The Future of Pandemic Mitigation

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Research Focus of the Schultz-Cherry Lab

Pathogenesis of RNA viruses especially in high risk populations

- Epithelial Responses
- Viral Evolution
- Immune Response/treatments/tools
- Virome/microbiome
- Influenza surveillance at the AHI

Influenza (Enteric Viruses) Viral enterotoxin

Astrovirus
Severe flu in California brings medicine shortages, kills 27

California flu season could be the worst in decades, numbers show

Severe flu brings medicine shortages, packed ERs and a rising death toll in California

Los Angeles Times
With 12 days of 'Man Flu' my truelove yelled to me...

1. I feel really poorly...
2. Do you think I'm dying?
3. I need a doctor...
4. Pass me the tissues...
5. I NEED MY BED...
6. Make me a hot toilet...
7. Where's the remote...
8. Are you sure I'm not dying?
9. Will you run me a hot bath?
10. Where's the Menthol Crystal?
11. Go to the chemist...
12. Men get 'Flu' worse than 'Women'

Of course it didn't last 12 days. It just felt like it did...
Phylogenetic comparison of influenza A(H3N2) HA genes

HA2 numbering

@ proposed serology antigens

Vaccine viruses
Reference viruses

Collection date
Sep-Oct 2014
Nov 2014
Dec 2014
Jan 2015

F159Y
K160T (+CHO @ 158)

N145S
N144S (-CHO)

Q311H
"The Problem Child of Seasonal Flu": Beware This Winter’s Virus

H3N2 is deadlier than many other influenza strains

Helen Branswell, STAT on January 9, 2018 Scientific American
1918 Pandemic

Op-Ed Contributors
We’re Not Ready for a Flu Pandemic
By MICHAEL T. OSTERHOLM and MARK OLSHAKER JAN. 8, 2018
New York Times
Knowing what to do...

...when we don’t know what to do!
Speaker 3: Stacey Schultz-Cherry, Ph.D., – working “The Future of Pandemic Mitigation” (30 min)

- The future of pandemic preparedness with regards to clinical advancements and current efforts to improve vaccines, antivirals, etc.
- Describe gaps in clinical care that are of concern should a virus like the 1918 virus appear.
- How public health surveillance and efforts can align with and help with clinical care improvements.
Watching and Waiting

- SARI
- ILI
- Office visits
- APHL
- CDC

National Influenza Centre
WHO Collaborating Centre for Reference and Research on Influenza
WHO Collaborating Centre for the Surveillance, Epidemiology and Control of Influenza
WHO Collaborating Centre for Studies on the Ecology of Influenza in Animals
WHO Essential Regulatory Laboratory
WHO H5 Reference Laboratory

flufighter®
NIAID Centers of Excellence for Influenza Research and Surveillance (CEIRS)

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University
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PI – Walter Orenstein
Emory University
Atlanta, GA

Co-PI – Dick Compans

Updated 3/2014

flu
defense

®
Virus Characterization Pipeline

Risk to humans
- H5, H7, H2
- Antigenically novel H1 or H3

Risk to specific group
- Poultry – H5, H7 and spill over events
- Swine – novel virus

- Molecular determinants of virulence (full genome)
- Receptor binding specificity
- Growth in primary human (swine) respiratory cells
- Antiviral susceptibility
- Pathogenesis in mice, chickens, swine, ferrets
- Transmission in ferrets
- Population-wide immunity

Algorithm to predict risk
(CDC IRAT; WHO TIPRA)
Assessing a Novel Virus in a Time of Limited Resources - Prioritizing Vaccine Distribution

- limited resources
- graded response

- Vaccine production
- Safety/dosing studies
- dx kits and FDA approval
- HG vaccine candidate and potency testing reagents

Additional studies needed

Negligible
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Study predicts 2018 flu vaccine will have 20 percent efficacy
... for the first time since 2015—will likely have the same reduced efficacy against the dominant circulating strain of influenza A as the vaccine given in ...

Medical Xpress

Experts Concerned About Effectiveness Of This Year’s Flu Vaccine
(CNN) — Last year’s seasonal flu vaccine effectiveness was just 42%, the ...
CBS Boston / WBZ

Flu vaccine, even when just 20% effective, saves tens of thousands of lives
Parents of young children have reason to be watchful as flu season ends In ...

Q13 Fox News
A universal flu vaccine should

- Be at least 75% effective
- Protect against group I and II influenza A viruses
- Have durable protection that lasts at least 1 year
- Be suitable for all age groups

Protection? Resistance?

Hemagglutinin

Typical neutralizing antibodies

Antibody to “Achilles' heel” portion of protein

Variable
Conserved

Flu Virus

Hemagglutinin Neuraminidase

Hemagglutinin graphic from ConsSurf.

Flu virus graphic from BBC.

On the left is an enlarged view of a hemagglutinin, illustrating antibodies attaching to both the highly variable “head” and conserved “stalk” regions. On the right is the flu virus with hemagglutinin in blue and neuraminidase in red.
Immune correlates of protection
Assays!
Duration
Immune history
Animal models vs human challenge
Immunogenicity vs risk adverse
For Dr. Schultz-Cherry:

• In light of the $12 million boost in funds from the Gates Foundation Grand Challenge to speed the development of a universal flu vaccine, how soon can we expect a universal influenza vaccine… Improved Vaccine YES!! Will take time. Expedited pipeline?

• and do we expect such a vaccine to protect the population from novel/avian influenza viruses and potential pandemics? Why or why not? People will certainly promise that but we won’t know until the pandemic emerges

• How many groups are working on a universal flu vaccine now; with the $12M, how many more will join in? Predictions of success? EVERYONE!!! Especially those HIV vaccine people

Can We Make A Better Vaccine?

Herd Immunity

10% of the population is immune

50% of the population is immune

90% of the population is immune

Figure 7.6 Microbiology: A Clinical Approach (© Garland Science)

Herd Immunity
Depends on 3 factors

Duration (D)
length of infectious period

Infectivity (I)
Measure of transmissability

Number of susceptibles (S)
in the population

Triple product = sID
A threshold sID exists for each potential epidemic situation, below which an epidemic is unlikely.
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How many antivirals did the FDA approve between Jan 1987 and Dec 2017?

1. HIV (43)
2. HCV (17)
3. CMV/HSV (11)
4. HBV (8)

Favipiravir (T-705) Japan
Baloxavir marboxil and pimodivir (Pol inhibitors) – Phase 3

<table>
<thead>
<tr>
<th>Year</th>
<th>Antiviral Name</th>
<th>Type</th>
<th>Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993</td>
<td>Flumadine</td>
<td>Rimantadine (RIM)</td>
<td>Small Molecule Mono</td>
</tr>
<tr>
<td>1999</td>
<td>Relenza</td>
<td>Zanamivir (ZAN)</td>
<td>Small Molecule Mono</td>
</tr>
<tr>
<td>1999</td>
<td>Tamiflu</td>
<td>Oseltamivir (OSE)</td>
<td>Small Molecule Mono</td>
</tr>
<tr>
<td>2014</td>
<td>Rapivab</td>
<td>Peramivir (PER)</td>
<td>Small Molecule Mono</td>
</tr>
</tbody>
</table>

Chaudhuri et al Antiviral Res 2018

Flu = 4
<table>
<thead>
<tr>
<th>Molecule</th>
<th>Biological activity</th>
<th>Viral target</th>
<th>Status</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>M2W332, benzyl-substituted amantadine derivatives</td>
<td>M2 blockers</td>
<td>A/M2 ion channel (S31N mutant)</td>
<td>Preclinical</td>
<td>[15, 16]</td>
</tr>
<tr>
<td>Remanamide 9, Spiramine 8</td>
<td>M2 blockers</td>
<td>A/M2 ion channel (wt, L26F and V27A mutants)</td>
<td>Preclinical</td>
<td>[18, 19]</td>
</tr>
<tr>
<td>Organosilane-based compounds</td>
<td>M2 blockers</td>
<td>A/M2 ion channel (wt and V27A mutant)</td>
<td>Preclinical</td>
<td>[20]</td>
</tr>
<tr>
<td>M2-7A Antibody</td>
<td>M2 blocker</td>
<td>M2 ion channel</td>
<td>Preclinical</td>
<td>[21]</td>
</tr>
<tr>
<td>Peramivir</td>
<td>Static acid analogue</td>
<td>Neuraminidase</td>
<td>Approved (Japan and Korea); FDA approval requested (USA)</td>
<td>[30]</td>
</tr>
<tr>
<td>Laninamivir</td>
<td>Static acid analogue</td>
<td>Neuraminidase</td>
<td>Approved (Japan); phase II clinical trials (USA)</td>
<td>[32]</td>
</tr>
<tr>
<td>Multimeric neuraminidase inhibitors</td>
<td>Multivalent static acid analogues</td>
<td>Neuraminidase</td>
<td>Preclinical</td>
<td>[38–49]</td>
</tr>
<tr>
<td>CH68 (neutralizing antibody)</td>
<td>Neutralizing activity against IAV H1N1 strains</td>
<td>Globular head domain of hemagglutinin</td>
<td>Preclinical</td>
<td>[45]</td>
</tr>
<tr>
<td>S13/91 and C05 (neutralizing antibodies)</td>
<td>Neutralizing activity against different IAV subtypes</td>
<td>Globular head domain of hemagglutinin</td>
<td>Preclinical</td>
<td>[46, 47]</td>
</tr>
<tr>
<td>Polyvalent synthetic static acid-containing inhibitors</td>
<td>Competitive inhibitors of the virus attachment</td>
<td>Hemagglutinin</td>
<td>Preclinical</td>
<td>[49–52]</td>
</tr>
<tr>
<td>Natural inhibitors containing static acid (e.g., serum amyloid P component)</td>
<td>Competitive inhibitors of the virus attachment</td>
<td>Hemagglutinin</td>
<td>Preclinical</td>
<td>[53]</td>
</tr>
<tr>
<td>Peptides against hemagglutinin (e.g., EB peptide, FluPep)</td>
<td>Inhibitors of virus attachment</td>
<td>Hemagglutinin</td>
<td>Preclinical</td>
<td>[54, 55]</td>
</tr>
<tr>
<td>Carbohydrate-binding agents (e.g., Cyanovirin-N, BCA)</td>
<td>Inhibitors of virus attachment</td>
<td>Specific glycosylation sites on hemagglutinin</td>
<td>Preclinical</td>
<td>[56, 60]</td>
</tr>
<tr>
<td>TB1/4, BMY-7709, 180299, Steckyllin, Thiobenzamide compounds, R05046466</td>
<td>Blockers of the low pH-induced conformational change of HA</td>
<td>Stem region of hemagglutinin</td>
<td>Preclinical</td>
<td>[64, 66–70]</td>
</tr>
<tr>
<td>C22</td>
<td>Inducer of the premature conformational change of HA</td>
<td>Stem region of hemagglutinin</td>
<td>Preclinical</td>
<td>[65]</td>
</tr>
<tr>
<td>Arbidol</td>
<td>Blocker of the low pH-induced conformational change of HA</td>
<td>Phospholipid membrane and protein motifs of HA enriched in aromatic residues</td>
<td>Approved (Russia and China)</td>
<td>[74]</td>
</tr>
<tr>
<td>Fl69, CR6261, CR8020, A06 and F10 (broadly neutralizing antibodies)</td>
<td>Inhibitors of fusogenic activity of IAV HA</td>
<td>Stem region of hemagglutinin</td>
<td>Preclinical</td>
<td>[75, 77–80]</td>
</tr>
<tr>
<td>CR8033 and CR8071 (neutralizing antibodies)</td>
<td>Inhibitors of fusogenic activity of IBV HA</td>
<td>Stem region of hemagglutinin</td>
<td>Preclinical</td>
<td>[76]</td>
</tr>
<tr>
<td>CR9114 (broadly neutralizing antibody)</td>
<td>Inhibitor of fusogenic activity of IAV and IBV HA</td>
<td>Stem region of hemagglutinin</td>
<td>Preclinical</td>
<td>[76]</td>
</tr>
</tbody>
</table>

**Cocktail Therapy**

GET YOUR DAILY DOSE...

**Diagram:**

- **ICPO**
  - INTRINSIC IMMUNITY
  - INFLAMMATORY IMMUNITY
  - INF/IN RESPONSE
  - TLR SIGNALING
  - NF-kB SIGNALING
  - CHROMATINIZATION
  - DNA damage response
  - Viral replication
  - Viral genome silencing
  - Viral transcription

**References:**

[15, 16], [18, 19], [20], [21], [30], [32], [38–49], [45], [46, 47], [49–52], [53], [54, 55], [56, 60], [64, 66–70], [65], [74], [75, 77–80], [76], [76]
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- Describe gaps in clinical care that are of concern should a virus like the 1918 virus appear.
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“But Timmy, you have to eat your antibiotics or you’ll never become a big strong bacteria.”
thinking Dogma
Science communication

scientists

the public
Decrease in Percentage say Vaccines ‘Very Important’ to Health of Society

Thinking about the common vaccines available today such as polio, tetanus, measles, and flu, how important do you believe vaccines are to the health of our society today?

May 2018: 70% Very important, 22% Somewhat important
Nov. 2008: 80% Very important, 17% Somewhat important

Source: ResearchAmerica surveys of U.S. adults conducted in partnership with Zogby Analytics in May 2018 and with Charlton Research Company in November 2008.

Decrease in Percentage say ‘Somewhat Confident’ in Adequate Supply of Vaccines

How confident are you that our current system ensures an adequate supply of necessary vaccines to prevent shortages?

May 2018: 20% Very confident, 47% Somewhat confident, 22% Not too confident, 11% Not at all confident, 0% Don’t know/Refused
Nov. 2008: 21% Very confident, 57% Somewhat confident, 15% Not too confident, 7% Not at all confident, 0% Don’t know/Refused

Source: ResearchAmerica surveys of U.S. adults conducted in partnership with Zogby Analytics in May 2018 and with Charlton Research Company in November 2008.

Decrease in Percentage say ‘Somewhat Confident’ in System to Evaluate Vaccines

How confident are you in our current system in the U.S. for evaluating the safety of vaccines and recommendations for when they should be given?

May 2018: 32% Very confident, 45% Somewhat confident, 12% Not too confident, 9% Not at all confident, 0% Don’t know/Refused
Nov. 2008: 32% Very confident, 53% Somewhat confident, 9% Not too confident, 6% Not at all confident, 0% Don’t know/Refused

Source: ResearchAmerica surveys of U.S. adults conducted in partnership with Zogby Analytics in May 2018 and with Charlton Research Company in November 2008.
Decrease in Percentage say ‘Strongly, Yes’ to Personally Benefiting From Vaccines

Do you believe that you have personally benefited from the development of vaccines over the last 50 years?

<table>
<thead>
<tr>
<th></th>
<th>May 2018</th>
<th>Nov. 2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strongly, Yes</td>
<td>59%</td>
<td>75%</td>
</tr>
<tr>
<td>Somewhat, Yes</td>
<td>28%</td>
<td>15%</td>
</tr>
<tr>
<td>Somewhat, No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strongly, No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Don't know/Refused</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Research America survey of U.S. adults conducted in partnership with Zogby Analytics in May 2018 and with Charlton Research Company in November 2008.

Decrease in Percentage say ‘Very Important’ to Vaccinate Children

How important do you believe it is for parents to have their children vaccinated?

<table>
<thead>
<tr>
<th></th>
<th>May 2018</th>
<th>Nov. 2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Important</td>
<td>71%</td>
<td>82%</td>
</tr>
<tr>
<td>Somewhat Important</td>
<td>19%</td>
<td>14%</td>
</tr>
<tr>
<td>Not too Important</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not at all Important</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Don't know/Refused</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Research America survey of U.S. adults conducted in partnership with Zogby Analytics in May 2018 and with Charlton Research Company in November 2008.
More than Half Did Not Get Flu Vaccine Last Season

Lack of Trust is Main Reason for Not Getting Flu Vaccine

Chair ASM’s Public and Scientific Affairs Board (PSAB) Biomedical Research

Source: A ResearchAmerica survey of U.S. adults conducted in partnership with Zogby Analytics in May 2018.
Briefing on New Vaccine Data and Highlights from Smithsonian's "Outbreak"

by American Society for Microbiology

DATE AND TIME
Mon, May 21, 2018
10:00 AM – 11:30 AM EDT

The American Society for Microbiology and Research!America, in collaboration with the American Society for Virology cordially invite you to celebrate the opening of "Outbreak: Epidemics in a Connected World." This Smithsonian exhibit marks the 100th anniversary of the Great Influenza pandemic.