Influenza Vaccine Production

Philip Hosbach
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Influenza Summit Meeting – April 19-20

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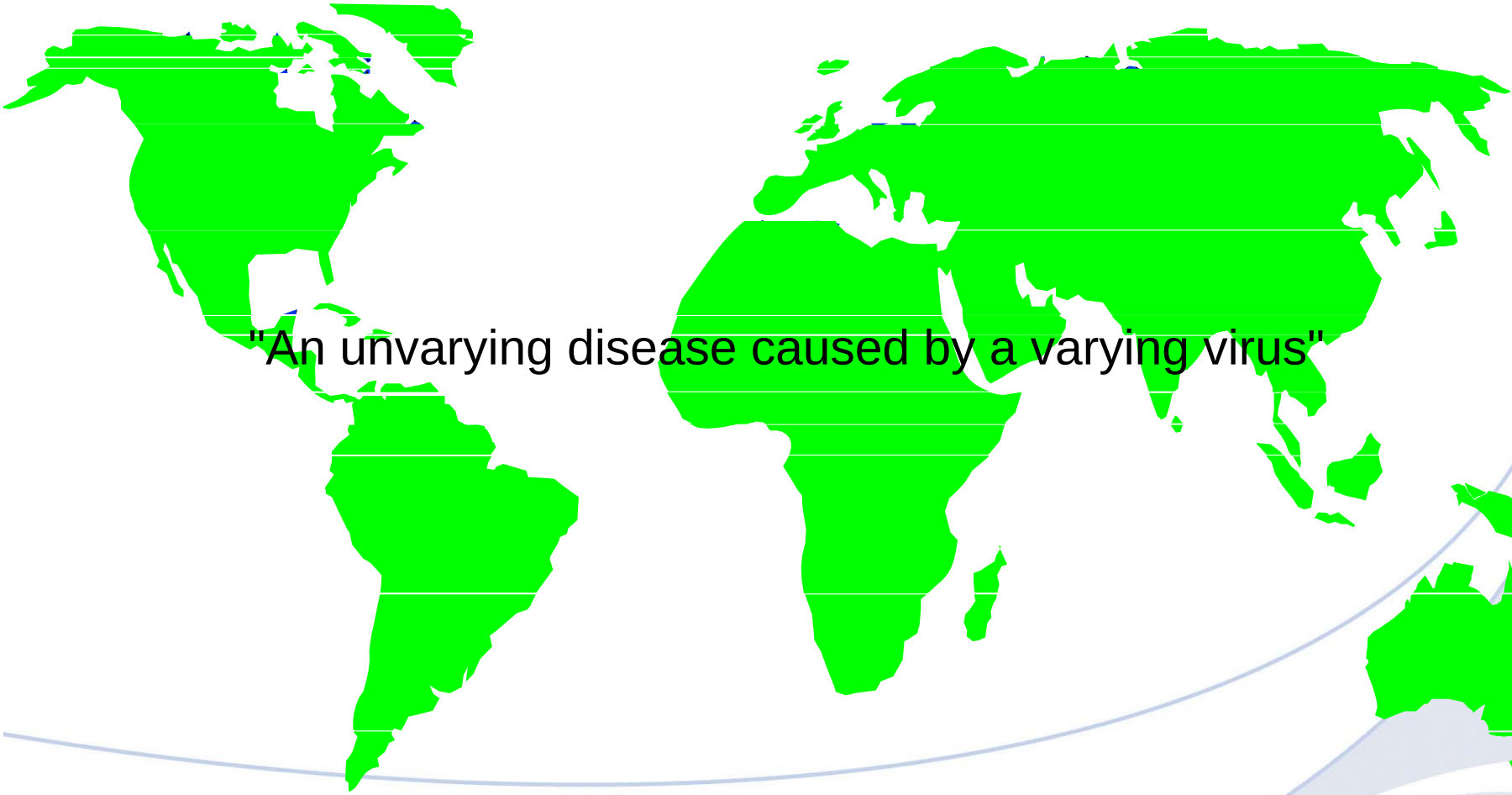
Influenza



"An unvarying disease caused by a varying virus"

Kilbourne, 1980

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The Influenza Virion

Single stranded RNA Virus

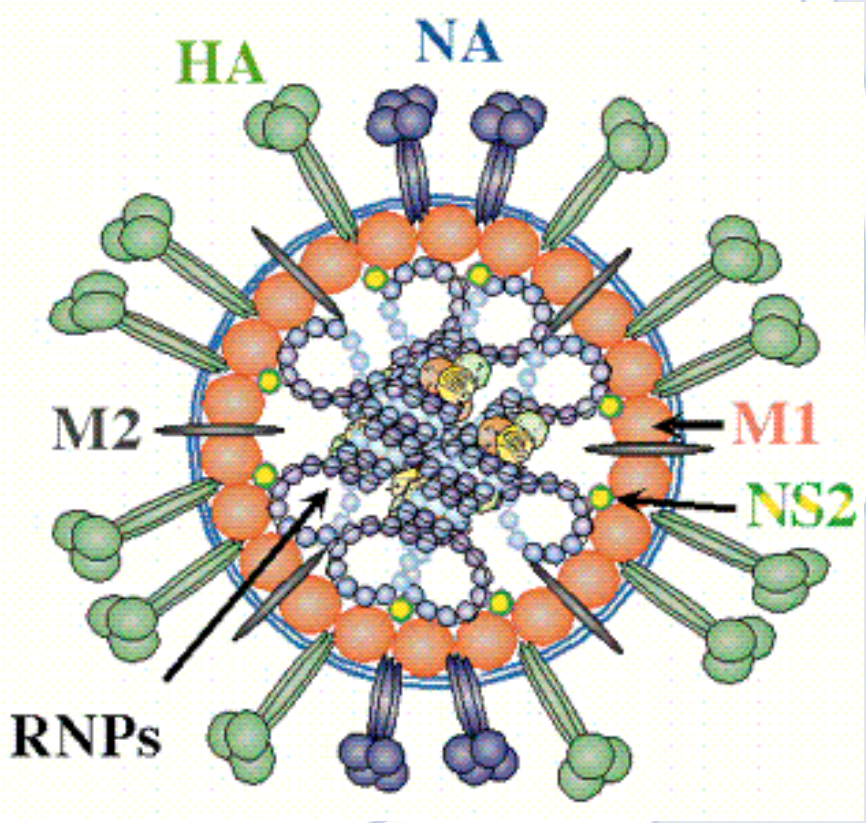
Outer surface:

2 types of glycoprotein project from a lipid envelope:

- **hemaglutinin (HA)** : attaches the virus to the host cell membrane and aids entry
- **neuraminidase (NA)** : contributes to the release of newly formed virions from infected cells

Inner surface:

Matrix and trans-membrane proteins (M1 and M2) line the envelope, providing rigidity



Paul Digard, Dept Pathology, University of Cambridge

Inactivated Influenza Vaccine Production Process

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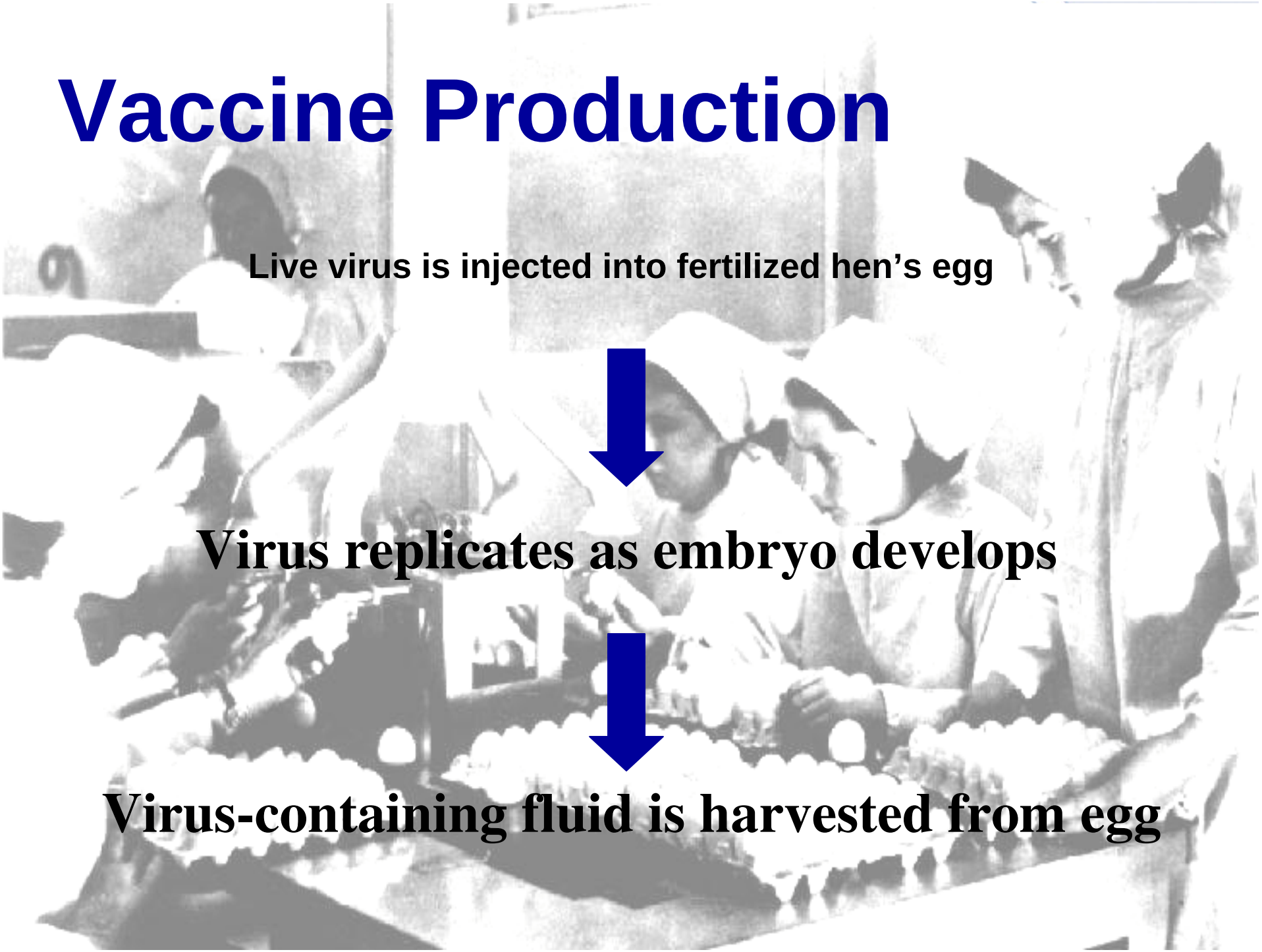
Vaccine Production



Live virus is injected into fertilized hen's egg

↓

Virus replicates as embryo develops

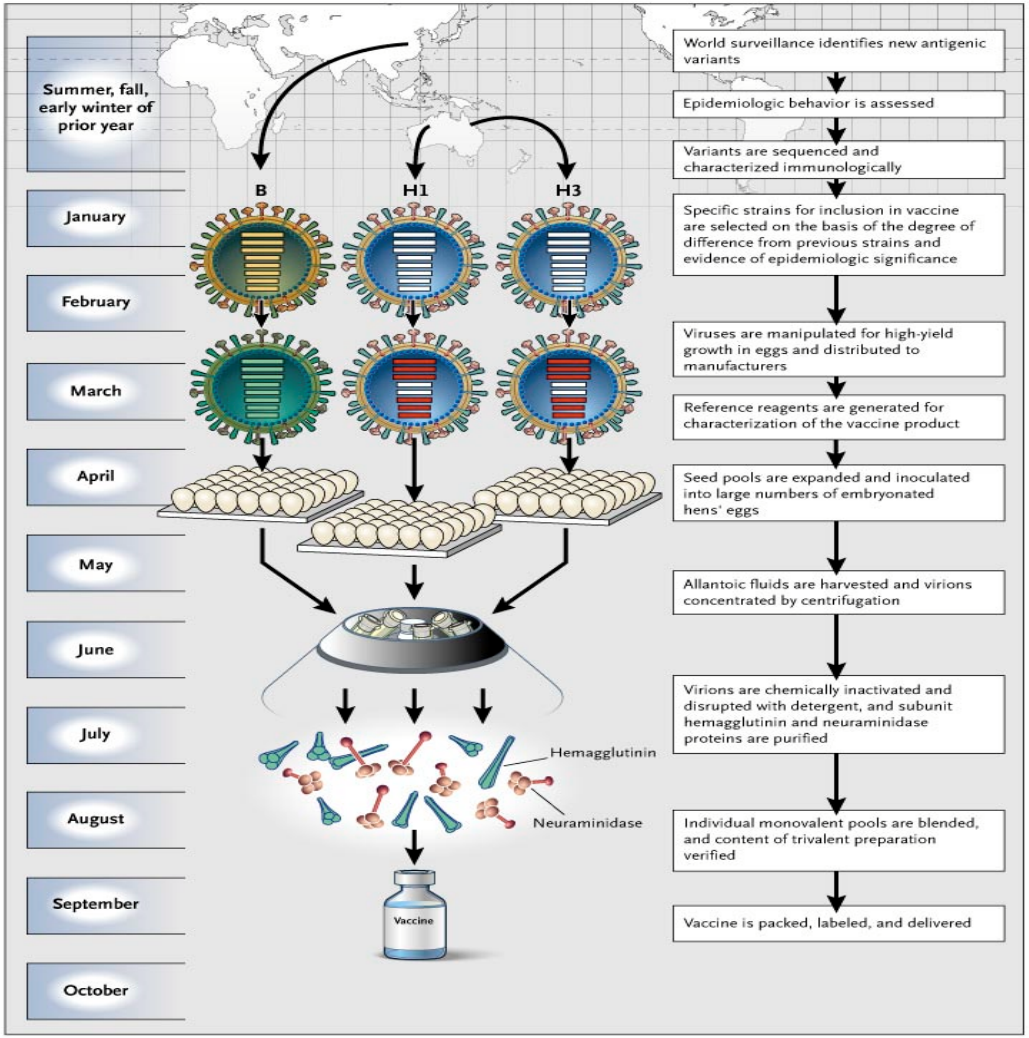
↓

Virus-containing fluid is harvested from egg

New Technology Applied to Egg Based Vaccines

- While eggs are still used, the process has seen continual improvements through the years to provide consistent yields with changing strains and improved product quality.
- Improvements include automated inoculation and fluid collection under laminar flow, closed systems for inactivation and purification, and Isolator technology for filling.

Inactivated influenza vaccine production process – overview



Treanor, J. N. Engl. J. Med. 2004;351:2037-2040

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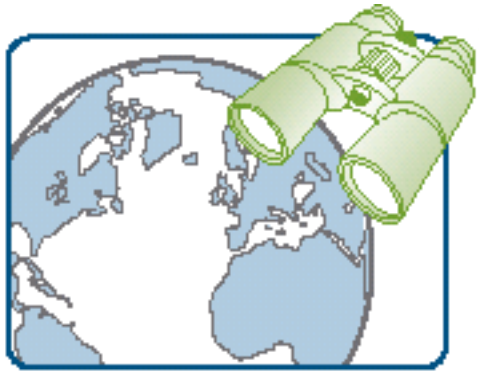
Inactivated influenza vaccine production process – strain selection

- Influenza vaccine protects against three prominent virus strains, which must be identified before production can begin
- Ongoing global surveillance is key to predicting which three strains will circulate each influenza season
- Two objectives in strain selection process
  - To make sure that the vaccine protects against the predominant strains
  - To select strains that grow well in eggs



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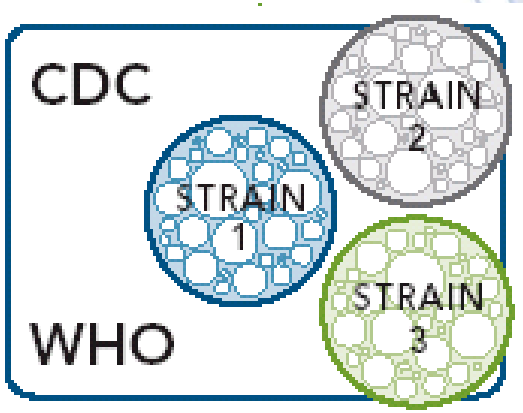
Inactivated influenza vaccine production process – strain selection

- The World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) identify dominant circulating virus strains

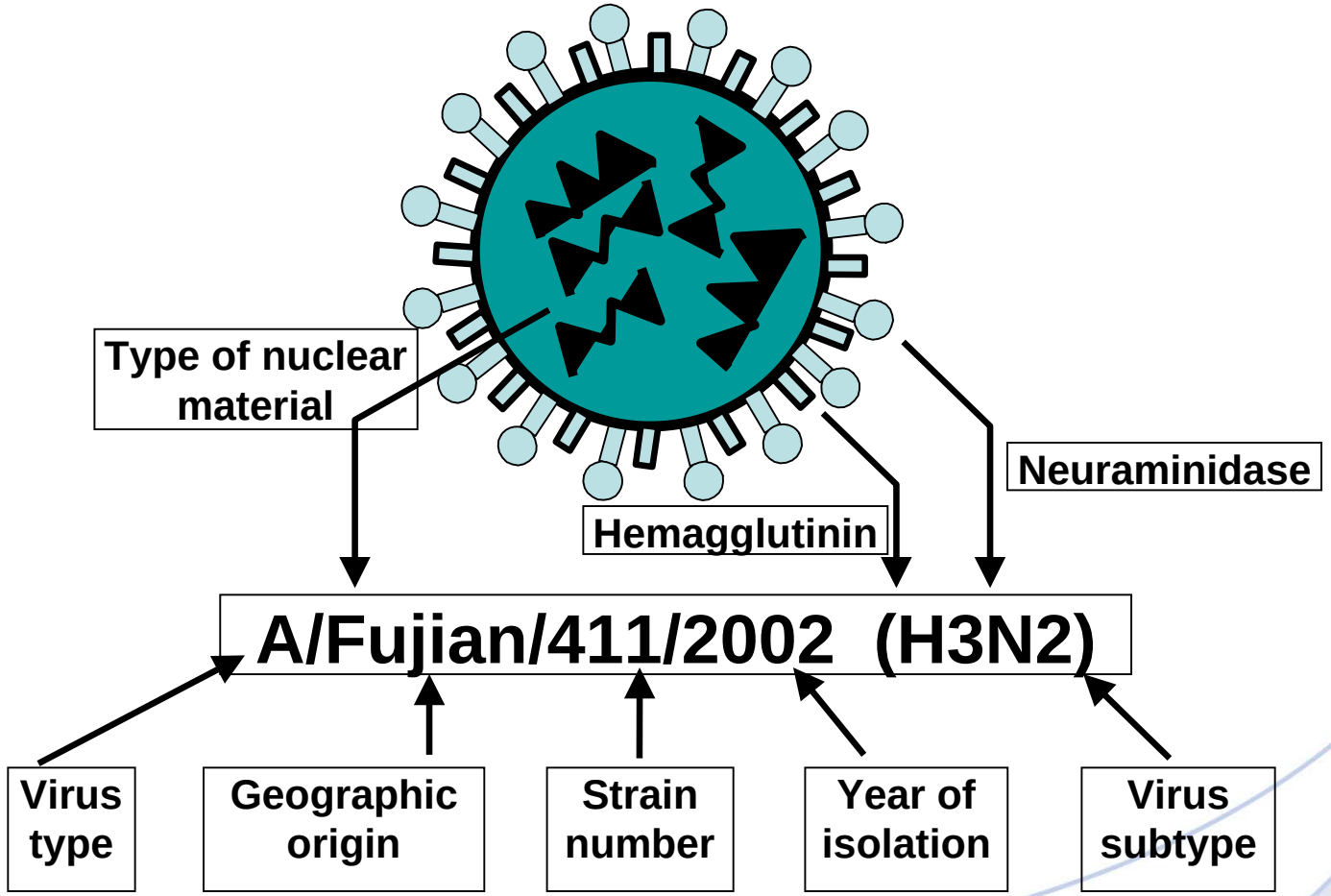
- FDA selects strains and distributes seed viruses to manufacturers to begin production

- 2006/2007 strains:
  - A/Soloman Islands/3/2006
  - A/Wisconsin/67/2005 strain
  - B/Malaysia/2506/2004 like strain



JANUARY-MARCH

Influenza Virus – Nomenclature

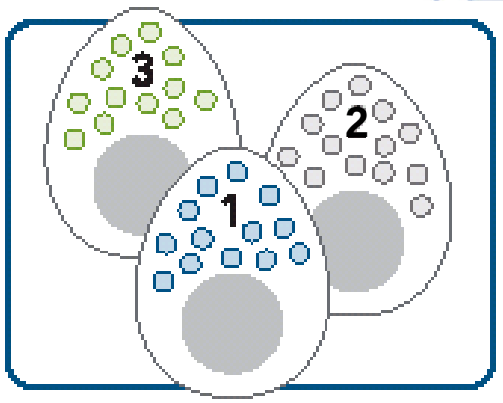


Strain selection timing affects production

Yields			
Strain 1 JAN	Strain 2 FEB	Strain 3 MAR	Effects
Low	High	High	Optimum for Launch and Availability
High	***Low***	High	Fewer Doses Available at Launch and Potential Shortfalls Throughout Season
High	High	***Low***	Delayed Launch and Availability

Inactivated influenza vaccine production process – manufacturing

- Each of the three strains is produced separately in millions of specially prepared chicken eggs
- Each production batch of vaccine is incubated in the eggs for several days to allow the virus to multiply
- The virus-loaded fluid is then harvested from the eggs

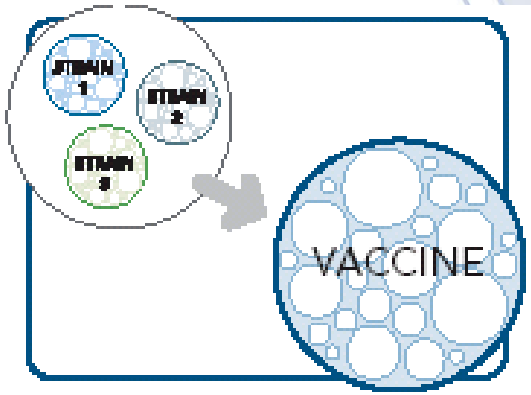


NOTE: Prior to strain selection by the WHO and FDA, manufacturers produce anticipated strains at-risk

JANUARY-JULY

Inactivated influenza vaccine production process – purification and testing

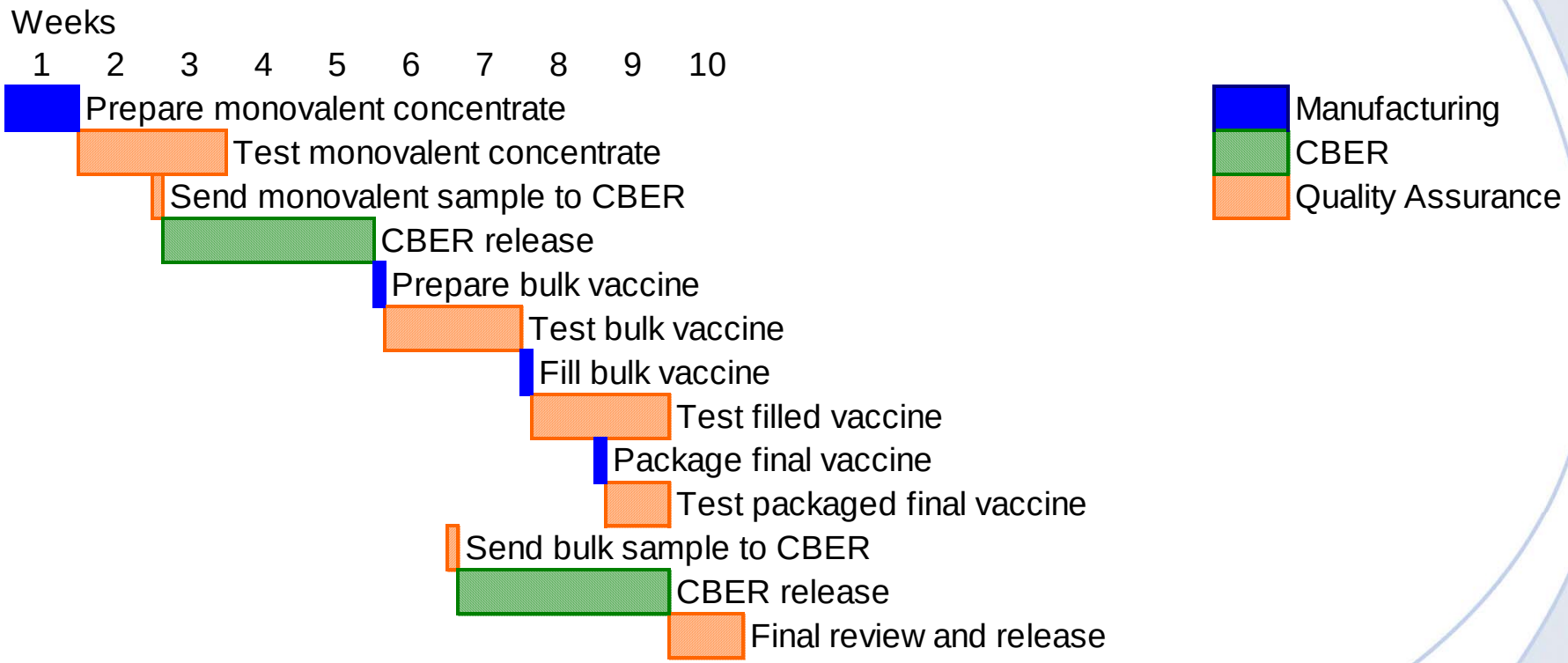
- Virus-loaded fluid undergoes multiple purification steps and chemical treatment to inactivate and split the virus
- Quality control tests are performed on all three strains for purity, sterility, and potency
- Inactivated viral fragments of the three strains are combined to create the bulk vaccine
- Manufacturer and FDA test the vaccine at multiple stages of production to ensure it is adequate for immunization



Manufacturer testing and FDA release protocols account for the majority of production time

JUNE-OCTOBER

Manufacturing Timeline Overview for One Lot



Assumptions:

Availability of potency testing reagents

Approved packaging components (labels, package inserts)

85% of lead time is product testing. Will be required regardless of technology used

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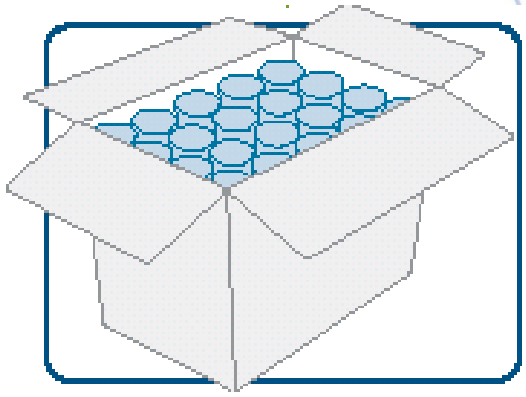
Inactivated Influenza Vaccine Production Process – Filling and Packaging

- Upon FDA licensing, manufacturers begin filling doses into vials and syringes
- Filling and packaging of the various presentations are prioritized based on need
  - Example: Pediatric dose to support two dose indication for naïve patients
- Following careful inspection, labels are applied to show batch, lot number, and expiration date
- Each lot must be “released” by the FDA before the vaccine can be shipped



JULY-DECEMBER

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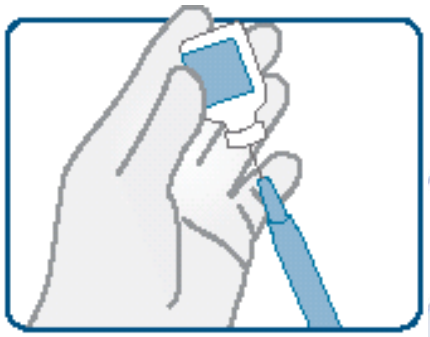
Inactivated Influenza Vaccine Production Process – Shipping and Immunization

- Shipments typically begin in August
- Depending on viral yield and demand, additional doses may be released and shipped into December and beyond

AUGUST-NOVEMBER; BEYOND AS NEEDED

- Immunizations generally begin in October or as soon as vaccine becomes available and continues through the the influenza season which typically ends in March
- Immunity develops approximately two weeks following immunization



OCTOBER AND BEYOND