Influenza Vaccines

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Influenza A Viruses

• Influenza A viruses categorized by subtype
  • Classified according to two surface proteins

  • Hemagglutinin (H) – 16 known
    – Site of attachment to host cells
    – Antibody to HA is protective

  • Neuraminidase (N) – 9 known
    – Helps release virions from cells
    – Antibody to NA can help modify disease severity
Seasonal and Pandemic Influenza: Highly Transmissible
Best Prevention = Annual Vaccination
Brief History of Influenza Vaccines

- Early 1940s: Inactivated influenza virus vaccines developed by U.S. military to mitigate disruption caused by respiratory outbreaks
  - Vaccine viruses were grown in eggs, purified and inactivated
- 1947: Significant antigenic change occurred in the circulating virus compared to the vaccine virus; vaccine failed to protect
- 1947: Recognition that global surveillance for influenza viruses to detect new epidemic and pandemic viruses was needed
- 1952: The World Health Organization’s Global Influenza Surveillance Network became active
- Early 1980s: Improvements in virus purification and measurement of antigen content of vaccine reduced local SE
- 1960-70s: Live Attenuated Influenza Vaccines developed in Russia and the U.S.
- Since 2004: Significant investments in new vaccine technologies by governments and industry
WHO Global Influenza Surveillance

- WHO Collaborating Centers: Atlanta, London, Melbourne, and Tokyo

- 125 NICs in 95 countries
- Focused on surveillance and vaccine strain selection
- Pandemic preparedness
- Surveillance for drug resistance
- Diagnosis, regents, training
Current Status of WHO System: Surge Capacity

- 175,000 isolates/yr (600 to 1200 M cases)
  - Demands on laboratories around the world increased dramatically with nH1N1 emergence and spread

- WHO CCs receive 6,500 – 8,000 samples/yr
  - CC at CDC has received more samples than entire system had in the past due to nH1N1

- WHO CCs and NICs sequence HA of 1,000 samples/yr; complete genomes sequenced
  - More viruses sequenced than ever before for nH1N1 viruses

- >400 M doses of trivalent seasonal influenza vaccine w/wide
  - nH1N1 vaccines are being produced for clinical trials but how much vax will be available and when?
Considerations for New Vaccine Strain

Recommendations

• Are there new antigenic variants?
  – Antigenic and genetic characterization

• Are new variants spreading?
  – Monitoring Influenza activity and virus isolation

• Are current vaccines able to induce antibodies to the new variants?
  – Serological evaluation of vaccinated individuals

• Are any new variants useful for vaccine production?
  – Cell substrate of isolation
  – Reassortants
Molecular Epidemiology and Vaccine Development

- Genetic Characterization
- Antiviral Resistance Monitoring
- Cell-Based Vaccines
- Vaccine Strain Selection
- Reverse Genetics
- Vaccine Candidate
- Pandemic Risk Assessment

hemagglutinin
New Antigenic Variant?
Antigenic Analysis

- Hemagglutination Inhibition
- Post infection ferret antisera
- Reference viruses
- WHO test of choice
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<th>WI/10*</th>
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Phylogenetic Tree of Hemagglutinin H1: Swine vs. Seasonal

Novel H1N1 Outbreak
Human cases of swine H1
Seasonal H1

(Garten, et al Science 2009)
Summary of Genetic and Antigenic Analyses of nH1N1 Viruses

- The combination of gene segments of nH1N1 viruses had not been reported previously.
- Reassortment had occurred between EA swine and NA swine lineage triple reassortant viruses.
- No genetic markers for severe disease in viral genes detected yet.
- Genetically and antigenically homogeneous but different from other circulating influenza viruses.
- Homogeneity made selecting a reference vaccine virus easy.
Serum Cross-reactive Antibody Response to a Novel Influenza A(H1N1) Virus After Vaccination with Seasonal Influenza Vaccines, MMWR May 2009

<table>
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<tr>
<th>Vaccine</th>
<th>Influenza season</th>
<th>Influenza virus</th>
<th>Age group</th>
<th>No.</th>
<th>% with fourfold or greater increase in antibody titer</th>
<th>% with MN titer of $\geq 40^a$</th>
<th>Geometric mean titer (GMT)$^b$</th>
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* A/California/04/2009.
† A fourfold or greater increase in antibody titer indicates seroconversion (a response to the vaccine).
‡ A linear regression model was used to predict the MN titer for seasonal H1N1 viruses that corresponded to a hemagglutination inhibition (HI) antibody titer of 40. (Serum HI antibody titers of 40 are associated with at least a 50% decrease in risk for influenza infection or disease [7]). In pediatric populations, an HI titer of 40 corresponds with an MN titer of 40.
§ A titer of 1280 was used for all samples with a titer of $\geq 1280$. The dilution of sera in the first well is based on the combination of a 1:10 serum dilution with an equal volume of diluted virus for a final serum dilution referred to as 1:10. In the statistical models, study participants were treated as random effects sampled from a larger population of study participants, and duplicate samples were treated as random effects nested within each study participant.
** Confidence interval.
†† Trivalent, inactivated influenza vaccine.
§§ Live, attenuated influenza vaccine.
Serum Cross-reactive Antibody Response to a Novel Influenza A(H1N1) Virus After Vaccination with Seasonal Influenza Vaccines, MMWR May 2009

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<tr>
<th>Vaccine</th>
<th>Influenza season</th>
<th>Influenza virus</th>
<th>Age group (yrs)</th>
<th>No.</th>
<th>% with fourfold or greater increase in antibody titer†</th>
<th>% with MN titer of ≥160§</th>
<th>Geometric mean titer (GMT)¹¹</th>
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<td>92 (71–121)</td>
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* ACalifornia/04/2009.
† A fourfold or greater increase in antibody titer indicates seroconversion (a response to the vaccine).
§ A linear regression model was used to predict the MN titer for seasonal H1N1 viruses that corresponded to a hemagglutination inhibition (HI) antibody titer of 40. (Serum HI antibody titers of 40 are associated with at least a 50% decrease in risk for influenza infection or disease [7].) In adult populations, an HI titer of 40 corresponds with an MN titer of ≥160.
†† A titer of 1280 was used for all samples with a titer of ≥1280. The dilution of sera in the first well is based on the combination of a 1:10 serum dilution with an equal volume of diluted virus for a final serum dilution referred to as 1:10. In the statistical models, study participants were treated as random effects sampled from a larger population of study participants, and duplicate samples were treated as random effects nested within each study participant.
** Confidence interval.
†† Trivalent, inactivated influenza vaccine.
Novel Influenza A (H1N1) Cases by Weekly Report Date as of 19 JUN 2009 (n=) *21,449

*Data for week ending 19 June 2009.
Dates not available for 92 cases.
Reassortment
Between Good Luck and Misfortune

Valentin de Boulogne  1620
Engineer Safe Vaccine Viruses
Reverse Genetics

BSL2-with level 3 enhancements

H5N1 avian flu virus

High Yield Attenuated virus (PR8)

HA gene
NA gene

Vero Cells

High Yield avirulent vaccine

BSL2 virus

9 days
Candidate Pandemic H1N1 Vaccines

WHO Safety Guidelines

- 2003 WHO Guidance
  - Development in BSL3-enhanced environment
  - High-yield reassortant with attenuated virus genes
  - Reduce virulence compared to parental wild-type virus
  - GLP laboratory protocols and QA program
  - Certified Vero cells free of adventitious agents
Pandemic Vaccines
QC and Safety Assessment

- QC procedures
  - Nucleotide sequence analysis
  - Antigenic characterization
  - Growth properties

- Lack of pathogenicity
  - Ferrets
    - No neural replication; minimal extraneural replication

- BSL2-enhanced to BSL2 Transfer

- Distribute to manufacturers & support scale-up

~3 days

Up to 10 days
## Cause of Death in Low Income Countries

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<td>Perinatal conditions</td>
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<td>Road traffic accidents</td>
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*Source: WHO Fact sheet № 310 / February 2007*
Short Term Goals for Pandemic H1N1 Vaccine Production

- Produce safe and effective pandemic H1N1 vaccines as quickly as possible
- Produce as much vaccine as possible
- Determine goals of vaccination programs
  - Reduce severity of pandemic and social disruption
  - Identify target populations for vaccination (set priority groups)
- Determine best ways to distribute vaccines
  - Reach target populations in resource poor and rich countries
- Distribute and administer safe and effective vaccine
- Mitigate the health and societal effects of the pandemic
Long Term Goals for Influenza Vaccine Production

- Increase global production capacity
  - Current manufacturers have built larger production facilities
  - Additional manufacturers are planning to produce vaccines, including those in middle income countries

- Increase vaccine production in middle income countries (and uptake of vaccine globally, including in resource poor countries)

- Increase types of influenza vaccines that are licensed
  - Many novel approaches are being explored

- Transfer technologies for vaccine production to middle income and resource poor countries, as possible
Key Questions

- How well are vaccine viruses growing for production?
  - Determines how much vaccine will be available and timing

- How quickly can clinical trials be completed?
  - Vaccines must be safe and effective

- What will the intensity of the expected fall wave in the NH?

- When will vaccine be available?
  - In time for expected wave of disease or later?

- For whom should it be recommended?
  - Depends on goals of vaccination program

- How will vaccine be shared with resource poor countries?
  - Planning and discussions underway at WHO and elsewhere
  - Target populations and delivery systems