Subdue the Flu: a 2015 update on influenza

Marilyn N. Bulloch PharmD, BCPS
Assistant Clinical Professor
Harrison School of Pharmacy
Auburn University
Disclosures

• I currently have no disclosures to make.

• I wish I did
Objectives

• Explain the pathophysiology of influenza
• Discuss currently available pharmacologic options for the prevention and treatment of influenza
• Describe pharmacologic agents for the prevention and treatment of influenza that are currently in development or in undergoing clinical studies in humans
• Compare and contrast novel and emerging strains of the influenza virus in humans and identify appropriate pharmacologic treatment options.
Influenza History

- Over 6,000 years old
- Term originated in 1700s in Italy
  - Other names: febris catarrhalis, epidemica, tussis epidemica
- 1173 – initial recognition
- 1580 – first pandemic
- 1931 – discovery that it can be grown in eggs
- 1932- human influenza isolated
- 1935 – 1st egg based vaccine
- World War II – given to service members in study
- 1946 – discovery of antigenic drift
- 1950s – antigenic shift studied

Shope RE. Public Health Reports. 1958;73:165-179
Kilbourne ED. History of Vaccine Development.
Epidemiology

• 1 in 5 people are infected each year
• Season
  – Northern Hemisphere – November – March
  – Southern Hemisphere – April - September
  – Tropics – Year round
• Hospitalization
  – 3-5 million per year
  – Highest when H3N2 predominates
  – Highest in patients ≥ 85 years
  – Children < 5 equal to rate of adults 50-64 years
• 30,000 deaths annually (up to 500,000 worldwide)
• Vast majority of deaths occur in older adults

Thompson WW et al. JAMA. 2004;292:1333-40
Murphy CG. Emergency Medicine Practice. 2009;11:1-26
Reperant et al. F1000Prime Reports. 2014;6:47
Peak Flu Season

[Bar chart showing the number of times each month was the peak flu season: February has the highest number, followed by March, April, and May, with October and November having the lowest numbers.]

Influenza Pathophysiology

Source: http://www.cdc.gov
Pathophysiology

Figure 3. Osterholm et al. *N Eng J Med.* 2005;352:1839
Symptoms of INFLUENZA

- **Fever**
- **Aches**
- **Chills**
- **Tiredness**
- **Sudden Onset**

**Central**
- Headache

**Systemic**
- Fever
  (usually high)

**Muscular**
- (Extreme)
  tiredness

**Joints**
- Aches

**Nasopharynx**
- Runny or stuffy
  nose
- Sore throat
- Aches

**Respiratory**
- Coughing

**Gastric**
- Vomiting

Source: http://www.cremhel.com
Complications

Common
• Acute bronchitis
• Secondary bacterial pneumonia
• Sinus infections
• Otitis Media
• Worsening of chronic co-morbidities

Uncommon/Rare
• Primary viral pneumonia
• Myocarditis
• Pericarditis
• Myositis
• Myoglobinuria
• Kidney failure
• Encephalitis
• Transverse-myelitis
• Guillain-Barre syndrome
• Toxic Shock Syndrome
• Parotitis

High Risk for Severe Disease

- **Age**
  - > 65 years
  - < 2 years
- **Chronic diseases** – lung, cardiovascular, kidney, liver
- **Hematologic disease** (i.e. sickle cell anemia)
- **Metabolic disorders** (i.e. diabetes)
- **Immunosuppression**
- **Compromised respiratory function**
- **Conditions that increase risk of aspiration**
- **Pregnancy or 2 weeks post-partum**
- **Long-term aspirin therapy**
- **Neuromuscular disease**
- **Intellectual disability or moderate-severe developmental delay**
- **Seizures**
- **Spinal cord injury**
- **American Indians or Alaskan Natives**
- **BMI ≥ 40**
- **Long-term care facilities**
Naming the Influenza Virus

- Antigenic type – A, B, C
- Host of origin (i.e. swine, chicken, equine, etc.)
  - No host origin given if human-origin
- Geographical origin – City
- Strain number
- Year of isolation
- Influenza A – hemagglutinin and neuraminidase description in parentheses (i.e. H3N2)

http://www.cdc.gov/flu/about/viruses/types.htm
Variations of the Influenza Virus

Source: www.medicalecology.com
Question

• Which of the following is the reason humans must receive the influenza vaccine each year?
  A. Antigenic shift
  B. Antigenic drift
  C. The inability to predict circulating influenza strains in advance
Changes in the Influenza Virus

Mutation

Antigenic drift

Antigenic shift

The 2014-15 Flu Season

• 20.3% of specimens tested were positive
• Dominant strain – Influenza A (H3N2)
• Ages ≥ 65 years most severely affected
• 17,584 hospitalizations (64.3 per 100K people)
  – 84.8% for Influenza A
  – 15.2% for Influenza B
• Mortality – 5-9.9%

Source: http://www.cdc.gov/flu/weekly/summary.htm
The Best Guess

<table>
<thead>
<tr>
<th></th>
<th>H3N2</th>
<th>H1N1</th>
<th>B/Yamagata</th>
<th>B/Victoria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount Matching</td>
<td>19.9%</td>
<td>100%</td>
<td>97.3%</td>
<td>97.4%</td>
</tr>
<tr>
<td>2014-2015 Vaccine</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Components of the 2014-2015 Northern Hemisphere Influenza Vaccine

- A/Texas/50/2012
- A/California/7/2009-like
- B/Massachusetts/2/2012-like (Yamagata)
- B/Brisbane/60//2008-like (Victoria) (Quadrivalent vaccines only)

Overall Efficacy -19%

Source: http://www.cdc.gov/flu
Benefits of Vaccination

- Prevented
  - 7.2 million influenza-associated illnesses
  - 3.1 million medical visits
  - 90,068 hospitalizations

Reed C et al. MMWR. 2014;63(49):1151-54
Recommendations for 2015

• Trivalent Vaccines
  – A/California/7/2009 (H1N1)pdm09-like virus;
  – A/Switzerland/9715293/2013 (H3N2)-like virus;
  – B/Phuket/3073/2013-like virus

• Quadrivalent Vaccines
  – Above Plus
  – B/Brisbane/60/2008-like virus

## Vaccine Reimbursement

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Brand</th>
<th>Cost</th>
<th>Medicare/Medicaid</th>
<th>Tricare</th>
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</thead>
<tbody>
<tr>
<td>IIV₃ IM</td>
<td>Afluria</td>
<td>$11.55</td>
<td>$34.98</td>
<td>$30.85</td>
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<td></td>
<td>Fluarix</td>
<td>$11.00</td>
<td>$37.19</td>
<td>$31.45</td>
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<tr>
<td></td>
<td>Flulaval</td>
<td></td>
<td>$31.67</td>
<td>$27.89</td>
</tr>
<tr>
<td></td>
<td>Fluvirin</td>
<td>$14.01</td>
<td>$43.49</td>
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</tr>
<tr>
<td></td>
<td>Fluzone</td>
<td>$10.69</td>
<td>$35.18</td>
<td>$31.35</td>
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<tr>
<td>IIV₃ Intradermal</td>
<td>Fluzone Intradermal</td>
<td>$16.72</td>
<td>$42.01</td>
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<tr>
<td>IIV₃ High-Dose</td>
<td>Fluzone High-Dose</td>
<td>$29.4</td>
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<tr>
<td>IIV₄</td>
<td>Fluzone Quadrivalent</td>
<td>$16.15</td>
<td>$39.93</td>
<td>$70.31</td>
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<tr>
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<td>Flulaval Quadrivalent</td>
<td>$15.05</td>
<td>$39.93</td>
<td>$70.31</td>
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<tr>
<td></td>
<td>Fluxone Quadrivalent</td>
<td>$17.5</td>
<td>$41.07</td>
<td>$38.72</td>
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<td>Fluxone Quadrivalent Preservative Free</td>
<td>$17.5</td>
<td>$41.07</td>
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<td>$16.05</td>
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<tr>
<td></td>
<td>Fluarix Quadrivalent Preservative Free</td>
<td>$16.05</td>
<td>$41.07</td>
<td>$38.72</td>
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<tr>
<td>ccIIV₃</td>
<td>Flucelvax</td>
<td>$19.68</td>
<td>$44.76</td>
<td>$39.97</td>
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<tr>
<td>RIV₃</td>
<td>Flublok</td>
<td>$32.75</td>
<td>$60.28</td>
<td>$55.79</td>
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<tr>
<td>LAIV₄</td>
<td>FluMist Quadrivalent</td>
<td>$23.7</td>
<td>$48.83</td>
<td>$43.91</td>
</tr>
</tbody>
</table>
Question

– True or False: The 2015-16 Trivalent Influenza Vaccine will contain B/Brisbane/60/2008-like virus
Influenza Treatment

The DIET
During and After
The Old Reliable Round Package

INFLUENZA
Horlick’s
Malted Milk
Very Nutritious, Digestible
The REAL Food-Drink, instantly prepared. Made by the ORIGINAL Horlick process and from carefully selected materials. Used successfully over 1/4 century. Endorsed by physicians everywhere. Ask for Horlick’s The Original and get Horlick’s The Original Thus Avoiding Imitations

INFLUENZA
Lung and Throat Affections.
"SANITAS" FUMIGATOR
(“Sanitas” Inhalers, 1/2 and 2/6)
"SANITAS" NO. 1 & 2. Boil in the best possible inhalatory, and a powerful antiseptic and Inhalator.
"SANITAS" Inhaling Powders—’Sanitas’ & ‘Sanitas’ No.1
Powder, etc., to be used in a syringe.

INFLUENZA RAGING
MILTON
MILTON kills the influenza germs. It did great work in past influenza raids.
A bottle of Milton will save a family. Don’t wait for influenza to attack you—take the initiative. Protect your children too.
Milton is clear and pure alike water—harmless to the human constitution, but death to the disease germs.

How to use MILTON for Fighting Influenza
Pour half a teaspoonful of Milton into a tumbler of tepid water. Gargle the throat or nose it up the nose. An ordinary spray can be used for the latter purpose. Do this three times a day.

Any man, woman, or child who does this, and takes ordinary care, will ward off the influenza.

Sold in 1/3 and 2/6 Bottles.
To be obtained from all Dealers.

#APA134Annual
Neuraminidase Inhibitors

Source: Http://www.drtedwilliams.net
The concept of neuraminidase inhibition

Influenza infection

- Neuraminidase enables the virus to bud from the host cell
- Newly formed virus
- Hemagglutinin
- Neuraminidase

Influenza viruses infect host cells turning them into “flu factories”

Neuraminidase inhibition

- Neuraminidase inhibition prevents the virus from escaping and spreading to other cells

Source: http://homepage.smc.edu/wissmann_paul/anatomy1/1antiviraldrugs.html
# Traditional Neuraminidase Inhibitor Dosing

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oseltamivir</th>
<th>Zanamivir</th>
<th>Peramivir</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration</strong></td>
<td>5 days</td>
<td>5 days</td>
<td>1 day</td>
</tr>
<tr>
<td><strong>Adult Dosing</strong></td>
<td>75 mg BID</td>
<td>10 mg BID</td>
<td>600 mg x 1</td>
</tr>
<tr>
<td><strong>Children Dosing</strong></td>
<td>&gt; 40 kg: adult dose</td>
<td>10 mg BID</td>
<td>Not used</td>
</tr>
<tr>
<td></td>
<td>23-40 kg: 60 mg BID</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15-23 kg: 45 mg BID</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≤ 15 kg: 30 mg BID</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 mo-1yr: 3mg/kg BID</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prophylaxis</th>
<th>Oseltamivir</th>
<th>Zanamivir</th>
<th>Peramivir</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration</strong></td>
<td>7 days</td>
<td>7 days</td>
<td>Not used</td>
</tr>
<tr>
<td><strong>Adult Dosing</strong></td>
<td>75 mg daily</td>
<td>10 mg daily</td>
<td>Not used</td>
</tr>
<tr>
<td><strong>Children Dosing</strong></td>
<td>&gt; 40 kg: adult dose</td>
<td>10 mg daily</td>
<td>Not used</td>
</tr>
<tr>
<td></td>
<td>23-40 kg: 60 mg daily</td>
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<tr>
<td></td>
<td>≤ 15 kg: 30 mg daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 mo-1yr: 3mg/kg daily</td>
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</tr>
</tbody>
</table>
## Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Oseltamivir</th>
<th>Zanamivir</th>
<th>Peramivir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>73%</td>
<td>62%</td>
<td>???</td>
</tr>
<tr>
<td>Prevention/post-exposure</td>
<td>68-89%</td>
<td>72-82%</td>
<td>-----</td>
</tr>
<tr>
<td>Prevention/pre-exposure</td>
<td>82%</td>
<td>84%</td>
<td>-----</td>
</tr>
</tbody>
</table>

- Decrease duration of fever and symptoms by ~ a day
- Can reduce death and duration of stay in hospitalized patients
- Beneficial up to 4-5 days after illness onset in hospitalized patients.

Source: [http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6001a1.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6001a1.htm)
Tamiflu (oseltamivir)

- Prodrug
- Use – Influenza A and B
  - Treatment – Any age
  - Prophylaxis - ≥ 3 months
  - Preferred in pregnancy
- Side effects of concern - Nausea/vomiting
  - Others – skin reactions (rare) transient psychiatric events (Japanese patients)

Tamiflu (oseltamivir)

- **2014 Cochran Review**
  - Decreased duration of symptoms by 16.8 hours (8.4 to 25.1; p<0.0001)
  - No evidence of reduced hospital admissions or complications

- **Dobson et al. (2015)**
  - Decrease in symptoms by 25.2 hours (97.5 hrs vs. 122.7 hrs)
  - 5.2% difference overall in alleviation of symptoms 24 hours after treatment initiation (p<0.0001)
  - Reduced complications
    - Respiratory tract infects requiring antibiotics (4.2% vs. 8.7%; RR=0.56; p=0.001)
    - Pneumonia (0.6% vs. 1.7%; RR 0.62; p=0.003)
    - Bronchitis (3.6% vs. 6.9%; RR 0.4; p=0.015)
    - All cause hospitalization (0.6% vs. 1.7%; RR=0.37; p=0.013)
Tamiflu (oseltamivir)

Time to Alleviation of All Symptoms

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Oseletamivir Placebo</th>
<th>Time ratio (95% CI)</th>
<th>Interaction p value</th>
<th>Estimated median (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65</td>
<td>1273</td>
<td>0.77 (0.71-0.83)</td>
<td>0.086</td>
<td>87.2</td>
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<tr>
<td>≥65</td>
<td>292</td>
<td>0.89 (0.76-1.05)</td>
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<td>147.9</td>
</tr>
<tr>
<td>High risk-1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1186</td>
<td>0.75 (0.59-0.82)</td>
<td>0.009</td>
<td>83.9</td>
</tr>
<tr>
<td>Yes (≥65 years/chronic illness/COAD)</td>
<td>379</td>
<td>0.93 (0.81-1.07)</td>
<td></td>
<td>145.9</td>
</tr>
<tr>
<td>High risk-2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1018</td>
<td>0.75 (0.59-0.82)</td>
<td>0.041</td>
<td>82.3</td>
</tr>
<tr>
<td>Yes (≥50 years/chronic illness/COAD)</td>
<td>547</td>
<td>0.88 (0.78-0.99)</td>
<td></td>
<td>129.8</td>
</tr>
<tr>
<td>Time since influenza onset (h)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;24</td>
<td>777</td>
<td>0.81 (0.73-0.90)</td>
<td>0.066</td>
<td>95.8</td>
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<tr>
<td>≥24</td>
<td>838</td>
<td>0.78 (0.71-0.86)</td>
<td></td>
<td>98.9</td>
</tr>
<tr>
<td>Total symptom score</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;14</td>
<td>665</td>
<td>0.74 (0.66-0.82)</td>
<td>0.096</td>
<td>77.5</td>
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<td>≥14</td>
<td>884</td>
<td>0.83 (0.75-0.92)</td>
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<td>114.7</td>
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<tr>
<td>Virus type</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>A</td>
<td>1373</td>
<td>0.78 (0.72-0.84)</td>
<td>0.19</td>
<td>94.7</td>
</tr>
<tr>
<td>B</td>
<td>183</td>
<td>0.69 (0.67-1.13)</td>
<td></td>
<td>122.3</td>
</tr>
</tbody>
</table>

Figure 3. Dobson et al. *Lancet.* 2015;So140-6736(14)62449-1
Relenza (zanamivir)

- Inhalation
- Use
  - Prevention - ≥ 5 years
  - Treatment - ≥ 7 years
- Avoid in patients with:
  - Reactive lung disease – bronchospasm
  - Allergy to milk protein
- Side effects of concern
  - Allergic reactions – oropharyngeal or facial edema
  - Others – diarrhea, bronchospasm, nausea, cough, nasal congestion, headache, dizziness, ENT infections

Peramivir (Rapivab)

- Birmingham based company
- Single dose – IM injection
- Use
  - Treatment - ≥ 18 years old
  - Chemoprophylaxis – not approved
- Side effects of concern – diarrhea
  - Others – skin reactions (rare) transient psychiatric events (Japanese patients)
- Approval studies primarily Influenza A subjects
- Reimbursed by Medicare as outpatient

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm427755.htm
The Adamantanes?

- Amantadine and rimantadine
- Inhibit M2 protein within influenza A virus
  - Increasing mutations in the M2 gene
- Different side effect profile and pharmacokinetics.
  - Amantadine
    - Requires dose adjustment for decreased kidney function.
    - Significant CNS effects – hallucinations, insomnia, headaches, dizziness, and depression
  - Rimantadine
    - Liver metabolism – no dose adjustments for kidney function
    - Less CNS impact
- Resistance levels as high as 99%!!!!
The Hospitalized Patient

- Treatment may help even 4-5 days after influenza onset
- Severe or complicated illness – oseltamivir preferred
- Optimal duration of therapy unknown
  - RT-PCR guided therapy > 5 days for severe and/or prolonged illness
- Oseltamivir 150 mg po BID have been used in critically ill and/or immunocompromised patients
- No oral access?
  - IV peramivir 600 mg (adults) or 10 mg/kg (children ≥ 6 years) daily for 5 days
- Avoid combining zanamivir with oseltamivir or peramivir - antagonism

http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6001a1.htm
Institutional Outbreaks

• Chemoprophylaxis at least 2 weeks
  – Continues until 7 days after last case identified

• Who gets chemoprophylaxis
  – ALL residents regardless of vaccine status
  – Staff – unvaccinated or vaccinated < 2 weeks
    • May consider for all staff if strain not covered by vaccine
Question

- Which antiviral is approved for the prophylaxis against Influenza B?
  A. Amantadine
  B. Zanamivir
  C. Peramivir
  D. B and C only
  E. A, B, and C
Recurrent Infections

INFLUENZA!
ALL PERSONS
Excepting Physicians and Nurses, are Forbidden,
Under Penalty of Law, of Entering or Leaving
This House, Without Written Permission
from the BOARD of HEALTH.
Recurrent Infections

62 yo female
  • Hospitalized
  • S/P bowel resection

Tested positive for H1N1
  • 5 days of oseltamivir
  • Symptoms resolved in 10 days

2 weeks later
  • Still in hospital
  • Symptoms return
  • Positive for H1N1

Retreated with oseltamivir
  • PCR negative after 48 hours of treatment
Recurrent Infections

38 yo male
• Hospitalized
• S/P mitral and aortic valve replacements

11 days after surgery
• Developed flu-like symptoms
• Tested positive for H1N1
• Treated with oseltamivir for 5 days
• Symptoms resolved in 5 days

Discharged

18 days later
• Readmitted with flu-like symptoms
• Positive for H1N1

Retreated with oseltamivir

Recurrent Infections

38 yo male
- 7 weeks s/p kidney transplant
- Developed flu-like symptoms
- Positive for H1N1

Treated at home
- Oseltamivir 75 mg BID for 10 days

3 days later
- Admitted to hospital
- Treated for presumed pneumonia
- Negative for influenza

Deteriorated
- Intubated
- Day 3 sputum cultures and Day 7 bronchoalveolar lavage positive for influenza

Day 7 hospitalization
- Oseltamivir restarted BID
- Day 11 adjusted to daily due to anuria

Day 17 and 19
- Still positive for H1N1

Day 23
- Nebulized zanamivir added

Day 30
- Oseltamivir resistance detected from day 3 sample
- IV zanamivir started
- Oseltamivir and nebulized zanamivir continued

Day 37
- Symptoms improved

Repeat Prophylaxis?

Female Adolescent
• No influenza exposure
• Camp in North Carolina

Given 10 days oseltamivir prophylaxis

2 days later
• Actually exposed to influenza

5 days later
• Positive for Influenza A
• Oseltamivir increased to BID

Developed flu-like symptoms
• Oseltamivir not adjusted

Second 10 day course of oseltamivir

2 days later
• Positive for H1N1
• Oseltamivir resistance detected

Patient recovered

CDC. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5835a.htm
Antiviral Resistance

• 2014-2015 Season
  – Neuraminidase inhibitors – only ONE resistant strain found
    • H1N1)pdm09 – oseltamivir or peramivir
  – Adamantanes – high levels for Influenza A
Coming Soon!
Creating New Antivirals

- 41 antivirals in some phase of development
  - Phase III: 3
  - Phase II: 12
  - Preclinical/Phase: 26

<table>
<thead>
<tr>
<th>Target</th>
<th>Drugs in Development</th>
<th>IV</th>
<th>Oral</th>
<th>Inhaled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuraminidase inhibitor</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Antibodies</td>
<td>16</td>
<td>16</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Viral targets</td>
<td>9</td>
<td>4</td>
<td>4</td>
<td>1</td>
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<tr>
<td>Host targets</td>
<td>12</td>
<td>1</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>
IV Zanamivir

- Aqueous solution
- Availability
  - Clinical trial
  - Emergency investigational new drug request (manufacturer)
    - Oseltamivir-resistant influenza
    - Severely ill patients unable to tolerate or absorb oseltamivir
    - Unable to take Zanamivir via inhaled device
- Dose: 600 mg IV BID for 5 days ± over 30 minutes
- Special Populations
  - Pediatrics – weight based dose
  - Kidney dysfunction – 1st dose 600 mg followed by dose per CrCl started 24-48 hours after initial dose
- No evidence that it is better than other routes
- Do not give with other routes of neuraminidase inhibitors

Laninamivir

• Inhaled long acting neuraminidase inhibitor (LANI)
• Acute, uncomplicated influenza
• 40 mg “One and Done” dosing – 58 hour half-life in respiratory tract
• Effective vs. oseltamivir-resistant influenza strains
• Good safety profile
• Current Status:
  – Approved in Japan for adults and children

Laninamivir

• IGLOO study
  – 639 patients in 12 countries from June 2013-April 2014
  – 39% (n=248) had PCR confirmed influenza A or B
  – 40 mg vs. 80 mg vs. placebo
  – No significant decrease in median time to symptom alleviation vs. placebo for either dose (102.3 hrs vs. 103.2 hrs vs. 104.1 hrs) p=0.248 and p=0.776)
    • Significantly earlier resolution of headache, fever, aches/pains, and fatigue with 40 mg group vs. placebo (58 hours vs. 72 hours; p=0.029)
  – Significant decrease in viral shedding on day 3 for 40 mg dose (p <0.001) but not 80 mg (p=0.07)
  – Significantly more patients culture negative on day 3 in both groups (p=0.002 and =0.02)
  – Significantly fewer secondary bacterial infections in 40 mg group (p=0.013)
  – ADRs similar: Diarrhea, headache, gastritis, urinary tract infection, sinusitis
Inhaled Laninamivir

A Collect medicine
- Tap Tap Tap
- Without sliding the medicine tray, tap the container gently, “Tap, tap, tap” to collect the medicine at the bottom of the inhaler.

B Prepare to inhale 1 - Inhale 1
- Slide
- Without removing the labels, slide Medicine Tray 2 in the direction of the arrow all the way to the end.
- Breathe in deeply
- Put the mouthpiece into your mouth and take a deep breath then hold your breath for 2 - 3 seconds. Exhale slowly without blowing into the mouthpiece.

C Prepare to inhale 2 - Inhale 2
- Slide
- Next, slide Medicine Tray 2 in the direction of the arrow all the way to the end.
- Breathe in deeply
- Put the mouthpiece into your mouth and take a deep breath then hold your breath for 2 - 3 seconds. Exhale slowly without blowing into the mouthpiece.

D Return to original position
- Slide Medicine Tray 2 back to its original position.

E To inhale what’s left repeat procedure A - C

F Over the age of 10
- Inhale the second package
  - Same instruction as the first package.
  - You have completed your treatment with INAVIR after inhaling the second package.

F 9 years of age and under
- You have completed your prescribed treatment with INAVIR.

Source: http://www.influ-news.info
Thiazolides

- Nitazoxanide (Alinia)
- Inhibits influenza replication by selectively blocking viral hem
- Effective against neuraminidase inhibitor-resistant strains (so far)
- ADRs – abdominal pain, emesis, diarrhea
- Food increases absorption

http://www.drugbank.ca/drugs/DB00507
http://www.accessdata.fda.gov/drugsatfda_docs/label/2005/021818lbl.pdf
## Thiazolides

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Treatment Groups</th>
<th>Results</th>
</tr>
</thead>
</table>
| Haffizulla et al | Phase IIb/III Double-blind Randomized Placebo-controlled 74 US primary care clinic Age 12-65 | - Nitazoxanide 300 mg (n=201)  
- Nitazoxanide 600 mg (n=211)  
- Placebo (n=212)  
- BID x 5 days       | - Median duration of symptoms significantly shorter compared to placebo with 600 mg (95.5 hrs vs. 116.7 hrs; p=0.0084) but not 300 mg (109.1 hrs vs. 116.7 hrs; p=0.52)  
- Significant effect seen with Influenza A 600 mg vs. placebo (56 hrs vs. 117.3; p=0.042)  
- No significant difference in time to symptom alleviation between groups for influenza B |

Favipiravir

- T-705, novel viral RNA polymerase inhibitor
- Department of Defense sponsored development
- Oral agent
- Phase II/III for adults with uncomplicated influenza
- Inhibits all serotypes and strains of influenza (so far)
- Dosing (proposed)
  - Day 1: 1800 mg po BID
  - Days 2-5: 800 mg po BID
- FAVOR Phase III studies
  - Randomized double-blind, placebo-controlled, multi-centered
  - 2021 patients

Furuta et al. Antiviral Research 2013;100:446-54
Figure 5. Furuta et al. Antiviral Research 2013;100:451

Favipiravir
Favipiravir Studies

- **Phase II study**
  - Multi-center, double-blind placebo controlled
  - 550 patients
  - Significant decrease in symptom alleviation vs. placebo (82.3 hrs vs. 97.3 hrs; p=0.01)
  - Significant faster viral clearance (p=0.0035)
  - Asymptomatic, transient uric acid elevations noted.

- **FAVOR Phase III studies**
  - Randomized double-blind, placebo-controlled, multi-centered
  - 2021 patients
  - Enrollment completed February 2015
  - Data in analysis

Frech et al. Abstract.
An Ounce of Prevention is Worth a Pound of Cure
Vaccines

Hemagglutinin (HA) → Neuraminidase (NA)

Live attenuated vaccine

Whole inactivated vaccine

Split vaccine

Subunit HA vaccine

Hemagglutinin (HA)

Hemagglutinin stalk

Carrier protein

DNA expressing viral protein of interest

Carrier plasmid

Gene expressing eg HA

Subunit HA+NA vaccine

Subunit HA stalk vaccine

Plasmid-based (DNA) vaccine

Vector-based vaccine

Figure 2. Reperant et al. F1000 Prime Reports. 2014;6:47
Vaccine Needs

- Flexible
- Universal
- Produced faster
Recombinant Influenza Vaccine

- For adults ≥ 18 years
- Currently only trivalent
- Egg-free and influenza-virus free
- Baculovirus Expression Vector System
- Three times more antigen
- Available within 2 months

Cost and Reimbursement
- Direct cost - $32.75
- Average wholesale price - $38.4
- CMS Reimbursement - $37.19 + administration ($22.98-$35.82)

Source: http://www.proteinsciences.com/VAC.htm#VAC3
Influenza Vaccine – In Development

- Quadrivalent Seasonal Influenza VLP
  - Contains influenza virus-like particles representing 4 different strains of influenza – each expresses strain-specific hemagglutinin and neuraminidase antigens.
  - From cells originating from armyworm (Spodoptera frugiperda) used to create highly evolved insect cell lines
  - Phase II study started in November 2014

- VAX2012Q (Quadrivalent)
  - 4 seasonal influenza strains each fused to flagellin protein which acts like a toll-like receptor ligand – activates innate immune response
  - Goal – produce greater quantities of vaccine in shorter amount of time than traditional influenza vaccine
  - Phase Ib/II study in patients 65-75 years started in December 2014

Influenza Vaccine – In Development

- FluNhance
  - Potential efficacy-enhancing additive to influenza vaccines
  - Contains recombinant neuraminidase
  - Less severe and shorter duration if do become infected
  - Reduces ability to shed virus
  - No eggs or mercury.
  - Phase II Study
    - By National Institute of Allergy and Infectious Diseases
    - Added to licensed seasonal vaccine
    - Safe
    - Does not reduce efficacy of HA protein

Source: http://www.proteinsciences.com/VAC.htm#VAC3
Universal Influenza Vaccine

- One and Done vaccination
- Protection even if virus mutate
- Origin
  - Immune recognition of conserved epitopes – provides protection against different influenza strains in animals
  - Finding/characterization of monoclonal antibodies – target conserved epitopes shared by different influenza strains
- Many methods under investigation
  - Targets “stem” or stalk region of HA protein
  - HA-specific monoclonal antibodies
  - Generate T-cell response
  - Synthetic - DNA

http://www.medicalnewstoday.com/articles/288082.php
http://www.fda.gov/BiologicsBloodVaccines/ScienceResearch/ucm353397.htm
http://www.medicalnewstoday.com/articles/288082.php
DNA Influenza Vaccine

Figure 1. Stachyra et al. Acta Biochichica Polonica. 2014;61:515
DNA Influenza Vaccine

Expression cassette
- Regulatory elements
- Intracellular targeting
- Codon optimization
- Other changes in the coding sequence
- Various forms and fragments of antigen

ANTI-INFLUENZA DNA VACCINE

Adjuvants
- Biological
  - Cytokines
  - CD40
  - MAD5
  - MDPI
  - ESAT-6
- Biochemical
  - Short peptides

Carriers
- Vaxfectin
- Chitosan nanoparticles
- Silver nanoparticles

Vaccination route
- Routine injection
- Needle-free injection
- Electroporation
- Helios gene gun
- Microneedles

Other strategies
- Application with other vaccines

Figure 3. Stachyra et al. Acta Biochicica Polonica. 2014;61:517
DNA Influenza Vaccine

- Induce humoral and cellular response
- Both MHC I and II presentation
- Ability to polarize T cell help for type 1 or 2
- Immune response only to chosen antigens
- Native structure of protein
- Structure and posttranslational modification of antigen like in natural infection
- Stability during storage and shipping
- Simplicity of formulation and preparation
- Fast to produce and modify
- Safety - without infective agent
- Ease of development and production
- Relatively inexpensive

- Lower efficiency in large animals and humans than small animals models
- Necessity for increasing response - enhancers, chemical or physical modifications
- Necessity for repeated or multiple doses
- No mass application methods for animals
- Lower immunogenicity than inactivated vaccine
- Limited to protein antigens
- Atypical posttranslational modifications of bacterial and parasite antigens
- (Negligible) threat of autoimmune reactions or integration of DNA into host genome

Advantages

Disadvantages

Figure 2. Stachyra et al. Acta Biochicica Polonica. 2014;61:516
SynCon®

- DNA “constructs” for key virus branches within:
  - Type A - H1N1, H3N2, H2N2, H7N9, H5N1
  - Type B
- Targets multiple influenza antigens
- Mix and match
- Utilizes universal consensus antigens
- Intradermal electroporation technology
- T-cell response
- Short production time
- Phase I studies show 47-71% efficacy

Source: http://www.inovio.com
Novel Influenza A Viruses

- Influenza A (H3N2) variant – Wisconsin
- Influenza A (H1N1) variant – Minnesota
- Both occurred in October 2014
- Both patients had contact with pigs the week preceding illness
- Both patients recovered.
- Avian influenza
  - H7N9
  - H5N1
  - H9N2

CDC MMWR
http://www.cdc.gov
http://www.who.int/influenza/vaccines/viruses/en
H7N9

• Avian influenza – low pathogenic
• First human detection – March 2013
  – 602 cases and 2227 deaths
• Location - Originated in China
• Most patients recently exposed to live poultry or contaminated environment (i.e. markets)
• Median age – 60 years
• Transmission
  – Droplet
  – May be transmitted by aerosol droplets
  – No evidence of sustained human-to-human transmission
H7N9

Genetic Evolution of H7N9 Virus in China, 2013

Multiple Reassortment Events

Setting: Habitats shared by wild and domestic birds and/or live bird/poultry markets

Source: http://www.cdc.gov/flu/images/avianflu/h7n9-reassortment-diagram.jpg
H7N9

- Characterized by rapidly progressing, severe pneumonia
- Prevention
  - No licensed vaccines
  - WHO recommends A/Anhui/1/2013-like virus be used for development
- Treatment
  - Not for uncomplicated illness in outpatients
  - Sensitive to neuraminidase inhibitors *in vitro*
  - Oseltamivir has been used clinically
    - CDC prefers oseltamivir in severe progressive disease
    - CDC states inhaled zanamivir and peramivir may be used
  - Other therapy - Convalescent plasma therapy
  - Resistant to adamantanes

http://www.who.int/influenza/human_animal_interface/influenza_h7n9/201309_h7n9_recommendation.pdf
http://www.cdc.gov/flu/avianflu/h7n9-virus.htm
http://www.healthmap.org/en
**H5N1**

- Avian Influenza – highly pathogenic
- Diversified genetically and antigenically
- Location – Asia, Africa, Middle East, Eastern Europe
  - Detected in North American birds
- 1-2% if humans exposed develop symptoms
- ????Possible human-to-human transmission????
- Prevention
  - Many vaccines in-development/developed
  - United States stockpiling supply – not commercially available
  - Support from CDC, FDA, and NIH
- Treatment
  - Oseltamivir 150 mg BID

http://www.healthmap.org/en
http://www.cdc.gov/flu/avianflu/h5n1-virus.htm
http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6001a1.htm
H9N2

- Avian Influenza
- Location – Egypt, China
- First human case – 1998
  - Total cases – 3; 0 deaths
- Mild symptoms
- No evidence of human-to-human transmission
- Prevention
  - Many vaccines in-development/developed
  - Support from CDC and NIH
  - Not available commercially

http://www.healthmap.org/en
http://www.cdc.gov/flu/avianflu/h5n1-virus.htm

#APA134Annual
Treating Patients for Novel Influenza A Virus

- Any neuraminidase inhibitor can be considered
- Oseltamivir preferred in severe disease
- Who to treat
  - Laboratory confirmed case – all patients
  - Probable case – test positive for Influenza A but negative for H3 or H1 – all patients
  - Exposed during travel - within < 10 days of illness to areas where novel virus detected – hospitalized patients only
  - Exposed to case – all patients
    - Contact within < 10 days of distance within 6 feet from 1 day before illness onset until illness resolution
  - Exposure to infected birds within 10 days – all patients

QUESTIONS?