2009 H1N1 and Children
Pediatrics Research Lab

Outline
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  - Influenza viruses A, B and C
  - Molecular characteristics
  - Neuraminidase (N) as a drug target
- Global and USA Summary
  - Children Younger than 2 years of age are at increased risk
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  - Thiomersal (Merthiolate™) and Autism
- Did we dodge a bullet with 2009 H1N1
  - The 1918 Pandemic-how bad can it get?
How is "H1N1" different from "2009 H1N1"

- HA gene: Encodes 3 distinct hemagglutinins, H1, H2, and H3 in human viruses
- NA gene: Encodes 2 different neuraminidases, N1 and N2
  - All H1N1 have the N1 and H1 subtype
  - The "Spanish" flu of 1918 was a H1N1 subtype
  - 2009 H1N1 virus—originally called "swine flu"—many of its genes were similar to the influenza viruses normally occurring in North American pigs.
- Further studies showed that the new virus has two genes from flu viruses that normally circulate in pigs in Europe and Asia as well as bird (avian) genes and human genes.
- The 2009 H1N1 is called a "quadruple reassortant" virus.

Influenza (Flu) Type A, B, and C Viruses

- Influenza type A and B viruses
  - Type A—responsible for seasonal flu epidemics each year
    - The emergence of a "new" influenza virus (e.g., 2009 influenza A H1N1) can result in a worldwide pandemic
    - Influenza B—often causes sporadic outbreaks of illness, especially in residential communities like nursing homes
      - Not divided into subtypes but can be further broken down into different strains.
  - Type C causes a mild respiratory illness and are not thought to cause epidemics

The Influenza A Virus

- A genus of a family of viruses called orthomyxoviridae. Influenzavirus A has only one species in it, i.e., "influenza A virus".
- It is hosted by birds, but may infect several species of mammals. All known subtypes are endemic in birds
- Negative sense, single-stranded, segmented RNA viruses.
- There are 16 different HA antigens (H1 to H16) and nine different NA antigens (N1 to N9)

Molecular Characteristics The Influenza A Virus

- A globular virion, ~100 nm in diameter, sheathed in a lipid bilayer derived from the host’s plasma membrane
- Studded in the lipid bilayer are two integral membrane proteins
  - some 500 molecules of hemagglutinin ("H") and
  - some 100 molecules of neuraminidase ("N")
- Within the lipid bilayer are some 3000 molecules of matrix protein
- 8 pieces of RNA
Gripping Glycans

The Influenza Virus Invades Cells of the Respiratory Passages

- Hemagglutinin (H) binds to glycoproteins of the epithelial cells of the host.
- The virus is engulfed by receptor mediated endocytosis.
- A drop in pH in the endosome (endocytic vesicle) produces a change in the structure of the viral hemagglutinin enabling it to fuse the viral membrane with the vesicle membrane - releasing the contents of the virus to the cytosol.
- Viral RNA enter the nucleus of the cell where copies are made that return to the cytosol where some serve as mRNA molecules to be translated into the proteins for fresh virus particles.
- Fresh virus buds off from the plasma membrane of the cell (aided by the neuraminidase) thus spreading the infection to new cells.

NA as a Drug Target

- Neuraminidase (NA) activity is required for the continued replication of virions.
- Replication is blocked by NA inhibitors which prevent virions from being released from the surface of infected cells.
- The NA inhibiting drugs oseltamivir (Tamiflu) and zanamivir (Relenza) work by preventing NA from releasing the budding virions.

H1N1 Neuraminidase

- Red atoms: drug and other heteroatoms (any atom that is not carbon or hydrogen)
The New Power of Bioinformatics

- An evolutionary analysis of 2009 H1N1 neuraminidase was completed within 2 weeks from the time the 1st patient virus samples were made available.
- Using the 3D model, the group was able to map the regions of the protein that mutated and to determine whether drugs and vaccines that target specific areas of the protein were likely to be effective.
- The NA structure had undergone extensive surface mutations compared to closely related strains such as the H5N1 avian flu virus or other H1N1 strains including the 1918 Spanish flu.
- The NA structure of the 2009 H1N1 influenza A virus strain was more similar to the H5N1 avian flu than to the 1918 H1N1 strain.
- Mutations rendered previous flu vaccinations directed against neuraminidase less effective.
- Commercial drugs, namely Tamiflu® and Relenza®, were likely to still be effective in treating the current H1N1 virus.
- See http://mendel.bii.a-star.edu.sg/SEQUENCES/H1N1/

Global and USA Summary

- 2009 H1N1 spread very rapidly across the globe and the USA.
  - From March to early June, cases were reported in more than 70 countries and on June 11th, 2009 the WHO declared an official influenza pandemic.
  - The global spread of H1N1 took only six weeks, while past pandemics took six months to attain the same reach.
  - By June 19th, H1N1 cases were reported in all 50 states, the District of Columbia, Puerto Rico and the U.S. Virgin Islands. Cases declined over the summer but a second wave hit the US after children returned to school.
  - It is estimated that 50 million Americans, or one in six, were infected with H1N1 over seven months (April through November, 2009).
  - More than 200,000 Americans have been hospitalized from complications of H1N1 and more than 10,000 have died. Most of the deaths occurred in people 64 and younger.

Better Communications

- Physicians in South America, where winter flu season hits during our summer, reported to US doctors that children were getting very sick with H1N1, not the elderly, as expected with seasonal flu.
- Children at high risk for serious H1N1 complications often had underlying health concerns, like asthma.
- When H1N1 spread through the US, there was a better idea of what to expect—this enabled high risk patients to get early aggressive treatment.

H1N1 Flu Less Transmissible Than Previous Pandemics

- The NEJM study looked at 216 two- to six-person households where one family member had the 2009 H1N1 flu.
  - Only 13% of family members caught the flu from the infected person. Transmission rates ranged from 28% in two-person families to just 9% in six-person families.
  - Children < 18 or younger were 2xs more likely to catch H1N1 from an infected family member as were family members aged 19 to 50.
  - People over 50 were about 80% less likely to catch the flu compared to younger adults.
  - When a family member did catch H1N1 symptoms appeared 2-4 days after symptoms appeared in the 1st family member that had the flu.
Children Younger Than 2 Years Old Are At Increased Risk

- Hospitalization rates for 2009 H1N1 influenza are 4.5-fold higher among children < 2 years of age, 2-fold higher among children 2-4 years of age, and 1.6-fold higher among children 5-17 years of age than among adults
- In April, 2009, the FDA authorized Tamiflu (oseltamivir) for use in children younger than 1 year under an Emergency Use Authorization (EUA)
- Patients with the following medical conditions: (1) Asthma; (2) Neurological and neuro-developmental conditions; (3) Chronic lung disease (such as cystic fibrosis); (4) Heart disease (such as congenital heart disease); (5) Blood disorders (such as sickle cell disease); (6) Endocrine disorders (such as diabetes mellitus); (7) Kidney disorders; (8) Liver disorders; (9) Metabolic disorders (such as inherited metabolic disorders and mitochondrial disorders); (10) Weakened immune system due to disease or medication (such as people with HIV or AIDS, or cancer, or those on chronic steroids); (11) People younger than 19 years of age who are receiving long-term aspirin therapy

Psychosocial Issues

- Celebrity Medicine, a New Pediatric Concern?

Celebrity Medicine, a New Pediatric Concern?

- Glenn Beck: H1N1 Vaccine may turn out to be "deadly."
- In response to Health and Human Services call for widespread use of the vaccination Rush Limbaugh says "You'll be healthier" if you don't listen to the government.

Jenny McCarthy Believes there is a Correlation between Vaccines and Autism

A Gallup Poll found that ½ of all adults were aware of McCarthy's warnings about childhood shots and about ½ now question vaccine safety.
Does The Influenza Vaccine Contain Thimerosal?

- Yes, for the majority of vaccines distributed in the US - some contain only trace amounts of thimerosal and are considered by the FDA to be preservative-free
- For the 2008-09 season, there is one thimerosal-free product licensed for 6-23 month old children
- For children between the ages of 2 and 5 years, there are 3 thimerosal-free products
  [http://www.cdc.gov/Flu/about/qa/vaxsupply.htm#table]

Thimerosal (Merthiolate™) and Autism

- An organomercury compound (49% Hg) used as an antiseptic and antifungal agent- it has been used as a preservative in vaccines
- Few studies of human toxicology
- In the body, it is metabolized or degraded to ethylmercury
- Ethylmercury distributes to all body tissues, crossing the blood-brain barrier and the placental barrier

Thimerosal and Autism

- Autism “epidemic” not caused by shifts in diagnoses; environmental factors likely (recent CA study)
- “A growing number of scientists and researchers believe that a relationship between the increase in neurodevelopmental disorders of autism, attention deficit hyperactive disorder, and speech or language delay, and the increased use of thimerosal in vaccines is plausible and deserves more scrutiny”

Autism and Vaccines

- The Institute of Medicine (IOM) concluded that “the evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism.” CDC supports the IOM conclusion
- “To date, studies conducted or funded by the CDC that purportedly dispute any correlation between autism and vaccine injury have been of poor design, under-powered, and fatally flawed” (National Autism Association)
- Except for influenza (flu), thimerosal is removed from, or reduced in, all vaccines routinely recommended for children 6 years of age and under manufactured for the U.S. market
H1N1 Vaccination Efforts Plagued by Problems

- Drug manufacture recalled about 800,000 pediatric doses of its vaccine against pandemic H1N1 influenza because of low potency
- Delays and supply shortages were major issues

Modernize Flu Vaccine Production

- Most H1N1 vaccine originated with 30 chicken eggs in a New York laboratory
- About 50 million Americans have contracted the H1N1 virus
- Modern cell-culture methods are available yet not approved by the FDA

The 1918-1919 Pandemic (H1N1)

- It infected 28% of all Americans
- A fifth of the world's population was infected
- The flu was most deadly for people ages 20 to 40
  - This pattern of morbidity was unusual for influenza which is usually a killer of the elderly and young children.

How Bad Can it Get?

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<td>World population</td>
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<td>75 million/0.68 million</td>
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Did we dodge a bullet with 2009 H1N1

yes