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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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June 12, 2016

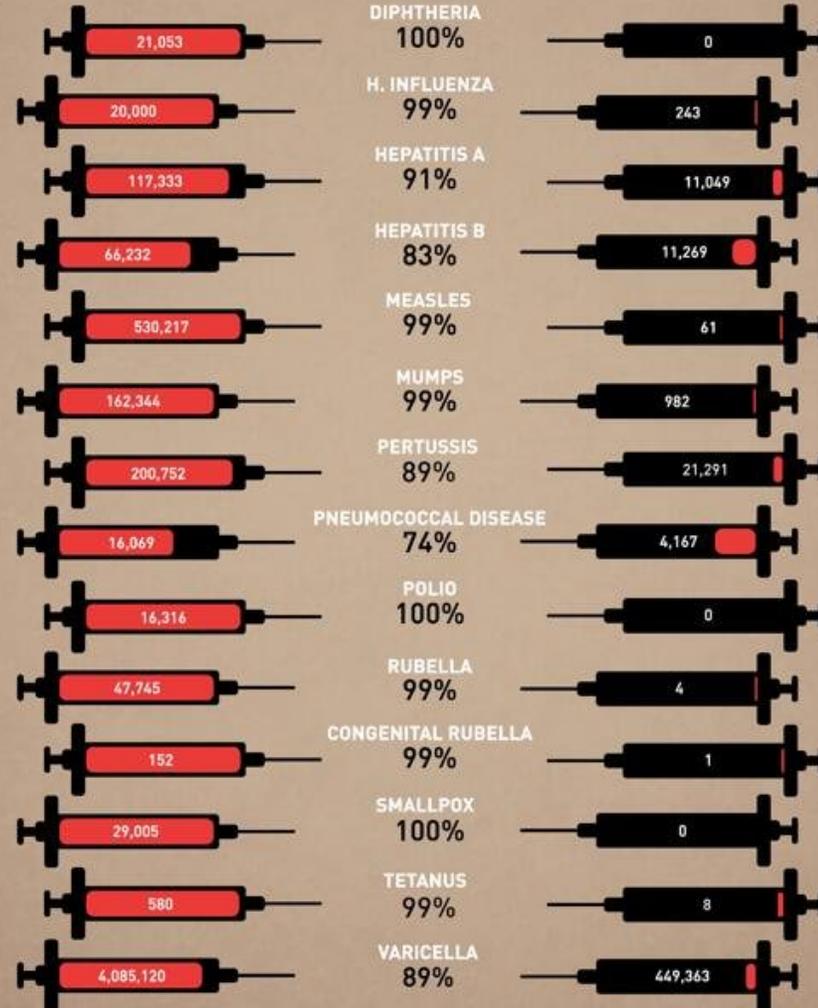


PRE-VACCINE ERA
ESTIMATED ANNUAL
MORBIDITY IN THE U.S.

%

MOST RECENT
REPORTS OF
CASES IN THE U.S.

DECREASE



INFORMATION COURTESY OF THE CDC JANUARY 2011

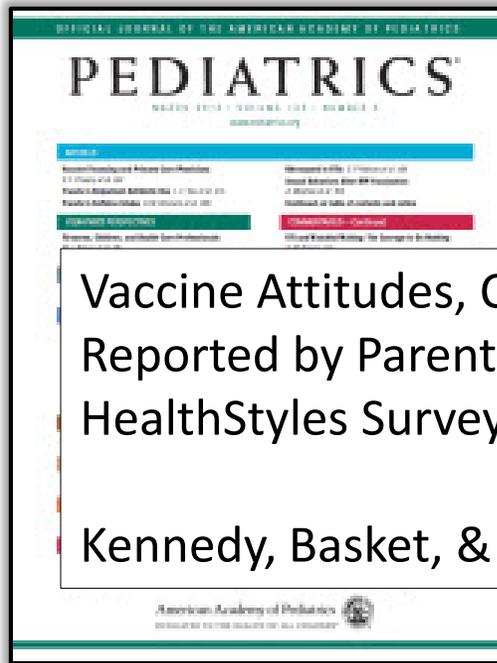
Courtesy Leon
Farrant, graphic
designer

Table 1. Americans Agreeing With Various Medical Conspiracy Theories, 2013^a

Medical Conspiracy Narrative	Respondents, % ^b (N = 1351)			
	Heard Before	Agree	Neither Agree nor Disagree	Disagree
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.	63	37	31	32
Health officials know that cell phones cause cancer but are doing nothing to stop it because large corporations won't let them.	57	20	40	40
The CIA deliberately infected large numbers of African Americans with HIV under the guise of a hepatitis inoculation program.	32	12	37	51
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.	19	12	46	42
Doctors and the government still want to vaccinate children even though they know these vaccines cause autism and other psychological disorders.	69	20	36	44
Public water fluoridation is really just a secret way for chemical companies to dump the dangerous byproducts of phosphate mines into the environment.	25	12	41	46

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

^a Percentages may not total 100% because of rounding.



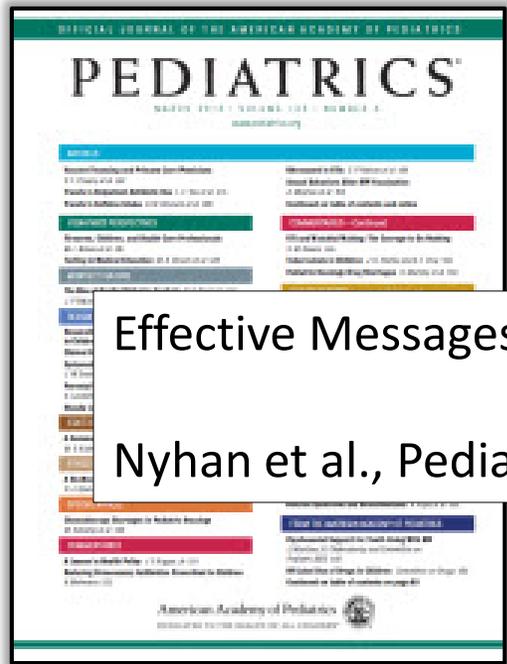
Vaccine Attitudes, Concerns, and Information Sources Reported by Parents of Young Children: Results from the 2009 HealthStyles Survey

Kennedy, Basket, & Sheedy. Pediatrics 127(S1): S92-99 (2011)

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

Nyhan et al., Pediatrics 133(4): 1-8 (2014)

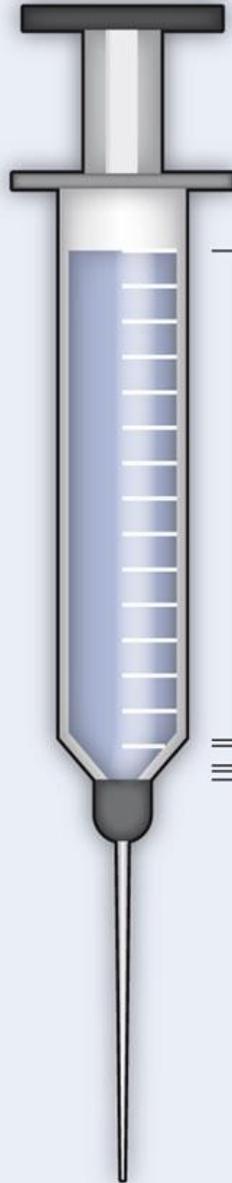
Tested 4 interventions:

- 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

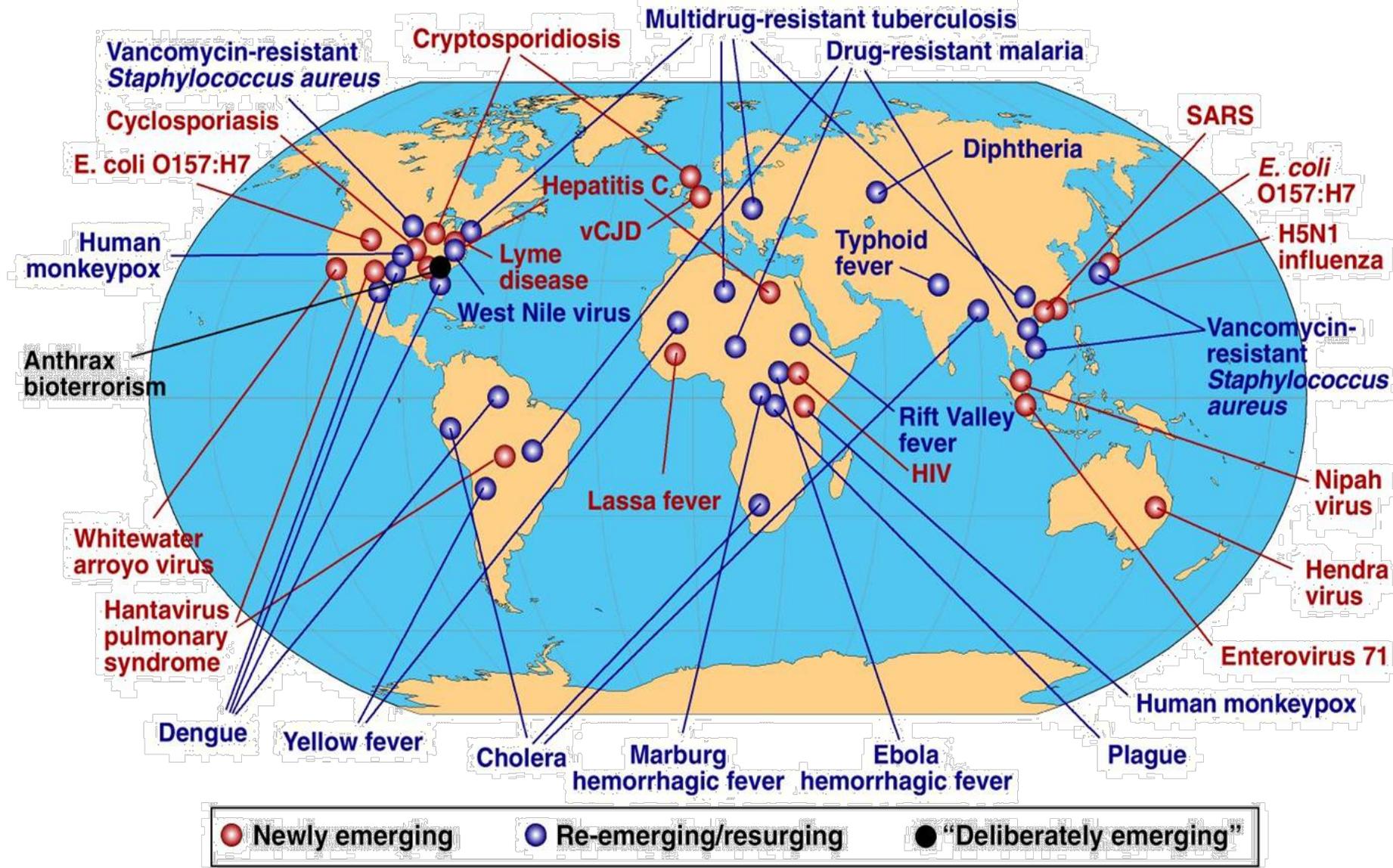
Host Response Directions

- 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



21 February 2008

International weekly journal of science

nature

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



PRICE \$3.95

FEB. 28, 2005

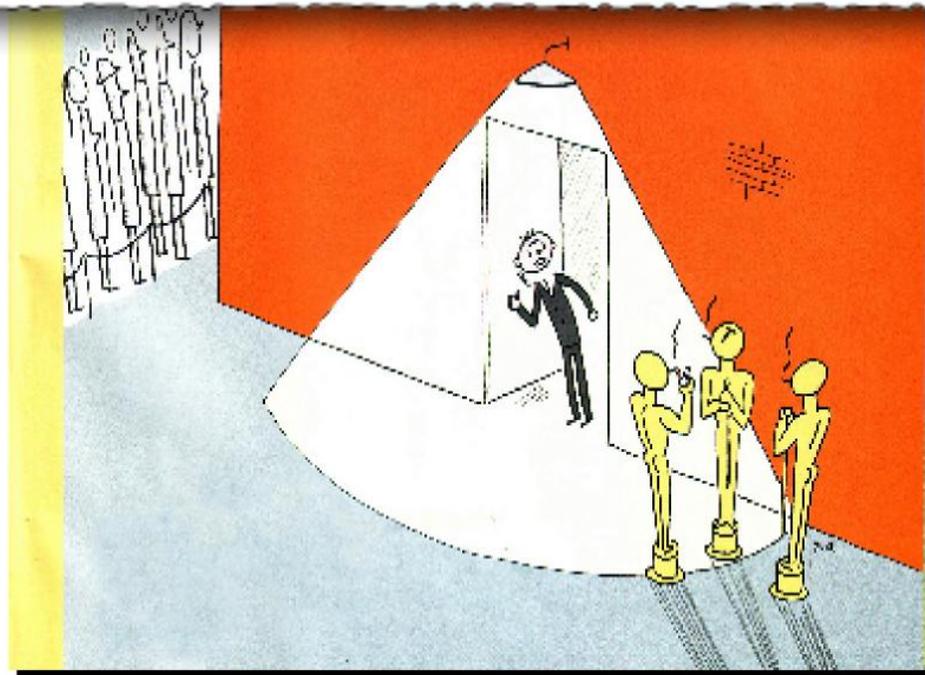
THE NEW YORKER

A Reporter at Large

NATURE'S BIOTERRORIST

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

By Michael Specter



The Washington Post

Tuesday, April 28, 2009

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. . .



First Reports of MERS – 2012



The
New England
Journal of Medicine

Established in 1812 as THE NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY

VOLUME 367

November 8, 2012

Number 19

Isolation of a Novel Coronavirus from a Man with Pneumonia in Saudi Arabia

AM Zaki, RAM Fouchier, et al.



Erica Saphire, Scripps Research Institute

Brazil links Zika fever to birth defects

🕒 29 November 2015 | [Latin America & Caribbean](#)



Countries and territories with confirmed cases of Zika virus (autochthonous transmission) in the Americas, 2015-2016.



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 (<http://blogs.cdc.gov/publichealthmatters/authors/ali-s-khan>)



(http://blogs.cdc.gov/publichealthmatters/files/2011/05/blogbanner_zombieprep_560x140.jpg)

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/) (<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.

(U) CONPLAN 8888

UNCLASSIFIED

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HEADQUARTERS UNITED STATES STRATEGIC COMMAND

CDRUSSTRATCOM CONPLAN 8888-11 "COUNTER-ZOMBIE DOMINANCE" 30 APR 2011

Classified by: N/A

Reason: N/A

Declassify on: N/A



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?

