Annex A.

Chronology of the Production of a Pandemic Influenza Vaccine

The production of pandemic influenza vaccines requires the thorough coordination of a series of complex processes; participants include public health laboratories, regulatory authorities, the World Health Organization (WHO), and vaccine producers. To begin, the international influenza surveillance system provides strains isolated from nasopharyngeal swabs obtained in the field to the WHO Collaborating Centers for Influenza Reference and Research (currently located in Atlanta, London, Melbourne and Tokyo). The vaccine production process which follows is summarized below:

Activities at the WHO Collaborating Centers

1. Preparation of the reference virus strain

In these laboratories the reference virus strain is prepared through a process called genetic regrouping. In this process, surface antigens (HA/hemagglutinin and NA/neuraminidase, the protective components of the vaccine) of the pandemic strain isolated in the field, are combined with the central components of a conventional laboratory vaccine strain that has been adapted for optimal yield in hen eggs. Hen eggs are the substrate currently used to produce most influenza vaccines in industrial conditions. Reference strains can also be produced through inverse genetics, a new molecular biology technique. **This process requires from three to six weeks**.

2. Verification/validation

Following the preparation of the reference virus strain through the WHO Collaborating Centers, the candidate vaccine virus is submitted to a series of identification tests, which include the analysis of the specific surface antigens (HA and NA) of the circulating virus. **This process requires three weeks.**

3. Reference reagents

The Collaborating Centers produce official WHO reference reagents, antigens, and specific antiserum of the selected vaccine strain that will be used to verify the antigenic content (potency) and the immunogenetic capacity of the commercial vaccines. This requires the production of the viral reference strain, the purification of the surface antigens from this strain, the vaccination of animals, the preparation and standardization of serum, and the distribution of these reagents to manufacturers. This process starts as soon as the reference virus strain is available. **It requires approximately four months** and tends to constitute a bottleneck in the global process of vaccine production.

Vaccine production activities

1. Optimization of the manufacturing processes and the acquisition of seed virus

As soon as the reference virus strain is received from the WHO Collaborating Centers, manufacturers optimize the production process in order to increase growth characteristics and yield. The objective of this process is to pass the reference virus strain to qualified operational seed virus banks that will use it to inoculate eggs and initiate the manufacture of wholesale vaccine lots. **This process requires approximately three weeks.**

2. Manufacture of wholesale vaccines

Most of the influenza vaccine production process is accomplished in fertilized hen eggs. The operational seed virus is injected into the eggs which are incubated for two to three days. The vaccine virus strain grows in the clear allantoic liquid of the egg, which increases the amount of viruses harvested for vaccine production. The vaccine is then harvested from the egg and is purified in order to eliminate any excess material. This partially purified virus is then chemically inactivated for safety and then commonly altered or fragmented by mixing it with detergents. The important remaining vaccine proteins are then purified again.

The production of each lot of antigen requires approximately two weeks and the production of a new lot can be initiated weekly. The size of the lot depends on the capacity and the growth yield with respect to the growth in each egg.

Quality control

Quality control can start only once the WHO laboratories have provided the reference reagents. The wholesale vaccine is characterized using the reference reagents to confirm that the concentration of the hemagglutinin antigen is correct. The sterility of the wholesale antigen is also confirmed. **This process requires two weeks.**

Packaging and distribution of the vaccine

The wholesale vaccine is diluted to the desired concentration, packaged in vials or syringes, and labeled in accordance with the specifications authorized for the manufacturers. A sample from the full packages is tested for sterility, which requires two weeks. Additionally, other tests are carried out in order to confirm the antigenic content and the general safety through the injection of animals. **This process lasts two weeks.**

Clinical trials

In Western Europe, but not in the United States, clinical trials are required to demonstrate the safety and the immunizing capacity of every new formulation of influenza vaccine. **This requires at least four weeks.**

Activities of the regulatory authority

1. Regulatory approval

Before the vaccine can be administered to people, the approval of the local regulatory authorities is required. If the vaccine is produced through the same procedures that were used

for the authorized conventional seasonal influenza vaccine and in the same manufacturing plant, this control can be done rapidly (from one to two days).

Timetable of Production of the influenza vaccine

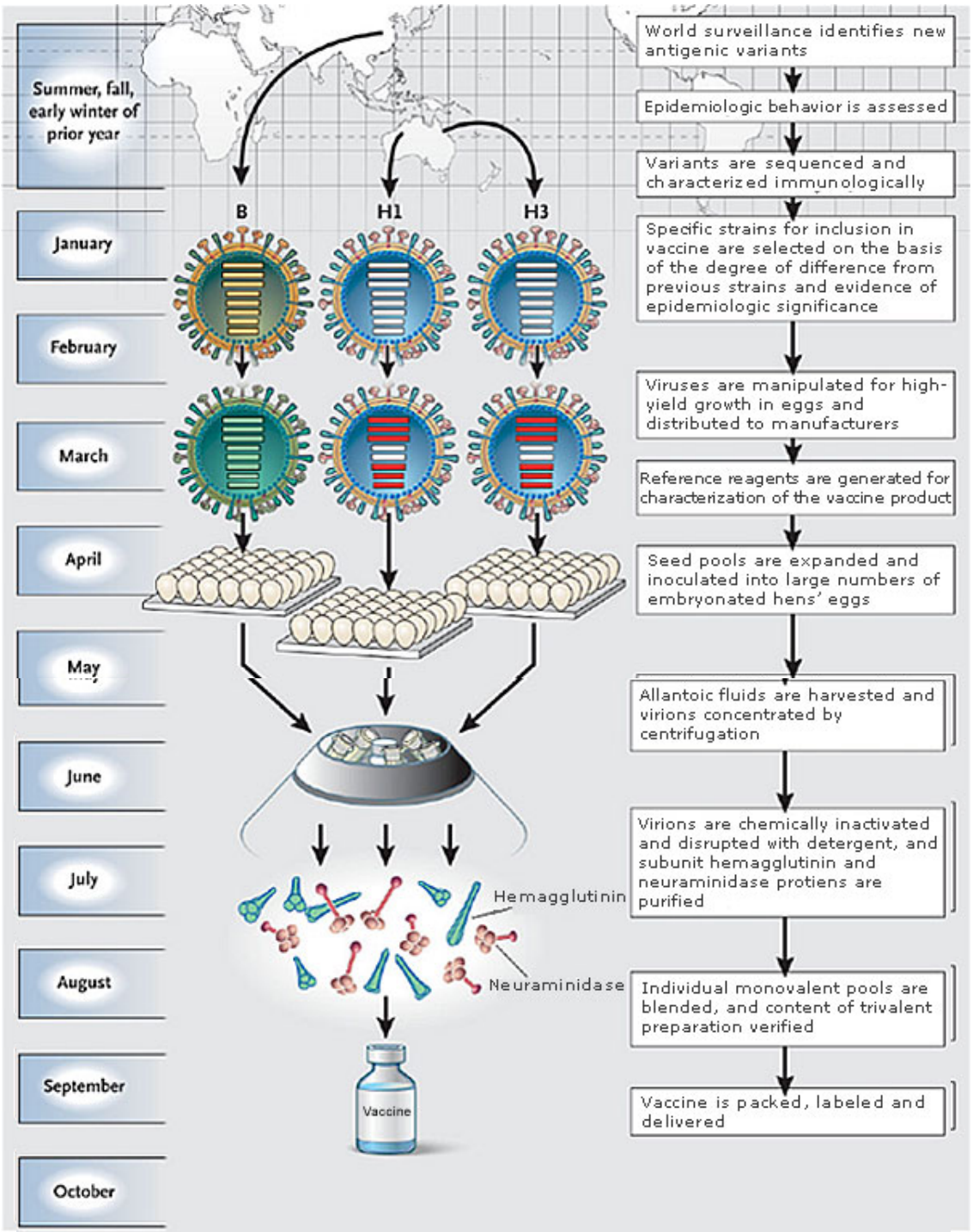

Diagram: Outline of the Annual Process of Development, Manufacturing and Distribution of Influenza Vaccines

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