Influenza Vaccine Production

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Influenza Summit Meeting – April 19-20
An unvarying disease caused by a varying virus

Kilbourne, 1980
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
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

- Summer, fall, early winter of prior year
- January
- February
- March
- April
- May
- June
- July
- August
- September
- October

World surveillance identifies new antigenic variants

Epidemiologic behavior is assessed

Variants are sequenced and characterized immunologically

Specific strains for inclusion in vaccine are selected on the basis of the degree of difference from previous strains and evidence of epidemiologic significance

Viruses are manipulated for high-yield growth in eggs and distributed to manufacturers

Reference reagents are generated for characterization of the vaccine product

Seed pools are expanded and inoculated into large numbers of embryonated hen's eggs

Allantoic fluids are harvested and virions concentrated by centrifugation

Virions are chemically inactivated and disrupted with detergent, and subunit hemagglutinin and neuraminidase proteins are purified

Individual monovalent pools are blended, and content of trivalent preparation verified

Vaccine is packed, labeled, and delivered

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.
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
Influenza Virus – Nomenclature

**A/Fujian/411/2002 (H3N2)**

- Virus type
- Geographic origin
- Strain number
- Year of isolation
- Virus subtype

Type of nuclear material
Hemagglutinin
Neuraminidase
Strain selection timing affects production

<table>
<thead>
<tr>
<th>Strain 1</th>
<th>Strain 2</th>
<th>Strain 3</th>
<th>Effects</th>
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<td>JAN</td>
<td>JAN</td>
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<td>Optimum for Launch and Availability</td>
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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
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
Manufacturing Timeline Overview for One Lot

Weeks
1 2 3 4 5 6 7 8 9 10
1. Prepare monovalent concentrate
2. Test monovalent concentrate
3. Send monovalent sample to CBER
4. CBER release
5. Prepare bulk vaccine
6. Test bulk vaccine
7. Fill bulk vaccine
8. Test filled vaccine
9. Package final vaccine
10. Test packaged final vaccine
11. Send bulk sample to CBER
12. CBER release
13. Final review and release

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
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
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 influenza season which typically ends in March (OCTOBER AND BEYOND)
- Immunity develops approximately two weeks following immunization