop candidate vaccine viruses (CVVs). These CVVs are provided to vaccine manufacturers, who use them to make vaccines by growing them either in chicken eggs or in cells. In both cases, virus-containing fluid is harvested, the influenza viruses are inactivated (killed) and the virus antigen is purified. The virus antigen is then used to make a vaccine, which is administered by injection.\(^3\)

**Live attenuated influenza vaccines**

LAIVs are made from attenuated (weakened) live influenza viruses. These vaccines are derived from a cold-adapted, attenuated influenza virus on which surface molecules called antigens have been engineered to be representative of the currently circulating viruses. Rather than being administered by injection, LAIV are administered intranasally. Administration results in a mild infection, which stimulates an immune response.

**Recombinant influenza vaccines**

Recombinant influenza vaccines are developed by inserting genes encoding hemagglutinin, an influenza surface antigen that stimulates an immune response in people, into insect or plant cells. These cells then produce the hemagglutinin antigen, which is harvested and purified. The virus antigen is used to make a vaccine, which is administered by injection.

**2) Technologies in use but for which there is not yet a licensed vaccine**

**Vaccines using synthetic CVVs**

As described above, GSD can now be used to develop synthetic CVVs without using original influenza virus material. With this technology, GSD from the original virus is downloaded from a database or obtained bilaterally and is used to produce a synthetic whole virus in a laboratory. The process involves generating laboratory-produced or “synthetic” DNA molecules using GSD and inserting these molecules into cells, which will then produce viruses that can serve as CVVs. These CVVs can then be used to develop vaccines by traditional (e.g., egg-based or cell-based) vaccine production methods. Vaccines developed using this technology have not yet received regulatory approval.\(^4\)

**3) Research and future vaccine technologies that could rely on GSD**

**Nucleic acid vaccines**

Generation of nucleic acid vaccines is another potential use of synthetic genetic information which is in an early phase of research. The process involves directly injecting a synthetic DNA sequence that contains the code for influenza proteins, such as hemagglutinin, into appropriate tissue (e.g., muscles or skin). The cells in the tissue that has been injected start producing influenza proteins, which in turn simulate an immune response.

**Universal vaccines**

Research is also under way on the potential for using influenza GSD in the production of what are called “universal vaccines.” Rather than generating vaccines that are based on the specific influenza viruses currently circulating, as described above, universal vaccines are based on pieces of genes that are similar across most influenza viruses. These genetic commonalities are called “conserved regions of the influenza genome” and are identifiable if GSD from multiple influenza viruses is compared across virus strains to find sequences that repeat consistently. Vaccines based on the conserved regions of the influenza genome may be able to provide broader protection against different influenza viruses and therefore allow for longer-term protection against influenza.

**Other new developments linked to GSD**

The increasing use of influenza GSD is also expected to contribute to improving the accuracy of diagnostic tools; predicting and improving vaccine efficacy; and developing antibodies and proteins for therapy.

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2. For more information, see http://www.who.int/influenza/vaccines/en/


See Summary of status of development and availability of avian influenza A(H7N9) candidate vaccine viruses and potency testing reagents, 5 March 2018 at http://www.who.int/influenza/vaccines/virus/candidates_reagents/summary_a_h7n9_cvv_20180305.pdf