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Title:	The High Throughput Laboratory Network
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The High Throughput Laboratory Network

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LabAutomation2007
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Emerging Infectious Diseases

"Faster"

"More Frequent"

"Monumental Decisions"

SARS

West Nile

Anthrax

Influenza

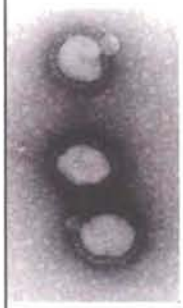
National Policy Development

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

National Academies Press
2002
(post 9/11)

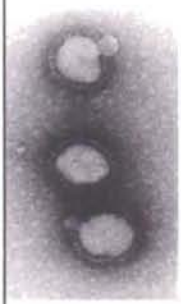
Recommendations
Lab Automation
High-Throughput
Public Health
National Security

Biological Tri-Correlates



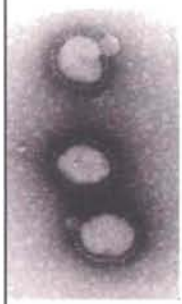
- Large Experimental Spaces:
  - Epidemiological
  - Genotypical
  - Phenotypical
- Correlations?

Why Influenza?



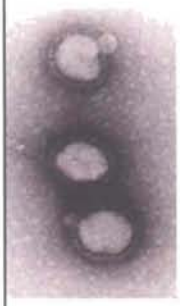
- Model for viral BW agent
- Extensive R&D/Surveillance/ Response Community
- Strong public health component
- Threat hugely underestimated

Epidemiological Information



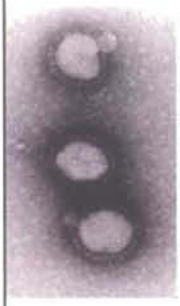
- Collection time/date
- Location
- Source (respiratory vs fecal)
- Host (human, animal)
- Age (years for humans; juvenile vs adult for animals)
- Clinical severity (ambulatory or hospitalized)
- Outcome (live vs die)
- Exposures or related cases (human vs animal)

Genotypic Information



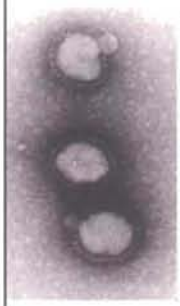
- Viral "relatedness" by RFLP, AFLP
- Sequence
  - 8 RNA segments coding for 10 proteins (PB1, PB2, PA, HA, NP, NA, M1, M2, NS1, NS2)
- PCR primers for RNA to DNA amplifications

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
- Hemaglutinin 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?
- Can enormous databases:
  - assist in improving influenza vaccines?
  - be used to predict influenza's next move?

WHO Global Surveillance: Severely Undersampled

10^9 million cases
10^4 samples

↓

1 per 10^5

↓

Vaccines

EDITORIAL

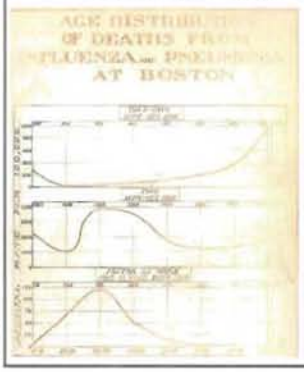
A Global Lab Against Influenza

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

Influenza Facts

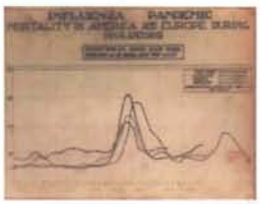
- Respiratory illness with fever
- Observed since Hippocrates, 400 BC
- *Influenza del freddo* (influence of cold)
  - Italian name – used in early 1800s
  - Noticed coincidence with cold weather
- Millions infected worldwide per year
- 114,000 hospitalizations, 36,000 deaths in US, despite widespread 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



"I had a little bird,
Its name was Enza.
I opened the window,
And in-flu-enza."

-1918 children's rhyme



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 billion * 0.4 * 0.25 = over half a billion deaths.

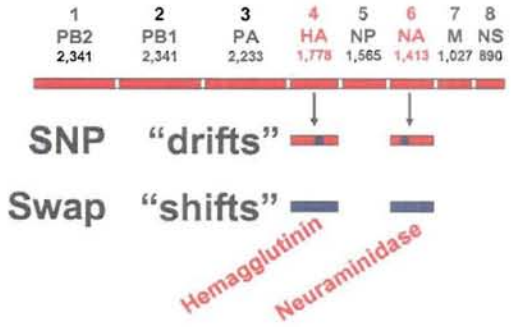
Influenza Facts

- 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

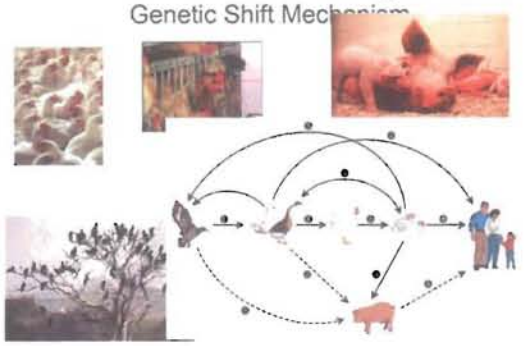
- Subtypes by surface antigens hemaggluntinin (H) and neuraminidase (N)
- H attaches to cell; N penetrates cell
- 15 H and 9 N subtypes
  - H1N2, H2N3, etc.
- Antigenic drifts and shifts

Two Segment View



Influenza Central Dogma

Genetic Shift Mechanism

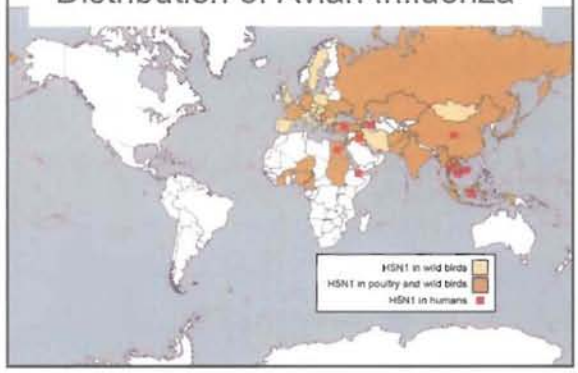


Avian Flu Cases Infecting Humans

STRAIN	LOCATION	INFECTIONS	MORTALITY
H5N1	Hong Kong, 1997	18 cases, 6 deaths	33%
H9N2	Hong Kong, 1999	2 cases	
H5N1	Hong Kong, 2003	2 cases, 1 death	50%
H7N7	Netherlands, 2003	83 cases of conjunctivitis, 1 death	
H9N2	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

Influenza Pandemic

Are We Ready?

Pandemic Preparedness Plans

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"

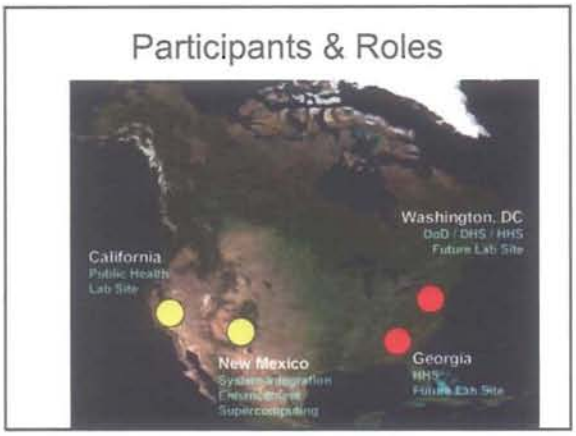
HTLN - Lab Concept

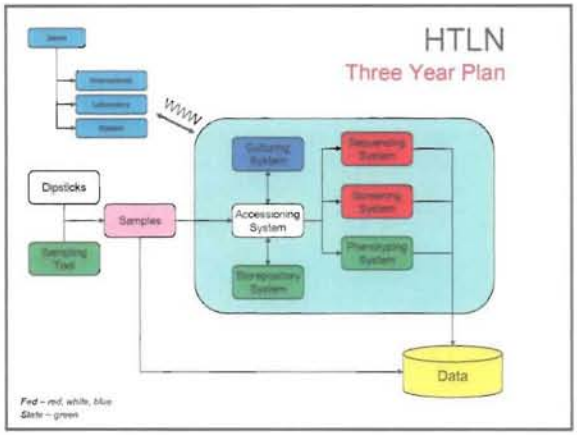
HTLN - Funding Summary

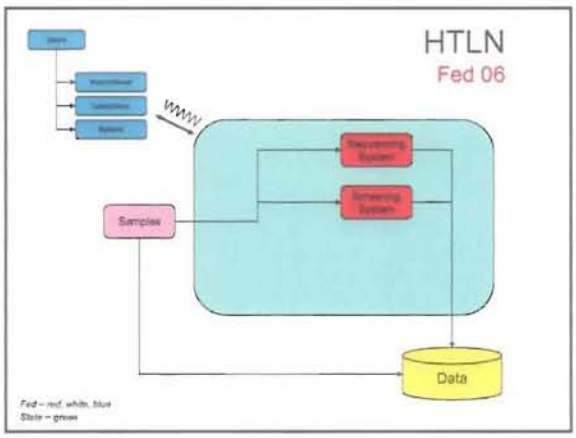
- FY06
  - $6M DoD Appropriations Bill
  - $9M State of CA DHS Funding
- FY07
  - $6M DoD Appropriations Bill
- NIH NIAID Contract $19M/5 years
- FY08 (planned)
  - $8M DoD Appropriations Bill

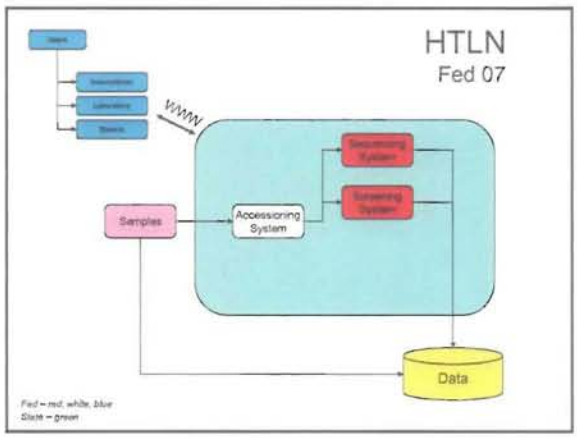
Development Plan

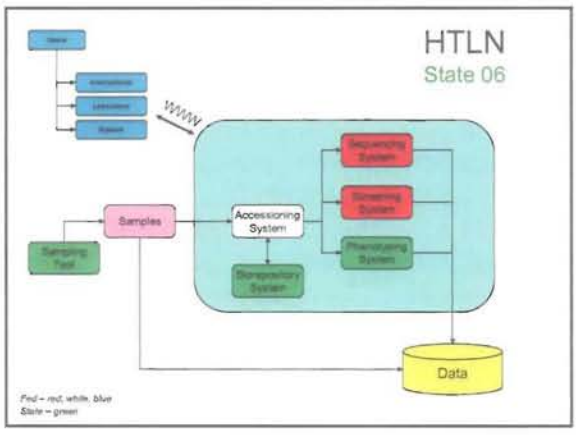
- Develop Grid Experimentation Architecture
- Instantiate with a HT node for genotypical assay (influenza sequencing)
- Install and operate node at partner lab
- Build 2nd node, install at partner lab
- Instantiate with a HT phenotypical assay (serotyping)


Participants & Roles
Washington, DC
DoD / DHS / HHS
Future Lab Site
California
Public Health
Lab Site
New Mexico
System Integration
Georgia
HHS


HTLN
Three Year Plan
Dipsticks
Samples
Accessioning System
Data
Fed – red, white, blue
State – green


HTLN
Fed 06
Samples
Data
Fed – red, white, blue
State – green


HTLN
Fed 07
Samples
Accessioning System
Data
Fed – red, white, blue
State – green


HTLN
State 06
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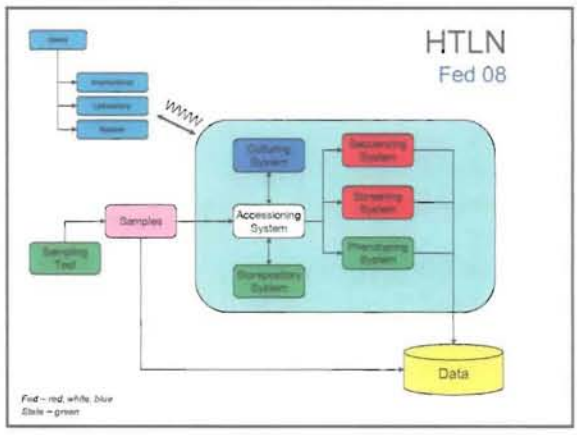
HTLN
Fed 08
Samples
Accessioning System
Data
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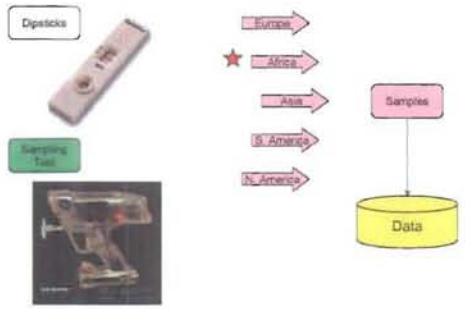
Program Description
Worldwide Surveillance Network

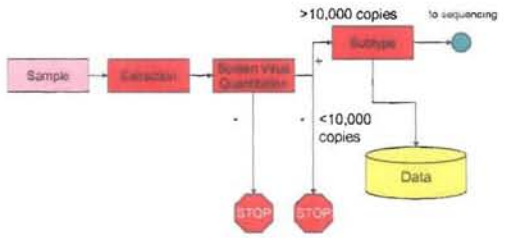


Phase 1
Deliverables

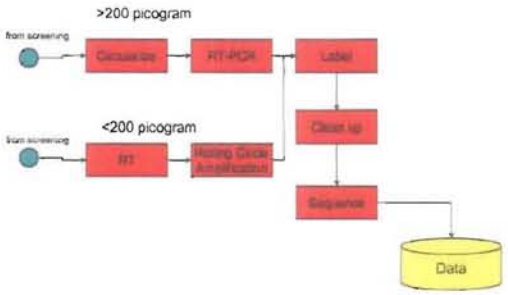
In 15 months, design, build, test and deliver HT methods *and* systems to UCLA for:

1. Influenza virus screening.
2. Influenza sequencing with a capacity of 10,000 fully assembled influenza genomes per year.

Process Flow
Virus Screening



Process Flow
Virus Sequencing



Future Program Directions

- Node expansion to other institutions
  - Public health labs
  - WHO labs
  - Ministries of Health labs
- Scope expansion to other bio-threat agents

Summary

- Long program development period
- Program is underway
- Complementary UCLA/LANL missions and skills
- Cross divisional LANL involvement
- Significant upside potential
- Lead the world in real-time surveillance