All about Flu: The Virus & the Vaccine

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Disclosures

• I have no conflicts of interest to disclose
Objectives

- Gain working knowledge of influenza virus
  - Virology
  - Epidemiology
  - Signs, symptoms, and complications
  - Pandemic vs seasonal flu
- Understand the basics of influenza vaccination
  - Benefits and limitations
  - Current landscape
  - Future goals
What is influenza?

- Influenza is a single stranded RNA virus
  - Segmented genome, 8 gene segments
- Two main types in humans
  - Influenza A
  - Influenza B

Influenza: simplified nomenclature

- Influenza A classified into subtypes
  - HA, hemagglutinin (H1 through H18)
  - NA, neuraminidase (N1 through N11)
  - Example: H1N1
- Two lineages of influenza B viruses
  - Yamagata
  - Victoria

https://www.cdc.gov/flu/images/virus/fluivirus-antigentic-characterization-large.jpg
What does influenza do?

• Influenza causes seasonal respiratory infection and illness (i.e. “the flu”)

BMJ 2016;355:i6258
# Influenza symptoms

<table>
<thead>
<tr>
<th>Signs and Symptoms</th>
<th>Influenza</th>
<th>Cold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom onset</td>
<td>Abrupt</td>
<td>Gradual</td>
</tr>
<tr>
<td>Fever</td>
<td>Usual</td>
<td>Rare</td>
</tr>
<tr>
<td>Aches</td>
<td>Usual</td>
<td>Slight</td>
</tr>
<tr>
<td>Chills</td>
<td>Fairly common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Fatigue, weakness</td>
<td>Usual</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Sneezing</td>
<td>Sometimes</td>
<td>Common</td>
</tr>
<tr>
<td>Stuffy nose</td>
<td>Sometimes</td>
<td>Common</td>
</tr>
<tr>
<td>Sore throat</td>
<td>Sometimes</td>
<td>Common</td>
</tr>
<tr>
<td>Chest discomfort, cough</td>
<td>Common</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td>Headache</td>
<td>Common</td>
<td>Rare</td>
</tr>
</tbody>
</table>
WHO world-wide estimates

Yearly seasonal influenza

• ~1 billion infections
• ~5 million cases of severe illness
• ~290,000-650,000 deaths

2014-15 West Africa Ebola outbreak

• 28,616 cases
• 11,310 deaths
CDC estimates of seasonal influenza burden in the US:

Deaths: 12,000 – 56,000
Hospitalizations: 140,000 – 710,000
Cases: 9,200,000 – 35,600,000
Influenza

• Most will recover from influenza within a week, sometimes two
• People are usually contagious from the day before developing symptoms through about one week; contagiousness usually correlates with fever
• Some may go on to have severe complications
Who is at highest risk?

- Children <5 (particularly <2)
- Adults 65 and older
- Pregnant women
- People in nursing homes or other long-term care facilities
- Native American/Alaska Natives
- People with:
  - Asthma or other lung disease
  - Heart disease
  - Neurological conditions
  - Immunocompromised (e.g. HIV/AIDS), cancer
  - Obesity
What are the complications of influenza?

**Symptoms**
- Neurological
  - Fever
  - Headache
  - Confusion
- Respiratory
  - Dry cough
  - Sore throat
  - Nasal congestion
- Gastrointestinal
  - Nausea
  - Vomiting
  - Diarrhoea
- Musculoskeletal
  - Myalgia
  - Fatigue

**Complications**
- Neurological
  - Febrile convulsions
  - Reyes syndrome
  - Meningitis/encephalitis
  - Transverse myelitis
  - Guillain-Barré syndrome
- Cardiac
  - Pericarditis
  - Myocarditis
  - Exacerbation of cardiovascular disease
- Respiratory
  - Otitis media
  - Croup
  - Sinusitis/bronchitis/pharyngitis
  - Pneumonia (viral or secondary bacterial)
  - Exacerbation of chronic lung disease
- Pregnancy
  - Increased maternal complications
  - Increased infant perinatal mortality
  - Increased risk of prematurity
  - Smaller neonatal size
  - Lower birth weight
- Musculoskeletal
  - Myositis
  - Rhabdomyolysis

*More common in children*
Influenza and pneumonia

• Pneumonia – infection and inflammation in the lower respiratory tract, lungs
• During influenza, pneumonia can be caused by the influenza virus (primary) itself or by superinfection with bacteria (secondary)
  • *Streptococcus pneumoniae*
  • *Staphylococcus aureus*
MYTH

• Healthy people are not at high risk for complications from influenza
Leading causes of mortality, USA 2015

1. Diseases of heart (heart disease)
2. Malignant neoplasms (cancer)
3. Chronic lower respiratory diseases
4. Accidents (unintentional injuries)
5. Cerebrovascular diseases (stroke)
6. Alzheimer’s disease
7. Diabetes mellitus (diabetes)
8. Influenza and pneumonia
9. Nephritis, nephrotic syndrome and nephrosis (kidney disease)
10. Intentional self-harm (suicide)

#1 cause of death due to infection in the US is lung infections caused by influenza or bacterial pneumonia

https://www.cdc.gov/nchs/data/nvsr/nvsr66/nvsr66_06.pdf
Table 1. Characteristics of 272 Hospitalized Patients Who Were Infected with the 2009 H1N1 Virus in the United States (April–June 2009).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>132 (49)</td>
</tr>
<tr>
<td>Age group*</td>
<td></td>
</tr>
<tr>
<td>0–23 mo</td>
<td>23 (8)</td>
</tr>
<tr>
<td>2–4 yr</td>
<td>20 (7)</td>
</tr>
<tr>
<td>5–9 yr</td>
<td>29 (11)</td>
</tr>
<tr>
<td>10–17 yr</td>
<td>50 (18)</td>
</tr>
<tr>
<td>18–49 yr</td>
<td>104 (38)</td>
</tr>
<tr>
<td>50–64 yr</td>
<td>32 (12)</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>14 (5)</td>
</tr>
<tr>
<td>Race or ethnic group†</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>83 (30)</td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>73 (27)</td>
</tr>
<tr>
<td>Black</td>
<td>53 (19)</td>
</tr>
<tr>
<td>Native Hawaiian, Asian, or Pacific Islander</td>
<td>15 (6)</td>
</tr>
<tr>
<td>Native American</td>
<td>9 (3)</td>
</tr>
<tr>
<td>Multiracial, not further defined</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>37 (14)</td>
</tr>
</tbody>
</table>

Median age = 21 years

Jain et al. NEJM 2009.
Table 4. Characteristics of Hospitalized Patients Who Were Not Admitted to an Intensive Care Unit (ICU) and Survived and Patients Who Were Admitted to an ICU or Died.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients Who Were Not Admitted to an ICU and Survived (N = 205)</th>
<th>Patients Who Were Admitted to an ICU or Died (N = 67)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median — yr (range)</td>
<td>19 (21–80)</td>
<td>29 (1–86)</td>
</tr>
<tr>
<td>&lt;18 Yr — no. (%)</td>
<td>98 (48)</td>
<td>24 (36)</td>
</tr>
<tr>
<td><strong>Shortness of breath — no. (%)</strong></td>
<td>104 (51)</td>
<td>58 (87)</td>
</tr>
<tr>
<td><strong>Neurocognitive disorder — no. (%)</strong></td>
<td>11 (5)</td>
<td>9 (13)</td>
</tr>
<tr>
<td><strong>Neuromuscular disorder — no. (%)</strong></td>
<td>10 (5)</td>
<td>9 (13)</td>
</tr>
<tr>
<td><strong>Pneumonia seen on chest radiography on admission — no./total no. (%)</strong></td>
<td>51/182 (28)</td>
<td>49/67 (73)</td>
</tr>
<tr>
<td><strong>Antiviral treatment — no./total no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any — no. /total no. (%)</td>
<td>144/203 (71)</td>
<td>56/65 (86)</td>
</tr>
<tr>
<td>≤2 Days after onset of symptoms — no. /total no. (%)</td>
<td>62/139 (45)</td>
<td>13/56 (23)</td>
</tr>
<tr>
<td>Days from onset of symptoms to initiation — no. (range)</td>
<td>3 (0–29)</td>
<td>5 (0–24)</td>
</tr>
<tr>
<td><strong>Antibiotic treatment — no./total no. (%)</strong></td>
<td>144/195 (74)</td>
<td>62/65 (95)</td>
</tr>
<tr>
<td><strong>Corticosteroid treatment — no./total no. (%)</strong></td>
<td>57/183 (31)</td>
<td>29/56 (52)</td>
</tr>
</tbody>
</table>

*Jain et al. NEJM 2009.*
Mortality in US adults admitted to ICUs with 2009 pH1N1 infection

Rice et al. NEJM 2012.
Pandemic vs seasonal epidemics

• “A pandemic is the worldwide spread of a new disease” (WHO)
  • Influenza pandemics are caused by new subtypes of influenza A
  • Most influenza infections occur in the context of seasonal epidemics
• “The occurrence of more cases of disease than expected in a given area or among a specific group of people over a particular period of time” (CDC)
A brief history of pandemic influenza

1918 “Spanish flu” pandemic

- 50-100 million deaths
- ~5% of world population
- Case-fatality rates 100-fold higher normal
Why was the Spanish flu so deadly?

• A perfect storm of factors
  • WWI
  • Mass movements of vulnerable populations
  • Emergence of a novel pandemic strain
Why was the Spanish flu so deadly?

- Exact pathogenesis still not quite clear
- Aberrant immune responses
- Secondary bacterial pneumonia
  ~80-90% of all deaths

Morens et al. J Infect Dis 2008
Morens et al. Crit Care Med 2010
Influenza A: Potential for pandemic strains

- Two mechanisms for pandemic strain emergence
  - Direct animal to human transmission of new strain
  - Gene reassortment
Influenza: Not just for people

- Birds
  - Wild aquatic birds, waterfowl
  - Domestic waterfowl, poultry
- Mammals:
  - Pigs
  - Dogs, cats, horses, bats, seals, whales

Influenza A: Potential for pandemic strains

Influenza A: Potential for pandemic strains

Belshe, NEJM 2005.
Influenza A: Potential for pandemic strains

- Segmented genome allows opportunity for gene reassortment
Influenza A: Potential for pandemic strains

Belshe, NEJM 2005.
2009 novel H1N1 influenza ("swine flu")
Where will the next pandemic come from?

- Anyone’s guess, but some areas to watch


Where will the next pandemic come from?

• Characteristics of viruses required for new pandemic:
  • Viruses that are antigenically new
  • Can easily be passed person to person

• Several viruses out there haven’t yet developed necessary mutations to pass efficiently person-to-person
  • Avian H5N1, H7N9
  • Swine, or variant influenza: H3N2v
Where will the next pandemic come from?

Yeah, Mother Nature's a mad scientist, Jerry.

LIFE, UH, FINDS A WAY.
What is certain in life?

- Death, taxes, and seasonal influenza
Pandemic vs seasonal influenza

- Emergence of pandemic strains results from *antigenic shift*
  - The surface proteins (HA, NA) look completely different from anything the population has seen before
  - Fortunately, this occurrence is relatively rare
- Every year, influenza viruses undergo a different process, known as *antigenic drift*
  - The surface proteins (HA, NA) are generally the same but have mutated just enough that the immune system can’t recognize them as well as before
Influenza gene mutation

Error rate of RNA replication is 1 mutation/virion

1 infected cell can therefore generate 10,000 mutated viruses!

(Boivin et al. J Biol Chem 2010.)

Pandemic vs seasonal influenza

- Antigenic drift (small changes that accumulate in the outer flu proteins over the course of the year) is the reason that flu is a problem every winter, leading to seasonal influenza epidemics.
Seasonal influenza: epidemiology

• “Flu season” occurs during the winter months in temperate climates
• In tropical climates, the season is less well defined and the viruses may circulate at lower levels year-round
• Reasons for this are still incompletely understood but likely related to temperature/humidity and possibly even school calendars
Seasonal influenza: epidemiology
Seasonal influenza: epidemiology
Seasonal influenza and deaths

- Every winter, we see death due to influenza
- Severity of season typically tracked by monitoring pediatric deaths
  - Nationally notifiable condition
  - General overall estimate of severity of each season
Seasonal influenza: epidemiology
Seasonal influenza and *Staphylococcal aureus*

- *Staphylococcus aureus* pneumonia carries a high risk of mortality in young, immunocompetent patients.
- The greatest risk factor for this type of pneumonia is influenza.

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>3/50 (6)</th>
<th>13/55 (23.6)</th>
<th>0.012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary CAP</td>
<td>9/50 (18)</td>
<td>7/55 (12.7)</td>
<td>0.45</td>
</tr>
<tr>
<td>Antibiotics before admission</td>
<td>3.8 ± 2.9</td>
<td>4.7 ± 2.5</td>
<td>0.11</td>
</tr>
<tr>
<td>Duration of symptoms, days, mean ± SD</td>
<td><strong>32/46 (69.6)</strong></td>
<td><strong>14/47 (29.8)</strong></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Summary, Part I

• Influenza is an important cause of seasonal respiratory illness
• Yearly seasonal influenza epidemics are certain to occur
• Worldwide pandemic influenza is always a possibility
• Influenza can be an important cause of mortality, even in the otherwise young and healthy
So, what to do?

“I’ll have an ounce of prevention.”
Pandemic influenza vs seasonal influenza

• We may not be able to predict/prevent the next influenza pandemic
• But there ARE many things we can do to combat influenza

God grant me the serenity
to accept the things I cannot change;
courage to change the things I can;
and wisdom to know the difference.
An ounce of prevention is worth a pound of cure

- Practice good respiratory etiquette and hand hygiene
- Stay home when you are sick
- VACCINATION is the single best way to prevent influenza infection
Who should get vaccinated?

• EVERYBODY ≥ 6 months of age
MYTH: The flu vaccine doesn’t work

https://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm
Flu vaccine effectiveness

- Flu vaccine effectiveness is usually determined by measuring how many outpatients who got vaccinated get confirmed influenza compared to those who don’t (US Flu VE Network) and only tell part of the story
- Inpatient studies to determine prevention of hospitalizations began in 2016 (US Hospitalized Adult Influenza Vaccine Effectiveness Network, HAIVEN)
- Most large studies fail to accurately capture other effects of vaccination
  - Decreased severity/duration of symptoms
  - Decreased complications
  - Decreased transmission to others
- Other studies have clearly demonstrated increased benefits in specific sub-groups (e.g. those with diabetes, pregnant women, other high-risk conditions)
MYTH: The flu vaccine doesn’t work

The estimated number of flu illnesses prevented by flu vaccination during the 2016-2017 season:

**5.3 million,**
about the population of the Atlanta metropolitan area.

The estimated number of flu medical visits prevented by vaccination during the 2016-2017 season:

**2.6 million,**
or more than the number of students in all K-12 schools in Florida.

The estimated number of flu hospitalizations prevented by vaccination during the 2016-2017 season:

**85,000,**
or more than the number of hospital beds in California and Oregon.


**get vaccinated**
www.cdc.gov/flu
Vaccine coverage

• IN 2017, only 38% of all US citizens got a flu shot prior to peak of flu season!
• Vermont tends to do slightly better than national average:

MYTH: The flu vaccine is dangerous

- You CANNOT get the flu from flu vaccine
- The most common side effects of flu vaccine:
  - Redness, swelling, pain at injection site
  - Headache
  - Low-grade fevers
  - Nausea
  - Muscle aches (myalgias)
Influenza vaccines: many options

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Trade Name (vaccine abbreviation)</th>
<th>How Supplied</th>
<th>Mercury Content (mg Hp0.3 mL)</th>
<th>Age Group</th>
<th>Vaccine Product Billing Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>GlaxoSmithKline</td>
<td>Fluarix (IV4)</td>
<td>0.5 mL (single-dose syringe)</td>
<td>0</td>
<td>6 months &amp; older</td>
<td>90686</td>
</tr>
<tr>
<td></td>
<td>FluLaval (IV4)</td>
<td>0.5 mL (single-dose syringe)</td>
<td>0</td>
<td>6 months &amp; older</td>
<td>90686</td>
</tr>
<tr>
<td></td>
<td>3.0 mL (multi-dose vial)</td>
<td>&lt;25</td>
<td>6 months &amp; older</td>
<td>90688</td>
<td></td>
</tr>
<tr>
<td>ID Biomedical Corp. of Quebec,a subsidiary of GlaxoSmithKline</td>
<td>FluMist² (LAIV4)</td>
<td>0.2 mL (single-use nasal spray)</td>
<td>0</td>
<td>2 through 49 years</td>
<td>90672</td>
</tr>
<tr>
<td>MedImmune</td>
<td>FluBlok (RIV3)</td>
<td>0.5 mL (single-dose vial)</td>
<td>0</td>
<td>18 years &amp; older</td>
<td>90673</td>
</tr>
<tr>
<td>Protein Sciences Corp.</td>
<td>FluBlok (RIV4)</td>
<td>0.5 mL (single-dose vial)</td>
<td>0</td>
<td>18 years &amp; older</td>
<td>90682</td>
</tr>
<tr>
<td>Sanofi Pasteur, Inc.</td>
<td>Fluzone (IV4)</td>
<td>0.25 mL (single-dose syringe)</td>
<td>0</td>
<td>6 through 35 months</td>
<td>90685</td>
</tr>
<tr>
<td></td>
<td>0.5 mL (single-dose syringe)</td>
<td>0</td>
<td>3 years &amp; older</td>
<td>90686</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.5 mL (single-dose vial)</td>
<td>0</td>
<td>3 years &amp; older</td>
<td>90686</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.0 mL (multi-dose vial)</td>
<td>25</td>
<td>6 through 35 months</td>
<td>90687</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.0 mL (multi-dose vial)</td>
<td>25</td>
<td>3 years &amp; older</td>
<td>90688</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluzone High-Dose (IV3-HD)</td>
<td>0.5 mL (single-dose syringe)</td>
<td>0</td>
<td>65 years &amp; older</td>
<td>90662</td>
</tr>
<tr>
<td></td>
<td>Fluzone Intradermal (IV4-ID)</td>
<td>0.1 mL (single-dose microinjection system)</td>
<td>0</td>
<td>18 through 64 years</td>
<td>90630</td>
</tr>
<tr>
<td>Seqirus</td>
<td>Afluria (IIV3)</td>
<td>0.5 mL (single-dose syringe)</td>
<td>0</td>
<td>5 years &amp; older³</td>
<td>90656</td>
</tr>
<tr>
<td></td>
<td>3.0 mL (multi-dose vial)</td>
<td>24.5</td>
<td>90658</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Afluria (IIV4)</td>
<td>0.5 mL (single-dose syringe)</td>
<td>0</td>
<td>5 years &amp; older³</td>
<td>90656</td>
</tr>
<tr>
<td></td>
<td>3.0 mL (multi-dose vial)</td>
<td>24.5</td>
<td>90658</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Flucelvax (cclIV4)</td>
<td>0.5 mL (single-dose syringe)</td>
<td>0</td>
<td>4 years &amp; older</td>
<td>90764</td>
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<tr>
<td></td>
<td>5.0 mL (multi-dose vial)</td>
<td>25</td>
<td>4 years &amp; older</td>
<td>90764</td>
<td></td>
</tr>
</tbody>
</table>

Influenza vaccines

• Trivalent versus quadrivalent
• Inactivated vs live-attenuated
• Method of manufacture
Influenza vaccines: a long road...

- Step 1: Strain selection for this year’s vaccine
- Recommendations made by WHO
  - Circulating viruses from over 100 countries reviewed
  - 5 WHO reference labs in USA, UK, Australia, Japan, China
- In USA, FDA reviews WHO recommendations, makes final determination of which strains to include
Flu vaccine strains, 2018-2019

- A/Michigan/45/2015 (H1N1)pdm09-like virus
- A/Singapore/INFIMH-16-00190/2016 (H3N2)-like virus
- B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage)
- B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage)

http://www.who.int/influenza/vaccines/virus/recommendations/201802_recommendation.pdf?ua=1
Trivalent versus quadrivalent vaccines

• Trivalent vaccines contain 3 strains of flu
  • Always contain 2 strains of influenza A PLUS
  • 1 lineage of influenza B (Victoria or Yamagata)

• Quadrivalent vaccines contain two strains of influenza B
• Most common influenza A viruses currently are H1N1, H3N2
Inactivated influenza vaccines

- Killed viruses or individual proteins (not infectious virus)
  - Multiple methods of manufacture
  - Traditional method: egg-based
  - Alternative methods
    - Cell-based
    - Recombinant protein-based
Egg-based influenza vaccines

Egg-based influenza vaccines

- Remains the mainstay of vaccine production
- Disadvantages
  - Long production time
  - Viruses become modified during culture, which may affect antibody targets
Egg-based influenza vaccines

Cell culture-based vaccines

Recombinant vaccines

- Cell infection
- BEVS (HA cloning)
- WHO candidate virus
- Insect cells high density culture
- Virus replication
- Centrifugation
- Detergent extraction
- Ion chromatography
- Membrane filtration
- Ultrafiltration
- Chromatography
- HA protein
- Formulation

Live-attenuated influenza vaccine

- Live but weakened (attenuated) virus
  - Virus has been changed so that it can only survive at colder temperatures
  - Causes asymptomatic infection in the nose but can’t spread further
- Delivered as a nasal spray for otherwise healthy people 2-49 years
- Less effective than shots for several previous flu seasons and was not recommended for past 2 years, but for 2018-2019 it is once again considered an acceptable option
Influenza vaccines

• Multiple options for different scenarios, patient populations
• Getting ANY vaccine far more important than the specific type!
Influenza vaccination: could it have helped?

- 80% of influenza deaths in children occur in children who were not vaccinated

https://www.cdc.gov/flu/about/disease/us_flu-related_deaths.htm
Influenza vaccines: Is there a better way?

AN INFLUENZA VIRUS

https://www.cdc.gov/flu/images/virus/fluivirus-antigentic-characterization-large.jpg
Universal influenza vaccine: the holy grail

• A flu vaccine that only needs to be given once and protects against all future flu infections

• Based on the idea that there must be some regions of the virus that are conserved across strains
Universal flu vaccine: possible targets

- HA stalk
- Globular HA head (conserved or optimized antigens)
- M2e channel
- Vaccines that stimulate cellular immune responses
Universal influenza vaccine: targets

Plotkin, JPIDS 2018.
Conclusions

• Influenza is a serious public health problem, in all populations
• Yearly epidemics interspersed with rare pandemics – get used to it!
• The best way to protect yourself and loved ones is yearly flu vaccine
• Flu vaccines are safe and effective, even if not as effective as we’d like
For more information

• https://www.cdc.gov/flu/index.htm
Thank you very much!

- Questions?