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Vaccines: Reaching for higher branches after the low hanging fruit has been picked

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Vaccines: Reaching for Higher Branches after the Low Hanging Fruit has been Picked

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National Institute of Allergy and Infectious Diseases
National Institutes of Health
June 12, 2016
PRE-VACCINE ERA
ESTIMATED ANNUAL MORBIDITY IN THE U.S.

% DECREASE

<table>
<thead>
<tr>
<th>Disease</th>
<th>% Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria</td>
<td>100%</td>
</tr>
<tr>
<td>H. Influenza</td>
<td>99%</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>91%</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>83%</td>
</tr>
<tr>
<td>Measles</td>
<td>99%</td>
</tr>
<tr>
<td>Mumps</td>
<td>99%</td>
</tr>
<tr>
<td>Pertussis</td>
<td>89%</td>
</tr>
<tr>
<td>Pneumococcal Disease</td>
<td>74%</td>
</tr>
<tr>
<td>Polio</td>
<td>100%</td>
</tr>
<tr>
<td>Rubella</td>
<td>99%</td>
</tr>
<tr>
<td>Congenital Rubella</td>
<td>99%</td>
</tr>
<tr>
<td>Smallpox</td>
<td>100%</td>
</tr>
<tr>
<td>Tetanus</td>
<td>99%</td>
</tr>
<tr>
<td>Varicella</td>
<td>89%</td>
</tr>
</tbody>
</table>

MOST RECENT REPORTS OF CASES IN THE U.S.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria</td>
<td>0</td>
</tr>
<tr>
<td>H. Influenza</td>
<td>343</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>11,049</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>11,269</td>
</tr>
<tr>
<td>Measles</td>
<td>41</td>
</tr>
<tr>
<td>Mumps</td>
<td>982</td>
</tr>
<tr>
<td>Pertussis</td>
<td>21,291</td>
</tr>
<tr>
<td>Pneumococcal Disease</td>
<td>4,167</td>
</tr>
<tr>
<td>Polio</td>
<td>0</td>
</tr>
<tr>
<td>Rubella</td>
<td>4</td>
</tr>
<tr>
<td>Congenital Rubella</td>
<td>1</td>
</tr>
<tr>
<td>Smallpox</td>
<td>0</td>
</tr>
<tr>
<td>Tetanus</td>
<td>8</td>
</tr>
<tr>
<td>Varicella</td>
<td>607,363</td>
</tr>
</tbody>
</table>

Information courtesy of the CDC January 2019

Courtesy Leon Farrant, graphic designer
Table 1. Americans Agreeing With Various Medical Conspiracy Theories, 2013\(^a\)

<table>
<thead>
<tr>
<th>Medical Conspiracy Narrative</th>
<th>Respondents, %(^b) (N = 1351)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Food and Drug Administration is deliberately preventing the public from getting natural cures for cancer and other diseases because of pressure from drug companies.</td>
<td>Heard Before</td>
</tr>
<tr>
<td></td>
<td>63</td>
</tr>
<tr>
<td>Health officials know that cell phones cause cancer but are doing nothing to stop it because large corporations won’t let them.</td>
<td>57</td>
</tr>
<tr>
<td>The CIA deliberately infected large numbers of African Americans with HIV under the guise of a hepatitis inoculation program.</td>
<td>32</td>
</tr>
<tr>
<td>The global dissemination of genetically modified foods by Monsanto Inc is part of a secret program, called Agenda 21, launched by the Rockefeller and Ford foundations to shrink the world’s population.</td>
<td>19</td>
</tr>
<tr>
<td>Doctors and the government still want to vaccinate children even though they know these vaccines cause autism and other psychological disorders.</td>
<td>69</td>
</tr>
<tr>
<td>Public water fluoridation is really just a secret way for chemical companies to dump the dangerous byproducts of phosphate mines into the environment.</td>
<td>25</td>
</tr>
</tbody>
</table>

Abbreviations: CIA, Central Intelligence Agency; HIV, human immunodeficiency virus.

\(^a\) Percentages may not total 100% because of rounding.
Vaccine Attitudes, Concerns, and Information Sources Reported by Parents of Young Children: Results from the 2009 HealthStyles Survey


93.4% Reported children receiving vaccine

79.8% Believed vaccines important to child health

79.0% Confident about vaccine safety
Effective Messages in Vaccine Promotion: A Randomized Trial


Tested 4 interventions:
- Lack of evidence for autism link
- Disease dangers
- Disease images
- Dramatic narrative

“decreased intent to vaccinate among parents who had the least favorable vaccine attitudes”
CALCULATING RISKS
Some vaccines have risks that are common but mild. A few have more serious risks, but these are very rare.

1. **COMMON: MORE THAN 1 IN 100 DOSES**
   - Redness, swelling or soreness at the site of an injection are common for many vaccines, as are mild fevers. Nausea, vomiting and diarrhoea have been reported for a few.

2. **LESS COMMON: 1 IN 100 TO 1 IN 100,000**
   - High fevers can occur in this range, as can fever-induced convulsions from vaccines such as that for measles, mumps and rubella (1 in 3,000 doses).

3. **RARE: 1 IN 100,000 TO 1 IN 1 MILLION**
   - Preliminary data suggest that current rotavirus vaccines are associated with intussusception, an infolding of the bowel, in about 1 in 100,000 first doses, but the overall risk is unclear. Severe allergic reactions to some vaccines are generally less common than this, in the order of 1 in 1 million.

4. **INCONCLUSIVE: NOT ENOUGH DATA**
   - Guillain-Barré syndrome, a paralytic disorder, has been associated with some seasonal influenza vaccines, but a causal link has not been firmly established. Serious disorders have been reported after other vaccinations, but many are so rare that determining causality is difficult.

From Nature 473:436 (2011)
21st Century Prophylaxis

• Vaccine

• Manufacturing

• Vaccination

• Host Response

• Preparedness
Vaccine Directions

• Antigen discovery and selection (including *in silico*)

• Common epitope approaches (universal vaccines)

• Targeting organisms for which drug resistance is emerging

• Novel vaccine concepts to address chronic infectious diseases

• Passive vaccination approaches
Manufacturing Directions

• Unique and diverse expression systems (beyond an egg and free living organisms)
  – Bacteria
  – Eukaryotic cells
  – Baculo- / insect lines
  – Plants
  – Synthetic / Cell free translation
• Disposable, large scale platforms
• Synthetic generation of agent
Vaccination Directions

• Adjuvants
  – Reduce number of doses
  – Reduce antigen load
  – Fine tune immune response

• Stabilization
  – Eliminate refrigeration requirement
  – Enhance shelf life
  – Enable novel packaging and devices

• Alternative delivery devices
  – Reduce trained health care worker need
  – Increase compliance
  – Improve throughput
Host Response Directions

• Murine immune system is at best a very crude model of human immunity (concomitantly, murine pathogenesis is an even cruder approximation of human disease)
• Animal models are focusing on identification of correlates and even true immunological surrogates
• Immunity is more than neutralizing antisera
• Improved assessment tools for human immune status and responses
Ancillary Issues

• Discovery, characterization, and validation of biomarkers for immune status

• Clinical endpoints

• Robust, reproducible cellular assays

• *In vitro / ex vivo* predictive systems

• Utilization of “correlates” versus “a correlate”
Global Examples of Emerging and Re-Emerging Infectious Diseases

- Vancomycin-resistant Staphylococcus aureus
- Cryptosporidiosis
- Cyclosporiasis
- E. coli O157:H7
- Human monkeypox
- Anthrax, bioterrorism
- Whitewater arroyo virus
- Hantavirus pulmonary syndrome
- Dengue
- Yellow fever
- Cholera
- Marburg hemorrhagic fever
- Ebola hemorrhagic fever
- Rift Valley fever
- HIV
- SARS
- Diphtheria
- Typhoid fever
- West Nile virus
- Lassa fever
- Human monkeypox
- Nipah virus
- Hendra virus
- Enterovirus 71
- Plague
- Human monkeypox

Legend:
- ○ Newly emerging
- ● Re-emerging/resurging
- ● “Deliberately emerging”
Global Examples of Emerging and Re-Emerging Infectious Diseases

- Antimicrobial-resistant threats
  - CRE
  - MRSA
  - C. difficile
  - N. gonorrhoeae
- H3N2v influenza
- Cyclosporiasis
- E. coli O157:H7
- Measles
- Human monkeypox
- Listeriosis
- Bourbon virus
- 2009 H1N1 influenza
- Adenovirus 14
- Anthrax bioterrorism
- Chikungunya
- Hantavirus pulmonary syndrome
- Dengue
- Zika virus
- Yellow fever
- Human African trypanosomiasis
- Enterovirus D68
- West Nile virus
- Cryptosporidiosis
- E. coli O104:H4
- Drug-resistant malaria
- Ebola virus disease
- Hepatitis C
- Lyme disease
- vCJD
- Lassa fever
- HIV
- Marburg hemorrhagic fever
- MDR/XDR tuberculosis
- Plague
- Ebola virus disease
- Human monkeypox
- Hendra virus
- Nipah virus
- SFTSV bunyavirus
- E. coli O157:H7
- SARS
- MERS-CoV
- Rift Valley fever
- Typhoid fever
- H10N8 influenza
- H7N9 influenza
- H5N1 influenza
- Akhmeta virus

- Newly emerging
- Re-emerging/resurging
- “Deliberately emerging”

October 2015
Global Trends in Emerging Infectious Diseases
KE Jones, Peter Daszak, et al.

“In the global human population, we report the emergence of 335 infectious diseases between 1940 and 2004.”
SARS: A New Challenge to Global Health
A Reporter at Large

NATURE’S BIOTERRORIST

Is there any way to prevent a deadly avian-flu pandemic?

By Michael Specter
World's Swine Flu Concerns Escalate

As the World Health Organization raised its alert level to phase 4, indicating a significantly increased risk of pandemic, global markets tumbled for a second day. . .
Isolation of a Novel Coronavirus from a Man with Pneumonia in Saudi Arabia

AM Zaki, RAM Fouchier, et al.
Selected efforts underway:

- Characterize virus
- Improve diagnostic specificity
- Test antivirals
- Develop animal models
- Natural history studies
- Evaluate the Zika & dengue interface
- Develop vaccine
Preparedness

• Emerging infectious diseases present unique challenges

• Surveillance systems are crude and limited

• Conduct of research is difficult even under optimal conditions

• Existing regulatory frameworks are not optimal for outbreaks
What do we need to prepare for?
(with apologies to Donald Rumsfeld)

• Expected knowns
  – Pandemic Influenza
• Unexpected knowns
  – Ebola (or any filovirus)
• Unknown knowns
  – Zika
• Unknown unknowns
  – ???
Expected knowns (flu)

• History suggests this can and will occur
• Experience with similar vaccines allows for straightforward (although not necessarily simple or easy) vaccine development in a timeline that can potentially align with the outbreak
• Existing infrastructure can be co-opted for development
• Safety will always be an issue
  – Dose and regimen
  – Special populations
Unexpected knowns (Ebola)

• Even with extensive microbiological and pathogenesis information, socioeconomic / cultural factors can dramatically impact disease transmission and severity
• New clinical experience may alter prevention & treatment
• Exogenous factors such as climate change, urban versus rural population centers, greater local and distant mobility, varying degrees of public health infrastructure, etc.
• Variable degrees of development efforts will need increased resources and streamlining
Unknown knowns (Zika)

• Extremely difficult to be prepared, mostly due to a long list of agents that have been identified with higher priority
• Need to rely on expert panels to identify candidate lists (pandemic / epidemic wanna-be’s)
• Likely need to be already working on vaccine candidates to impact future outbreaks
• Pandemic / epidemic potential may evolve to endemic
• Resource limitations major impediment
For Consideration

• WHO Workshop on Prioritization of Pathogens (12/8-9/2015)
  – Urgent
    • Crimean-Congo hemorrhagic fever
    • Filoviruses (EVD & Marburg)
    • Highly pathogenic emerging Coronaviruses (MERS Co-V & SARS)
    • Lassa Fever
    • Nipah
    • Rift Valley Fever
  – Serious
    • Chikungunya
    • Severe Fever with Thrombocytopenia Syndrome
    • Zika
So what’s an unknown unknown?

- Basically, something we’ve never seen before
- Little precedence with known infectious agents
- No information regarding natural immunity
- Sparse human pathogenesis
- Limited information from animal models
- Initially, mostly sequence information

- How can we be prepared?
Preparedness 101: Zombie Apocalypse

Posted on May 16, 2011 by Ali S. Khan

Walking Dead fans, check out our latest post: [http://go.usa.gov/Q4J](http://go.usa.gov/Q4J)

There are all kinds of emergencies out there that we can prepare for. Take a zombie apocalypse for example. That's right, I said z-o-m-b-i-e a-p-o-c-a-l-y-p-s-e. You may laugh now, but when it happens you'll be happy you read this, and hey, maybe you'll even learn a thing or two about how to prepare for a real emergency.

A Brief History of Zombies

We've all seen at least one movie about flesh-eating zombies taking over (my personal favorite is [Resident Evil](http://www.imdb.com/title/tt0120804/)), but where do zombies come from and why do they love eating brains so much? The word zombie comes from Haitian and New Orleans voodoo origins. Although its meaning has changed slightly over the years, it refers to a human corpse mysteriously reanimated to serve the undead. Through ancient voodoo and folk-lore traditions, shows like the Walking Dead were born.
Zombie Threat Summary

- **Pathogenic zombies (PZ)**
  - PZs are zombie life forms created after an organism is infected by a virus or bacteria or some other form of contagion
- **Radiation zombies**
- **Evil Magic zombies**
- **Space zombies**
- **Weaponized zombies**
- **Symbiant-Induced zombies**
- **Vegetarian zombies**
- **Chicken zombies**
ZOMBIE APOCALYPSE

WHAT YOU THINK IT LOOKS LIKE:

WHAT IT ACTUALLY LOOKS LIKE:
Moving Faster

- Initiate early development on experts’ derived lists
- Don’t wait for specimens; work from sequences
- Platform selection for ease of candidate selection & manufacturing
  - Several vaccine manufacturers are offering proposals
- Move towards universal / broadly protective responses

- Rate limiting issues:
  - Sequence breadth
  - Animal models
  - Assay development
  - Clinical trial capacity in theater
Possible additional considerations

- Broad spectrum antivirals
- Passive vaccination / prophylaxis
Questions?