Preventive and Therapeutic Strategies against Pandemic Influenza

Challenges and Opportunities

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Figure: Global public-health measures needed to prevent influenza pandemic
Sambhara et al (2007)
Lancet Infectious Diseases, 7:503

Figure: “Target” paradigm of H5N1 pandemic vaccine development
Pandemic Influenza Vaccines

- **Cell-derived**
  - Wild-type seed virus
  - Whole inactivated
  - RG-seed virus
  - Whole inactivated
  - Detergent split

- **Egg-derived**
  - RG-seed virus
  - Whole inactivated
  - Detergent split
  - Cold-adapted

- **Recombinant proteins**
  - Insect, Plant, or mammalian
  - Cell derived

- **Viral Vectors**
  - Adeno
  - Pox
  - VSV

- **Virus-like Particles (VLP)**
  - Insect
  - Cell derived

- **M2e Vaccine**
Pre-pandemic influenza Vaccines i

- Egg-derived rgH5N1 vaccines
- Clade 1 vaccine
  - Needed at least 2 doses of split vaccine at 90µg/dose (Treanor et al 2006) 53% of the vaccinees had a neutralization titer of ≥40
  - 2 doses of split vaccine 30µg with alum as an adjuvant (Bresson et al 2006) 41% of vaccinees had 4-fold increase in neutralization titers
  - 2 doses of whole-inactivated vaccine at 10µg with alum as an adjuvant (Lin et al 2006) 50% of the vaccinees had a neutralization titer of ≥40.
Egg-derived rgH5N1 vaccines with Novel Adjuvants

GSK
- 2 doses of 3.8µg with ASO3 (a proprietary adjuvant) induced about 80% seroconversion (Leroux-Roels, et al 2007)
  - Cross-reactivity with clade 2 viruses

Sanofi-Aventis: Bird flu vaccine trial showed high response at low dose
UPDATE September 18, 2007.
- 2 doses of 1.9µg or 3.75µg of antigen with a proprietary adjuvant generated seroprotective immune response in more than 70% and 80% of the vaccinees.

Novartis: 2 doses at 1.9µg with a proprietary adjuvant showed significant seroprotection rates and cross-clade reactivity.
Challenges: Vaccine availability in a pandemic

- Why Avian HA is NOT very immunogenic?
- Lack of manufacturing capacity to make enough doses of vaccine for 1.2 billion people who may be at risk
- H5N1 viruses are highly lethal to poultry and ensuring the availability of eggs for vaccine production becomes a problem
- Production capacity of egg-independent vaccine strategies
- Availability of vaccine to the developing world at an affordable price
- Short timeframe to make a vaccine during a pandemic
Passive Immunization Strategies for Pandemic Influenza

Immunocompromised

• EBV-transformed B cells as a source of antibodies
• Antibody Phage displays
• Humanized mAb
• Polyclonal human antibodies from transgenic animals carrying human Ig loci
  • Hematech
  • Therapeutic Human polyclonals (Roche)
• Medarex
Anti-Viral Strategies

Block viral entry or interfere with viral replication, assembly, or budding
Anti-viral Drugs against Influenza

M2 ion-channel Blockers
- Adamantine
- Rimantidine

Neuraminidase inhibitors
- TAMIFLU (oseltamivir phosphate)
- Relenza (zanamivir)
High Levels of Adamantane Resistance Among Influenza A (H3N2) Viruses and Interim Guidelines for Use of Antiviral Agents—United States, 2005-06 Influenza Season

Amantadine also is used to treat symptoms of Parkinson disease and may continue to be used for this indication.

Resistance of influenza A viruses to adamantanes can occur spontaneously or emerge rapidly during treatment. A single point mutation in the codons for amino acids at positions 26, 27, 30, 31, or 34 of the M2 protein can confer cross-resistance to both amantadine and rimantadine. Neither replication, transmission, nor virulence of adamantane-resistant influenza A viruses are impaired by the point mutations conferring resistance. A recent report on the global prevalence of adamantane-resistant influenza A viruses indicated a significant increase of drug resistance, from 1.8% during the 2001-02 influenza season to 12.3% during the 2003-04 season. In the United States, the frequency of adamantane resistance in 1,499 influenza A viruses have been subtyped; 760 (99.3%) were influenza A (H3N2) viruses, and five (0.7%) were influenza A (H1N1) viruses. During October 1, 2005–January 14, 2006, a total of 123 influenza A viruses collected from 23 states were tested at CDC for adamantane resistance. Among the 120 influenza A (H3N2) viruses tested, 109 (91%) demonstrated the S31N substitution in the M2 protein that confers resistance to amantadine and rimantadine. Conventional sequencing on a subset of 20 viruses confirmed this substitution. Among the three influenza A (H1N1) viruses tested, none contained any mutations associated with resistance. As of January 14, all U.S. influenza viruses screened for antiviral resistance at CDC had demonstrated susceptibility to neuraminidase inhibitors. Procedures for virus propagation,
Oseltamivir Resistance — Disabling Our Influenza Defenses
Anne Moscona, M.D.

As the potential for an influenza pandemic has galvanized the medical community and the public into action, physicians and patients alike have been heartened by the availability of effective medicines to treat the disease. The recent emergence of oseltamivir-resistant variants is therefore a matter of immediate concern.

Why is resistance developing to oseltamivir? Several years ago...
A Piece of My Mind

“Our world sometimes presents us with situations that cannot be simplistically categorized as pro-choice or pro-life, and other patients across the nation will be faced with decisions like the ones we made on that fateful day.” From “A Question of Faith.”

SEE PAGE 1412

Medical News & Perspectives

Neuraminidase Inhibitor Resistance in Influenza B

Widespread use of antiviral therapy can lead to drug resistance, and resistance to neuraminidase inhibitors has been documented in type A influenza. During an influenza B epidemic in Japan, Hatakeyama and colleagues assessed the prevalence and transmissibility of influenza B viruses with reduced sensitivity to neuraminidase inhibitors and identified genetic mutations associated with neuraminidase resistance. The authors identified influenza B viruses with reduced sensitivity to neuraminidase inhibitors from both neuraminidase-treated and untreated patients. The transmission of these mutant viruses appeared to have been person to person within the same family and possibly through community contacts. In an editorial, Moscona and McKimm-Breschkin discuss what is known about neuraminidase inhibitor-resistant influenza and what the implications are for the development of new antiviral therapies and their clinical use.

SEE PAGE 1435 AND EDITORIAL ON PAGE 1492
AVIAN FLU

Isolation of drug-resistant H5N1 virus

The persistence of H5N1 avian influenza viruses in many Asian countries and their ability to cause fatal infections in humans have raised serious concerns about a global flu. We found that the dose required for 50% inhibition of neuraminidase activity (IC50) in the isolate was 90 nM, which exceeds the IC50 for oseltamivir-sensitive viruses (0.1–10 nM). We bound in vitro to different configurations of sialyl glycopolymers, similar to those on the host's cell-surface receptor. We compared binding by two of the viral clones (clones 7 and 9) with binding by an avian flu virus (A/duck/Mongolia/301/2001) and another human flu virus (A/Kawasaki/1/2001). We found that both H5N1 clones bound to α-2,3-linked polymer and (less efficiently) to α-2,6-linked polymer.
Anti-Viral Resistance

Containment

Surveillance for Anti-viral usage & resistance

Monitor Non-human use of Antiviral drugs

Compliance by Hospitals and Patients

Research: Developing New Compounds

New Strategies

Engagement of industry

Disease Control and Prevention

Anti-Viral Resistance Containment
Attrition on the road: Research and Development of new drugs

Screen 7 million compounds
10,000 hits
12 candidates
6 candidates
1 Final Product

Discovery         Early Development         Full Development

Concept            12-24 years            Customer

Adapted from Pfizer Inc
Anti-Viral Strategies

Block viral entry or interfere with viral replication, assembly, or budding

Modulate Innate Immunity
INNATE IMMUNITY
FRONT LINE OF HOST DEFENSE
Key Roles of innate immunity

1. Block the entry of microbes into host tissue (first line of defense)

2. Very rapidly eliminate microbes that succeed in entering the host tissue

3. Instructs cells of the adaptive immune system (T and B cells) to eliminate the microbe if innate immunity is unsuccessful
Pathogen Sensors in Innate Immunity

Specific Receptor-Ligand interactions

Pathogen-associated molecular patterns

Pathogen-recognition receptors
Host cell
Pathogens

- Motile
  - nonmotile
- Unicellular
  - multicellular
- Extracellular
  - Intracellular
- Capsulated
  - Non-capsulated
- Toxins
- Have own biosynthetic machinery
- Hijack host’s biosynthetic machinery
- Localized
- Superficial
- Systemic
Pathogen Sensors

- Soluble
- Membrane bound
- Vesicular
- Cytosolic
PRR ligation- signaling cascades

- PRR Ligation
- IFN Module
- TIR Module
- TAK1 Module
- NFκB Module
- Caspase Module
- MAP Kinase Module

Gene Transcription

- Pro-inflammatory cytokines
- Anti-microbial defenses
- Outcomes
  - Phagocytosis
  - Tissue repair
  - Adaptive Immunity

Outcomes

- Anti-microbial defenses
- Pro-inflammatory cytokines
- Tissue repair
- Adaptive Immunity
Sambhara and Lehrer (2007), Expert Review of Anti-infective Therapy, 5: 1