JEOPARDY FROM INFLUENZA
OR
INFLUENZA JEOPARDY?
2017 – 2018

GERIATRIC GRAND ROUNDS
OCTOBER 5, 2017

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RULES

1. Yell out the answer if you know it... or... Raise your hand politely to be called on!
2. Correct answers will receive prizes (oh boy!)
3. Wrong answers will embarrass you enormously and will never be forgotten
QUESTION #1

On average, how many deaths are there annually in the US attributable to influenza?

INFLUENZA EPIDEMIOLOGY

Average annual Influenza-attributable deaths in US:

36,000 – 48,000

- Good / Bad / Average years
- >90% of deaths in a normal year are in those >65
- Mortality and hospitalizations increase with age
- Increased cardiopulmonary disease and deaths
- This year??? Based on current Southern Hemisphere experience, probably worse than Average
QUESTION #2

What common types of Influenza Viruses are there (in humans), i.e., how are they named?

BONUS: Is it a DNA or RNA Virus?

Double Bonus: What do the H and N stand for?

A and B
1, 2 and 3

Non-Avian Combinations in Humans:
• H1N1
• H2N2
• H3N2

[18 H / 11 N variants in other birds / mammals]
THE INFLUENZA A VIRUS

“H”
(Hemagglutinin)

RNA Strands

“N”
(Neuraminidase)

(8 RNA strands code for 11 proteins; Carry all the information necessary to infect someone)

QUESTION #3

How is influenza spread from person to person?
GETTING INFECTED…

A Cough or Sneeze by an infected person leaves Flu viruses floating on water droplets in the air

The virus is inhaled by the unsuspecting victim…

…where it finds a home in the Oro- or Nasopharynx

QUESTION #4

What are the MAJOR and minor symptoms of Influenza?
Major Symptoms: Sudden onset of:

- HIGH Fever
- Nonproductive Cough

Other common symptoms / clues:
- Muscle aches – often profound
- Sore throat or nasal congestion
- Headache
- Confusion or Delirium
- LTCs: multiple cases in a short period of time

QUESTION #5

Once the virus is inhaled, how does it spread within a given person?
VIRAL REPLICATION

Virai Proteins reassemble and add a shell to form new virions

Respiratory Tract Cell

VIRAL REPLICATION

Neuraminidase opens cell membrane to release new virions

Virions migrate to cell surface

Off to find the next respiratory tract cells to infect!
QUESTION #6

How do Neuraminidase Inhibitors work?

Bonus: What are their names?

Double Bonus: Do they work against A, B or both?

Triple Bonus: How well do they work?

They block the Neuraminidase Enzyme, thus preventing viral release by an infected cell.
**AVAILABLE NEURAMINIDASE INHIBITORS**

- **Oseltamivir (Tamiflu)**
  - Increasing resistance… 10-20%?
- **Zanamivir (Relenza)**
  - Inhaled, No resistance; faster onset
- **Peramivir (Rapivab) [Injectable]**
  - Limited primarily to hospital use

**NEURAMINIDASE INHIBITORS**

- Work against both Flu A & B
- Decrease intensity and duration of symptoms (1-2 days)
QUESTION #7

How expensive is Tamiflu?

Roughly $10 per pill.

So... how much would it cost a facility to prophylax 50 patients for 2 weeks?
QUESTION #8

How long does it take after exposure before the patient becomes symptomatic?

Bonus: When is an ‘infected’ person contagious?

MULTIPLICATION & MIGRATION OF THE VIRUS

Exposure / Initial Infection (Time 0)

Replication: 24 - 48 Hours

Symptoms Begin

48 Hours

Migration to Lungs
People are contagious from about 24 hours before symptoms start until the cough abates*

*So... when can / should facilities accept influenza + patients from the hospital?

QUESTION #9

What is the best way not to suffer the ravages of this disease?
GET VACCINATED!!

Unless you’ve had:
- Documented serious reaction to a previous Vaccine
- Guillain-Barre associated with the vaccine

QUESTION #10

What are the common side effects that occur with the vaccine?
Side Effects

At the injection site...

- Redness
- Soreness
- Swelling

Less common: fever / body aches

Egg allergy is NOT a contraindication and there is a recombinant vaccine made without eggs

My comment to every patient I vaccinate:

It is good to have redness, Soreness, and or swelling at the injection site!

(Signs of a healthy immune system that recognizes the antigen)

QUESTION #11

Can you actually get Influenza from a vaccination?

Bonus:
- If ‘yes’, how common is it?
- If ’no’, why not?
MAKING A VACCINE – STEP 1
INOCULATE EGGS WITH THE VIRUS

MAKING A VACCINE – STEP 2
INCUBATE UNTIL EGG IS FULL OF LIVE VIRUS
MAKING A VACCINE – STEP 3
SEPARATE VIRUS FROM EGG, DISCARD EGG

MAKING A VACCINE – STEP 4
THOROUGHLY KILL VIRUS (CHEMICALLY, MULTIPLE TIMES)
MAKING A VACCINE – STEP 5
CHOP KILLED VIRUS INTO SMALL PIECES

MAKING A VACCINE – STEP 6
DISCARD THE KILLED RNA
(THE PART THAT CAUSES DISEASE)
MAKING A VACCINE – STEP 7
MIX REMAINING “H” & “N” PIECES WITH SALINE TO MAKE THE VACCINE

QUESTION #12

How effective is the standard trivalent vaccine…

… in healthy adults?
… in persons >65 years old?
… in the elderly, NH population?
COMPARING STANDARD-DOSE INFLUENZA VACCINE EFFECTIVENESS AMONG AGE GROUPS$^{1,2}$


QUESTION #13

What vaccines are available? i.e., name the major choices and differentiate between them

Double Bonus!
• Name this year’s candidate viruses…
## MAJOR FLU VACCINES FOR 2017-18

<table>
<thead>
<tr>
<th>Vaccines</th>
<th>Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard Trivalent</strong></td>
<td>[H₃N₂; H₁N₁; B₁]</td>
</tr>
<tr>
<td><strong>Quadrivalent</strong></td>
<td>[H₃N₂; H₁N₁; B₁, B₂]</td>
</tr>
<tr>
<td><strong>High Dose Flu zone (&gt;65)</strong></td>
<td>4 X [H₃N₂; H₁N₁; B₁]</td>
</tr>
<tr>
<td><strong>Adjuvant Vaccine (&gt;65)</strong></td>
<td>[H₃N₂; H₁N₁; B₁] + MF59</td>
</tr>
</tbody>
</table>

RIV3 = Recombinant, egg-free vaccine (18 – 49)  
[H₃N₂; H₁N₁; B₁]

## DOUBLE BONUS ANSWER...

- A/Michigan/45/2015 (H1N1)pdm09-like virus
- A/Hong Kong/4801/2014 (H3N2)-like virus
- B/Brisbane/60/2008-like (B/Victoria lineage) virus
- B/Phuket/3073/2013-like (B/Yamagata lineage) virus
QUESTION #13

In seniors, does Standard vaccination…

• Decrease Influenza mortality?

• Decrease mortality from other causes? (If ‘yes’, which ones?)

• Standard Dose, Trivalent Vaccines do not appear to decrease influenza-specific mortality…

• but…
INFLUENZA VACCINATION LOWERED RISK OF MAJOR CAUSE-SPECIFIC MORTALITY

“Influenza vaccine is strongly associated with a lower mortality risk, not only for pneumonia and COPD, but also for other major cause-specific mortalities, which indicates that influenza vaccination might reduce the domino effects of complications from influenza in the elderly.”


FACTORS IMPACTING VACCINE SUCCESS IN SENIORS

• Age-related decline in humoral & cellular immunity
• Decreased response to vaccines (20-25%)\(^1,\)\(^2\)
• Changes in T-cells and cytokine production impact magnitude, quality & persistence of antibody responses to vaccine

QUESTION #14

Are High Dose and Adjuvant vaccines more effective?

ANTIBODY RESPONSE: FLUZONE HD VS TRIVALENT VACCINE (PHASE III TRIAL)¹,²

Fluzone High-Dose Vaccineᵃ

Superiority of immune responses achieved for A (H1N1) and A (H3N2); non-inferiority for B.

All comparisons, *P* < 0.0001.

Fluzone Trivalent Vaccineᵇ

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ᵃ N = 2576 Fluzone High-Dose vaccine. ᵃ N = 1275 Fluzone vaccine.

**CLINICAL EFFICACY OF HD VAX**

Randomized and blinded trial

- 32,000 participants ≥65 in 126 study sites in US / Canada
- Trial spanned 2 (mild) influenza seasons (2011-12 and 2012-13)
- Participants randomized 1:1 to receive 1 dose of Fluzone High-Dose vaccine or Fluzone vaccine and then followed for illness until the end of each season

Serious adverse events collected for 6 months post-vaccination


**COMORBIDITIES**

- 2/3 had a chronic condition; 1/3 had 2 or more chronic conditions
- The most common comorbid conditions:
  - Diabetes mellitus (23%)
  - CHD (17%)
  - COPD (9%)
  - Asthma (9%)
  - Atrial fibrillation (7%)
  - Valvular heart disease (4.6%)
  - CHF (3%)

- Approximately 74% of both groups received flu vaccine the previous season

RELATIVE & ABSOLUTE EFFICACY FOR PREVENTING LAB-CONFIRMED INFLUENZA

<table>
<thead>
<tr>
<th>High Dose Vaccine [N = 15,990] n (%)</th>
<th>Trivalent Vaccine [N = 15,993] n (%)</th>
<th>Relative Efficacy % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>228 (1.4)</td>
<td>301 (1.9)</td>
<td>24.2 (9.7; 36.5)</td>
</tr>
</tbody>
</table>

Absolute Efficacy: For every 100 persons given HD instead of Trivalent, 17 more persons would be protected from developing influenza

REDUCED HOSPITALIZATIONS

- 823 Facilities / 53,000 patients
- Respiratory-related hospital admissions significantly lower in the facilities (409) that received the High Dose Vaccine (12% RR Reduction)

[www.thelancet.com/respiratory; 7/20/17; http://dx.doi.org/10.1016/S2213-2600(17)30235-7]
ADJUVANT VACCINE

• An oil in water vaccine used in Europe since 1997
• MF59 is an immunologic adjuvant using squalene, an organic compound that is believed to present vaccine better to immune components (eg, CD4 Memory Cells), leading to a better immunologic response
• Randomized study of 171,000 person-seasons of vaccinated seniors evaluated over 3 influenza seasons
• Frail seniors at high risk (eg, older age, smokers, COPD, recent infection or transfusion, CHD, CKD, DM, PVD) had a standing rec to use adjuvant vaccine, so randomization included a disproportionate percentage of higher risk patients in the Adjuvant Vaccine group

ADJUVANT VACCINE

• Despite having the higher risk group, hospitalization or pneumonia was 25% lower in Adjuvant Vaccine group

(Mannino, S, et al. Effectiveness of Adjuvanted Influenza Vaccination in Elderly Subjects in Northern Italy; American Journal of Epidemiology, Vol 176, No 6; 8/31/12)
QUESTION #15

The High Dose vaccines are significantly more expensive, ie, about $42 / dose instead of $11.

Do insurers pay for Flu vaccination? If so, how much?

**Medicare & Medicare Part C pay for vaccinations:**

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Appx Cost</th>
<th>Charge Code</th>
<th>Revenue Code</th>
<th>Reimbursement (per dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trivalent</td>
<td>$11</td>
<td>90656 or 90686</td>
<td>636</td>
<td>$16 - $19</td>
</tr>
<tr>
<td>High Dose</td>
<td>$42</td>
<td>90662</td>
<td>771</td>
<td>$42.72</td>
</tr>
<tr>
<td>Administration Fee</td>
<td>$25.15</td>
<td></td>
<td></td>
<td>$25.15</td>
</tr>
</tbody>
</table>

*Bonus: What is Medicare Part C?*
BILLING COLORADO MEDICAID...

$0

TIME FOR THE QUICK FINISH!
RAPID TESTING

RT-PCR: Gold Standard (vs culture), but slow turnaround (hours as they are typically done in batches in labs)

POINT OF CARE TESTS (by Non-Lab Personnel)
Rapid Immunoassays: Detect viral antigen; simple to do; results in 30-60 minutes
Digital Immunoassays [DIAs]: Digital scan of a test strip to enhance antigen detection
Rapid Nucleic Acid Amplification [NAATs]: Modified RT-PCR to reduce analytic times

RAPID TEST CHARACTERISTICS

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity [A / B] (%)</th>
<th>Specificity [A / B] (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid Immunoassays</td>
<td>54 / 53</td>
<td>&gt;98 / &gt;98</td>
</tr>
<tr>
<td>Digital Immunoassays [DIAs]</td>
<td>80 / 77</td>
<td>&gt;98 / &gt;98</td>
</tr>
<tr>
<td>Rapid Nucleic Acid Amplification [NAATs]</td>
<td>92 / 95</td>
<td>&gt;98 / &gt;98</td>
</tr>
</tbody>
</table>

RAPID TESTING

- Effective 12/18, tests detecting influenza antigens need to have a sensitivity of >80% vs an RT-PCR comparator
- Frequent problems collecting specimen
- Begin Treatment based on Clinical Suspicion during Flu Season with Outbreaks
- Only need to test index cases
- One Positive during endemic flu = Outbreak

MISCELLANEOUS...

Antivirals
- Only work if started <48 hours from start of symptoms
- When in doubt, start treatment – STAT – based on clinical judgment
- Cohort sick patients in LTCFs when possible
- Open the doors and windows on nice days!
- Don’t start antibiotics unless you document a real secondary pneumonia!
- Cough / lethargy can last 2 – 3 weeks depending on frailty
- Prolonged cough is often due to secondary Reactive Airways triggered by influenza
DEEP BREATH…

• Manufacturers are not making as much trivalent
• Vaccinate now! Looks like it could be an early year…

UNANSWERED QUESTIONS

Should I prophylax facilities with outbreaks?
When will the next Pandemic be and which Flu type will it be?
What can I do to protect myself and others from Avian Flu?
Why does the Influenza virus mutate every couple of years?
How common is Guillan-Barre with / without vaccination?
YOUR UNANSWERED QUESTIONS?