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Title: The High Throughput Laboratory Network

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The High Throughput Laboratory Network

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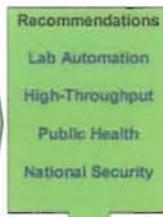
LabAutomation2007
January 27-30, 2007

Emerging Infectious Diseases

SARS
Anthrax
“Faster”
“More Frequent”
“Monumental Decisions”
West Nile
Influenza



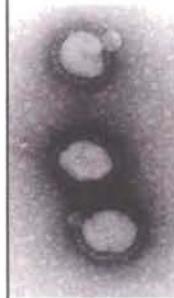
National Policy Development



IOM / NAE Colloquium
April 1999
(pre 9/11)

National Academies Press
2002
(post 9/11)

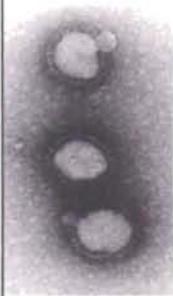
Biological Tri-Correlates



- Large Experimental Spaces:
 - Epidemiological
 - Genotypical
 - Phenotypical
- Correlations?



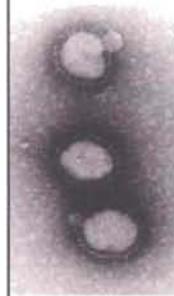
Why Influenza?



- Model for viral BW agent
- Extensive R&D/Surveillance/Response Community
- Strong public health component
- Threat hugely underestimated



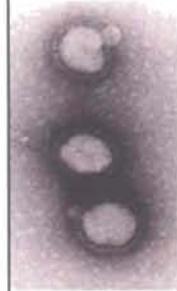
Epidemiological Information



- Collection time/date
- Location
- Source (respiratory vs fecal)
- Host (human, animal)
- Age (years for humans; juvenile vs adult for animals)
- Clinical severity (ambulatory or hospitalized)
- Outcome (live vs die)
- Exposures or related cases (human vs animal)



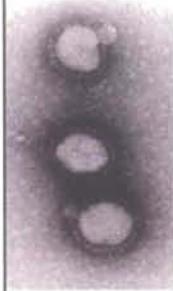
Genotypic Information



- Viral "relatedness" by RFLP, AFLP
- Sequence
 - 8 RNA segments coding for 10 proteins (PB1, PB2, PA, HA, NP, NA, M1, M2, NS1, NS2)
- PCR primers for RNA to DNA amplifications



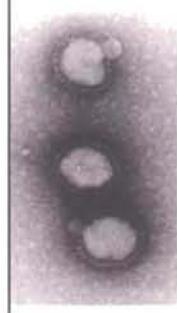
Phenotypic Information



- Viral type (A vs B) by antibody binding
- Viral subtype (H1-15 and N1-9) by antibody binding
- Viral epitope mapping (sites A-E)
- Heme agglutination
- Hemagglutinin inhibition (HI) assay
- Neuraminidase inhibition
- Resistance of M2 protein to antiviral drugs (amantadine, rimantadine)
- Virus neutralization assay (antibody binding)



Important Influenza Questions



- What viral factors govern influenza virulence across strains?
- Why was the 1918 pandemic strain so virulent?
- Why do certain influenza subtypes readily spread in animals but not humans?
- Are influenza shifts and drifts open-ended or limited to certain "constraints"?
- Why does influenza A undergo greater variation than influenza B?
- Does influenza evolve according to any particular spatial and/or temporal patterns?
- Are drug resistant strains of influenza emerging?
 - assist in improving influenza vaccines?
 - be used to predict influenza's next move?



WHO Global Surveillance: Severely Undersampled



10⁹ million cases
10⁴ samples
↓
1 per 10⁵
↓
Vaccines

EDITORIAL

A Global Lab Against Influenza

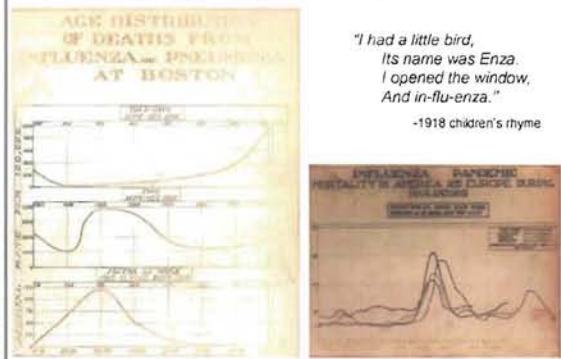
During the 1918 influenza pandemic, the world was introduced to the concept of a global disease. The 1918 influenza pandemic was the first major influenza pandemic of the 20th century, and it is estimated to have killed between 50 and 100 million people worldwide. The 1918 influenza pandemic was a wake-up call for the world to take action against influenza, and it has been a wake-up call ever since. The 1918 influenza pandemic was a wake-up call for the world to take action against influenza, and it has been a wake-up call ever since.

"The building block technologies to create the first global lab against influenza are available..."

Influenza Facts

- Respiratory illness with fever
- Observed since Hippocrates, 400 BC
- *Influenza del freddo* (influence of cold)
 - Italian name – used in early 1800s
 - Noticed coincidence with cold weather
- Millions infected worldwide per year
- 114,000 hospitalizations, 36,000 deaths in US, despite widespread vaccination
- Only communicable disease still listed as a leading cause of death in US, ranked 7th
- Major genetic changes resulted in pandemics – 1580, 1918, 1967, now?

1918 Influenza Pandemic



Pandemic Requirements

- Possess a new surface protein for which there is little or no immunity in humans
- Able to cause illness in humans
- Efficient human to human transmission



H5N1 meets 2 of 3!

So what's the worst that could happen?

- A pandemic of human-adapted avian influenza such as the 1997 H5N1 virus.
- Such a reassortant could easily have a mortality rate of 30-40%.
- Within a few months 10-25% of the world's population could be infected.
- $6.3 \text{ billion} * 0.4 * 0.25 = \text{over half a billion deaths.}$

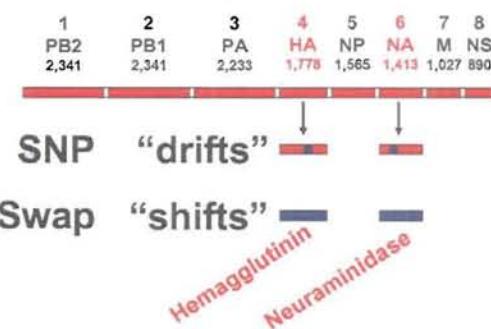
Influenza Facts

- Single stranded, helically shaped RNA virus
- Types A, B, and C
 - A: moderate to severe illness, highly infectious; also in pigs, birds.
 - B: milder illness; primarily children, not subtyped
 - C: mild, subclinical

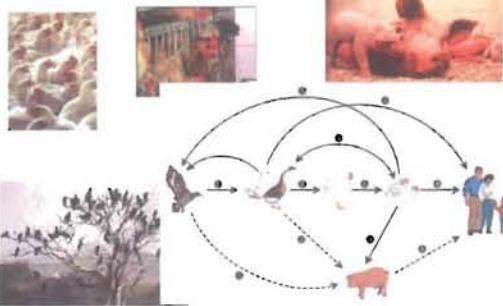
Influenza Facts

- Subtypes by surface antigens hemagglutinin (H) and neuraminidase (N)
- H attaches to cell; N penetrates cell
- 15 H and 9 N subtypes
 - H1N2, H2N3, etc.
- Antigenic drifts and shifts

Two Segment View



Influenza Central Dogma Genetic Shift Mechanism

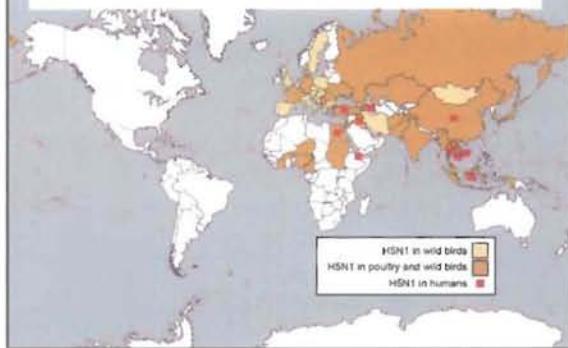


Avian Flu Cases Infecting Humans

STRAIN	LOCATION	INFECTIONS	MORTALITY
H5N1	Hong Kong, 1997	18 cases, 6 deaths	33%
H5N2	Hong Kong, 1999	2 cases	
H5N1	Hong Kong, 2003	2 cases, 1 death	50%
H7N7	Netherlands, 2003	83 cases of conjunctivitis, 1 death	
H5N2	Hong Kong, 2003	1 case	
H5N1	Vietnam, 2004	27 cases, 20 deaths	74%
H5N1	Thailand, 2004	16 cases, 11 deaths	69%

Mortality (163/269 cases): 60.5% overall, 70% in 2006

Distribution of Avian Influenza



H5N1 Influenza

Flu in wild birds sparks fears of mutating virus



Influenza Pandemic Are We Ready?

Flight	Destination	Departure
UA 800	San Francisco	15:00
UA 180	Seattle	15:15
UA 181	Seattle	15:30
UA 182	Seattle	15:45
UA 183	Seattle	16:00
UA 184	Seattle	16:15
UA 185	Seattle	16:30
UA 186	Seattle	16:45
UA 187	Seattle	17:00
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Problem Statement

- For fundamental understanding and prediction, scientific data about emerging biological pathogens is:
 - Insufficient
 - Not representative
 - Of variable quality
 - Unevenly accessible
 - Acquired too slowly
- Actionable information needed

Program Vision

High Throughput Laboratory Network (HTLN)

- HTLN program will build an international laboratory infrastructure
- Infrastructure will consist of automated analysis methods and systems (nodes) that:
 - are high throughput
 - provide surge capacity
 - operate in research, surveillance, response, and attribution modes

HT Laboratory Network for Influenza Characterization



US Patent (5,841,975) "Method and Apparatus for Globally Accessible Automated Testing"

HTLN - Lab Concept



HTLN - Funding Summary

- FY06
 - \$6M DoD Appropriations Bill
 - \$9M State of CA DHS Funding
- FY07
 - \$6M DoD Appropriations Bill
- NIH NIAID Contract \$19M/5 years
- FY08 (planned)
 - \$8M DoD Appropriations Bill

Development Plan

- Develop Grid Experimentation Architecture
- Instantiate with a HT node for genotypical assay (influenza sequencing)
- Install and operate node at partner lab
- Build 2nd node, install at partner lab
- Instantiate with a HT phenotypical assay (serotyping)

