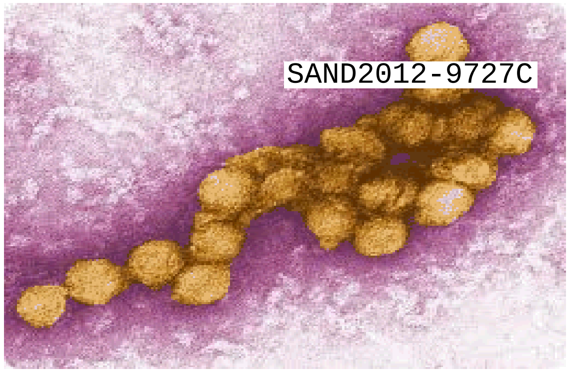


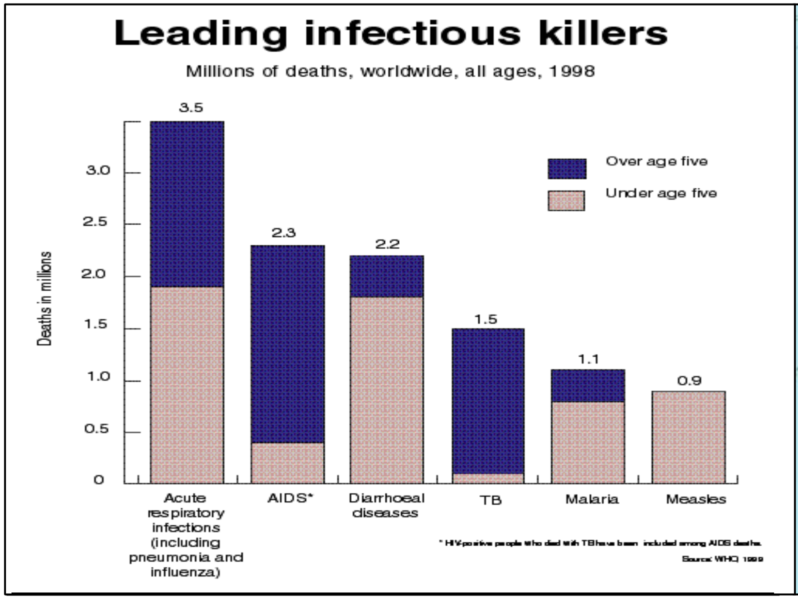
SAND2012-9727C

Human disease surveillance: Novel approaches to predict and monitor outbreaks and pandemics

Stanley Langevin, PhD

Sandia National Labs

Infectious diseases: the great threat

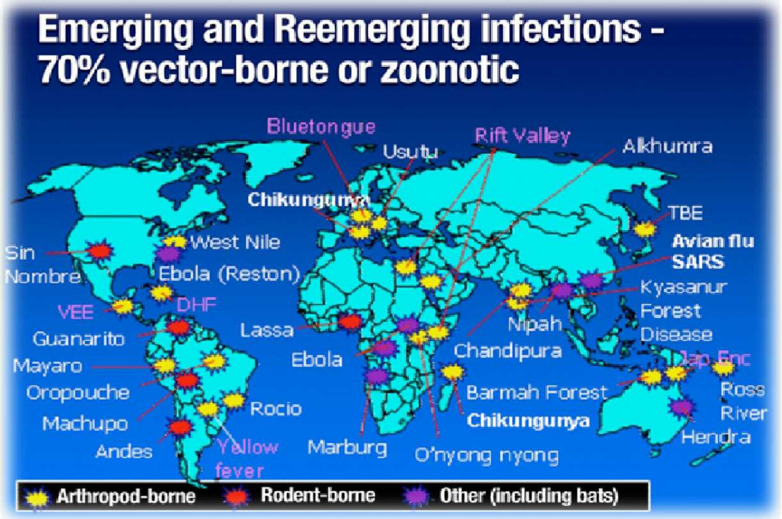


Leading infectious killers

Millions of deaths, worldwide, all ages, 1998

* HIV-positive people who died with TB have been included among AIDS deaths.

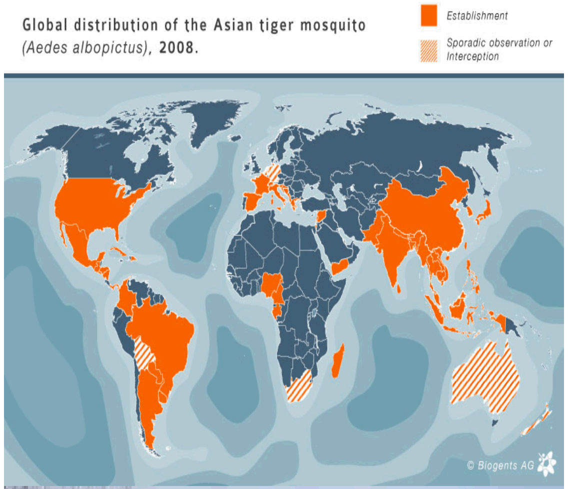
Source: WHO 1999



Emerging and Reemerging infections - 70% vector-borne or zoonotic

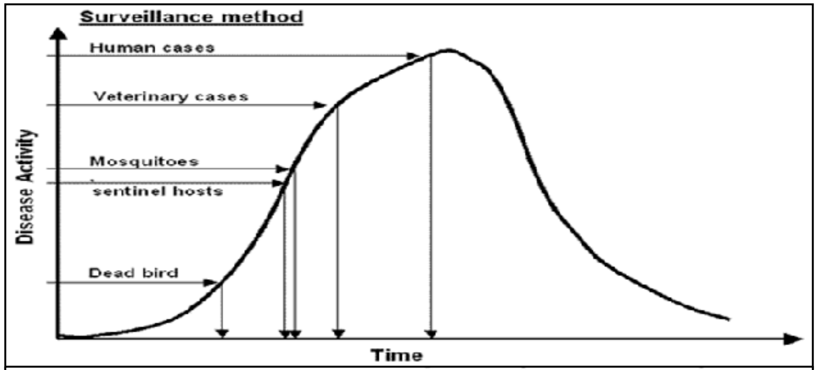
- A few human pathogens account for 90% of infectious disease related deaths worldwide
- Disproportionate global disease burden
- Urbanization and globalization increase the magnitude and frequency of epidemics

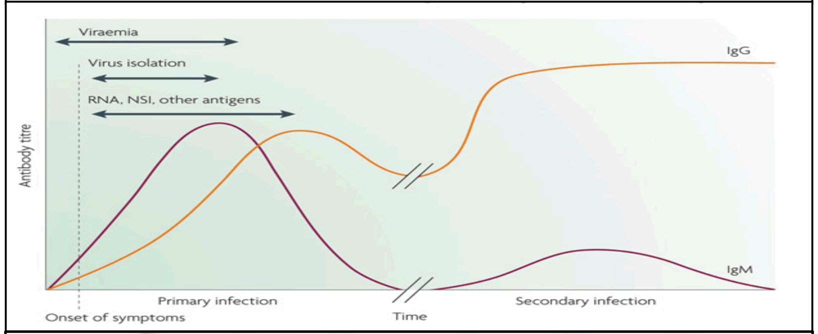
Mechanisms of vector-borne disease emergence

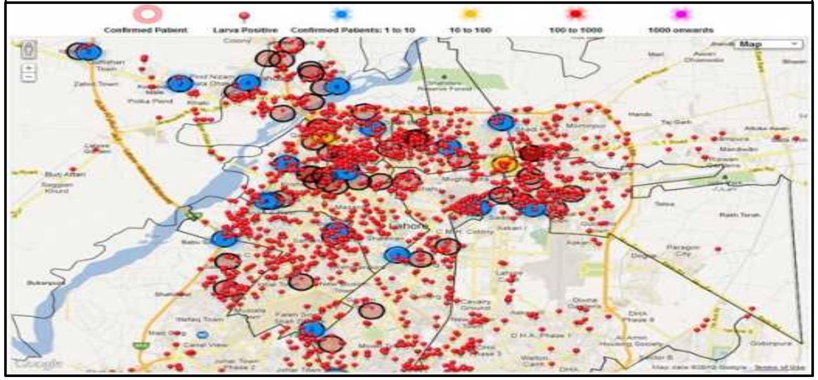

Global distribution of the Asian tiger mosquito (*Aedes albopictus*), 2008.

- Globalization/changing human migration patterns
- Climate change
- Geographic expansion of vector populations
- Viral adaptation- transmissibility/virulence
- Infect highly susceptible naïve host population

Effective surveillance can predict human disease







- Wildlife mortality surveillance- Dead birds predict WNV human disease

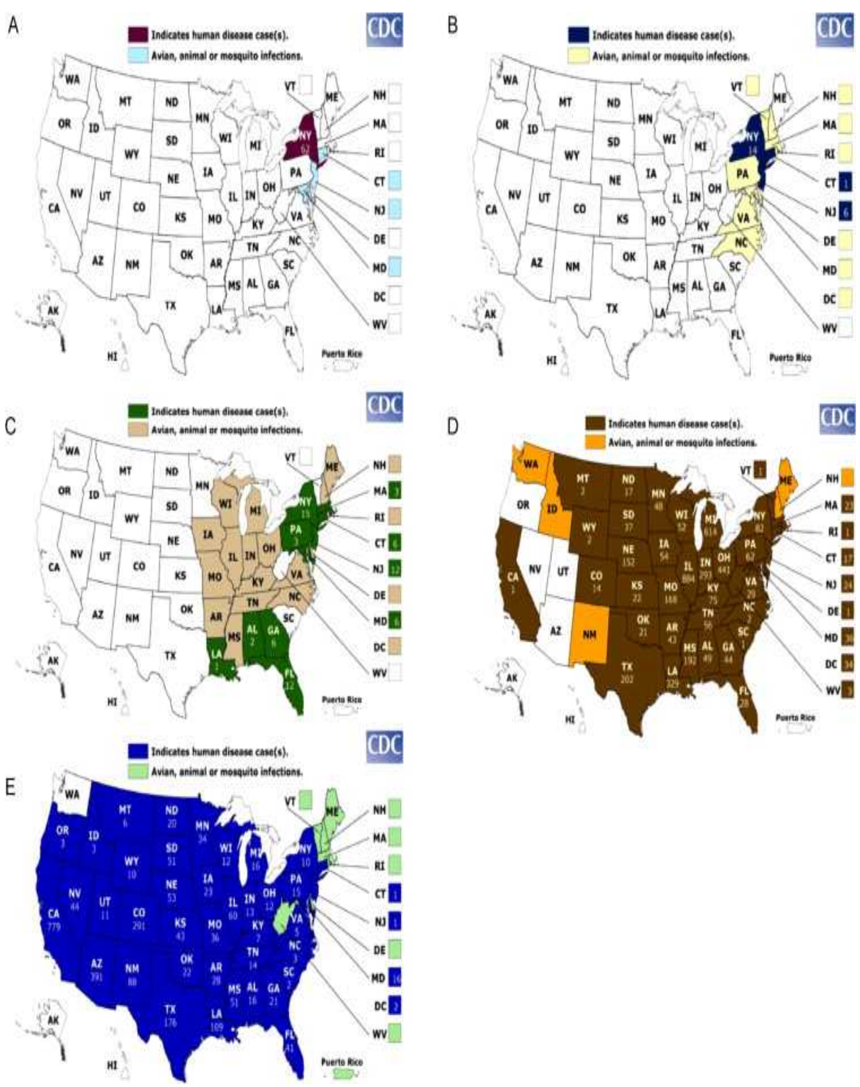
- Human and wildlife serosurveys can approximate herd immunity levels

- Screen vector populations for human diseases

- Use media sources (medical internet sites, twitter feeds, facebook) as a predictive outbreak tool.

Challenge: All require a dedicated Surveillance infrastructure and resources

Tracking WNV: Dissemination throughout the Americas



- **First evidence of WNV in Western Hemisphere**
  - -New York City, 1999
- **Genotype identical to WNV isolate from Israel**
  - -Importation
- **Highly virulent phenotype in NA birds**
  - -up to 100% morality rates
- **Implemented dead bird surveillance**
  - -Virulent phenotype in birds
- **Track WNV spread in "real-time"**
  - - detected throughout US in 5 years
- **Impact of exotic pathogen exposed to naïve host populations**
  - -up to 50% population decline

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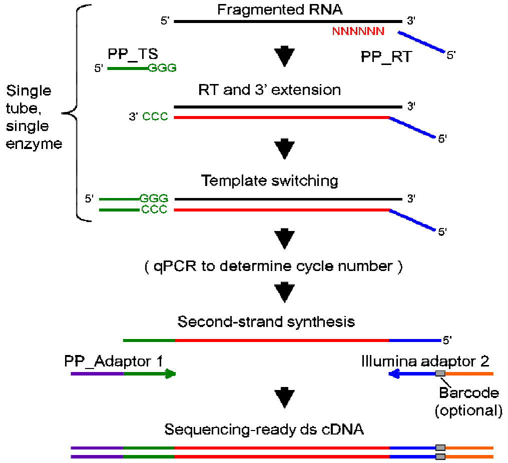
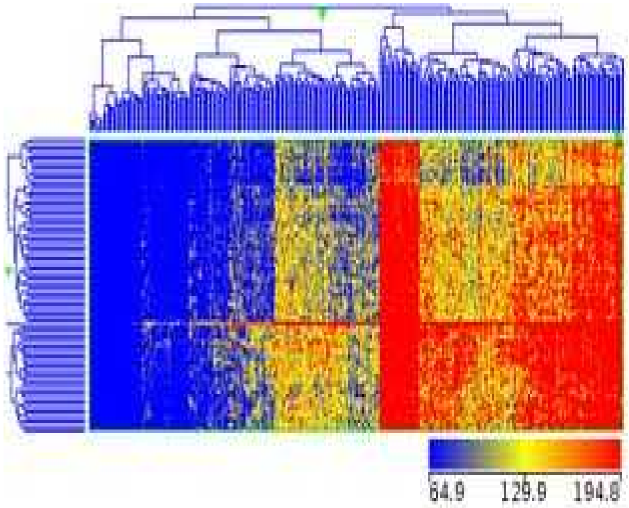
Current methods for pathogen detection

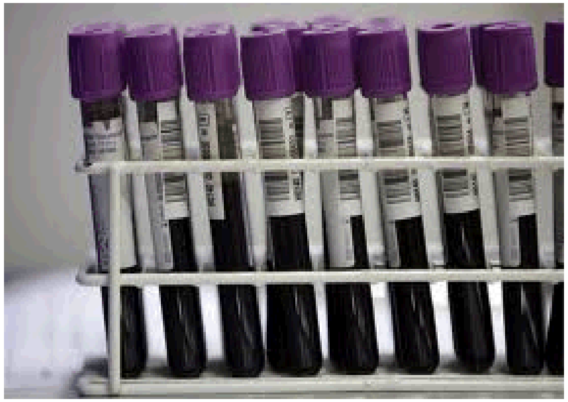
- Antigen/Antibody (immunoassays)
- PCR (RT-PCR, qPCR)
- Propagate (cell culture, growth medium)

RapTOR: deep sequencing for pathogen detection





RapTOR: a tool for human disease surveillance

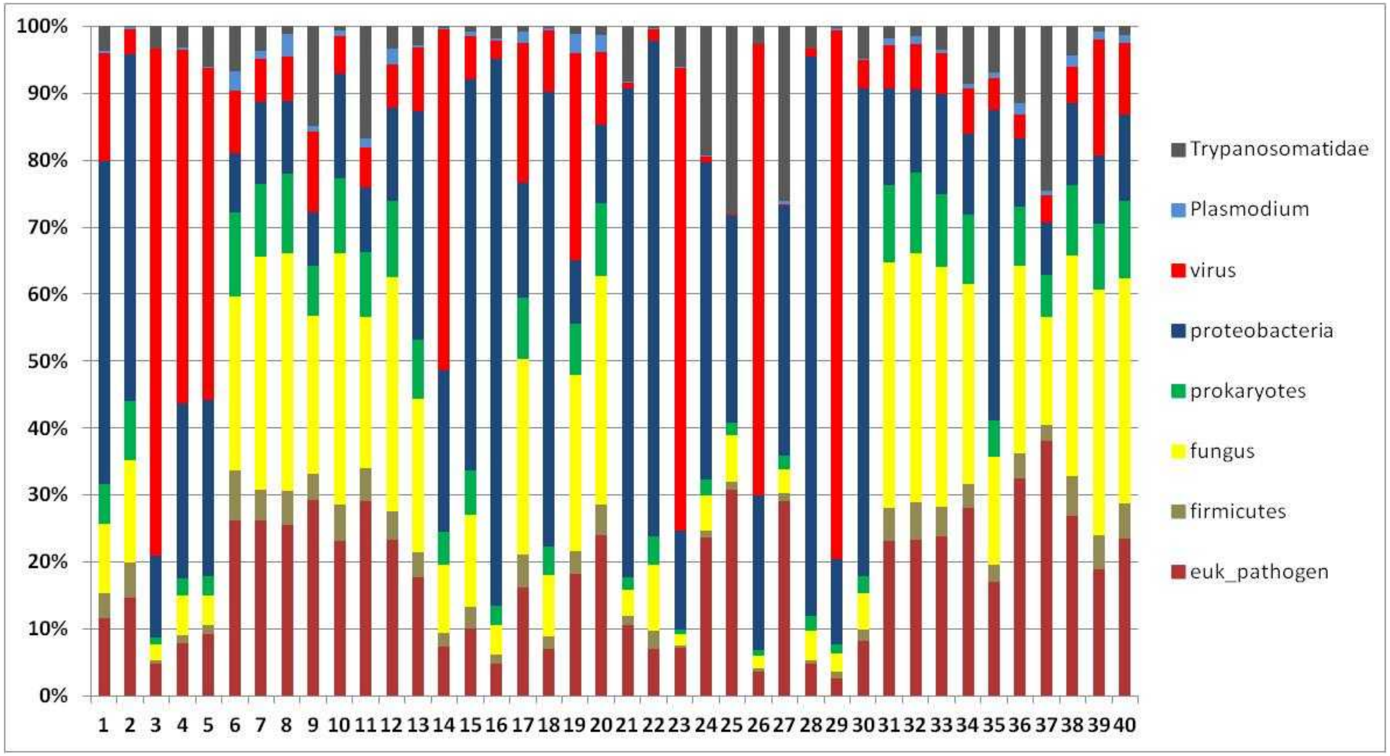


- A cost-effective sample prep protocol for deep sequencing clinical and environmental samples
- Compatible pathogen enrichment assays
- Automated bioinformatics analysis pipeline
- Identify known and unknown human pathogen sequences

RapTOR: bioinformatics pipeline

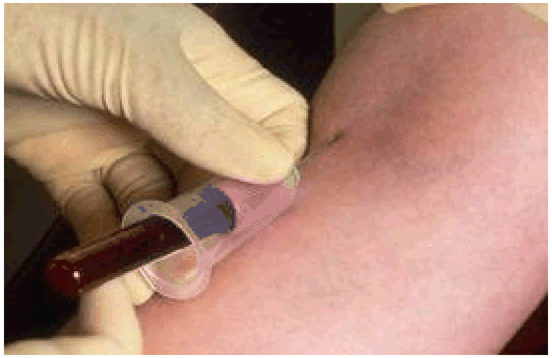
- Automated
- Eliminates low quality sequences and primer contamination
- Contains filters to remove highly abundant host sequences
- Aligns unmapped non-host sequences against all genomes in the Refseq database.

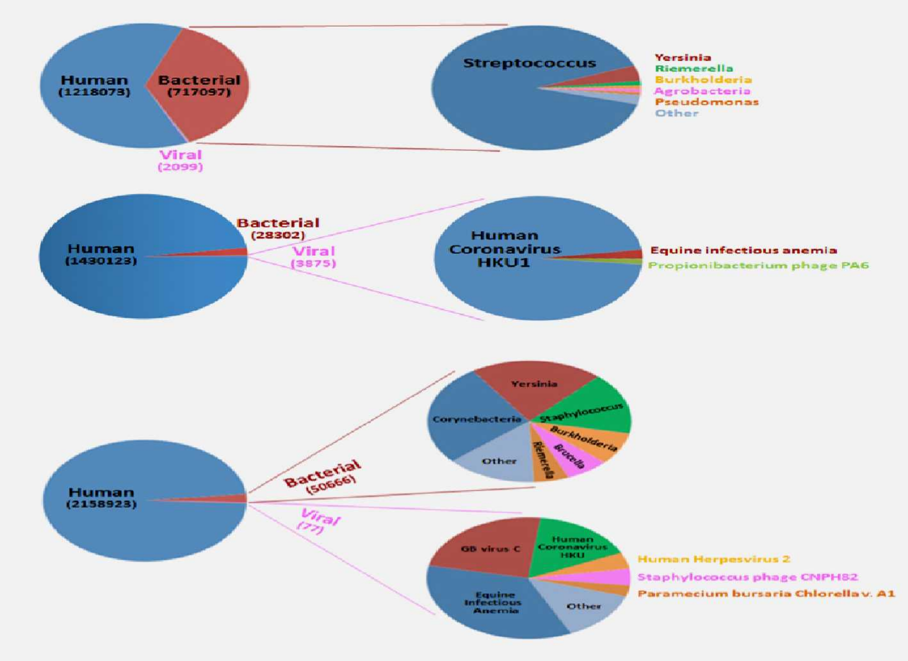
RapTOR: High level metagenomics analysis



- Align unmapped non-human sequences against human/veterinary pathogen sequence database
- Use high level analysis to rapidly identify eukaryotic pathogens and track human disease trends at a population level.

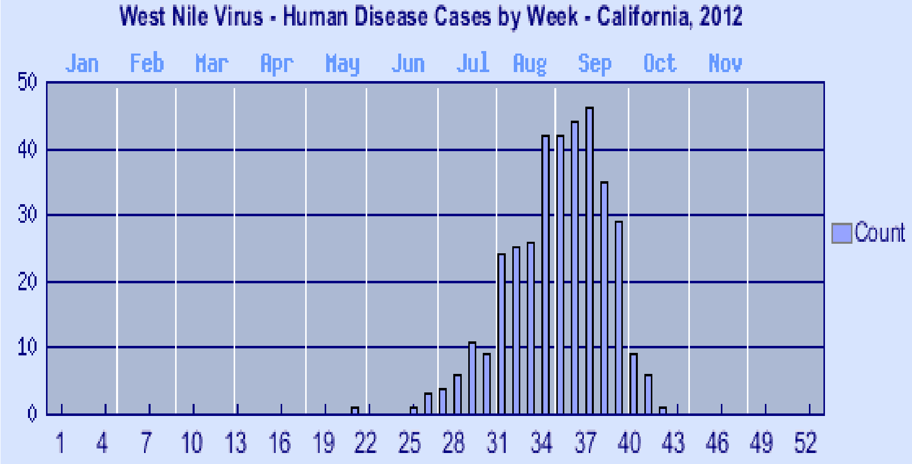
Validation of RapTOR for clinical samples





DeRisi 96 sample bioinformatic challenge

2012 CA WNV outbreak



CDC arbonet 2012

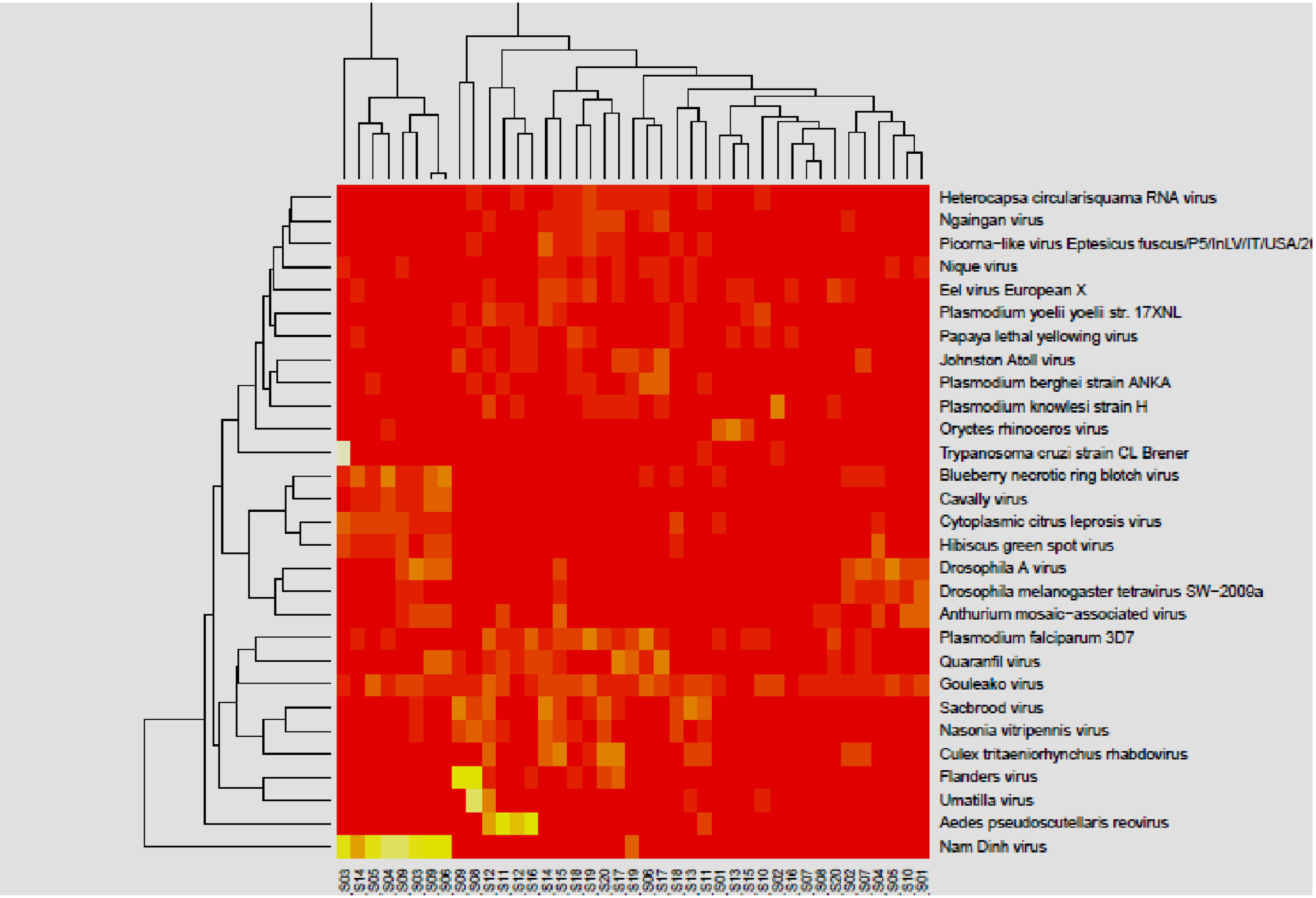
WNV Report as of 11/2/12

Human cases in US = 4891
Human cases in CA = 377
Mosquito pos pools = 2814
Chicken sentinel pos = 507

WNV positive pools for deep sequencing

- 40 WNV positive *Culex* pools (n=50)
- 4 distinct geographic locations
- 3 different Culex species
- All collected during peak transmission

Geographic distribution of mosquito-borne viruses in California



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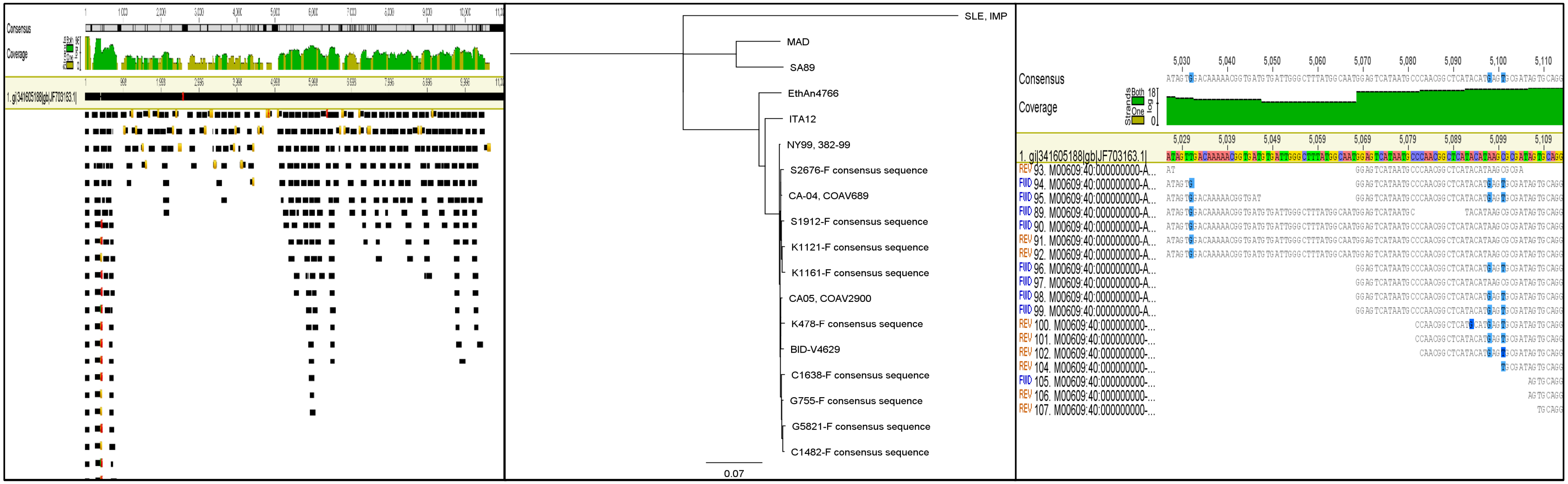
RapTOR: pathogen genotype characterization

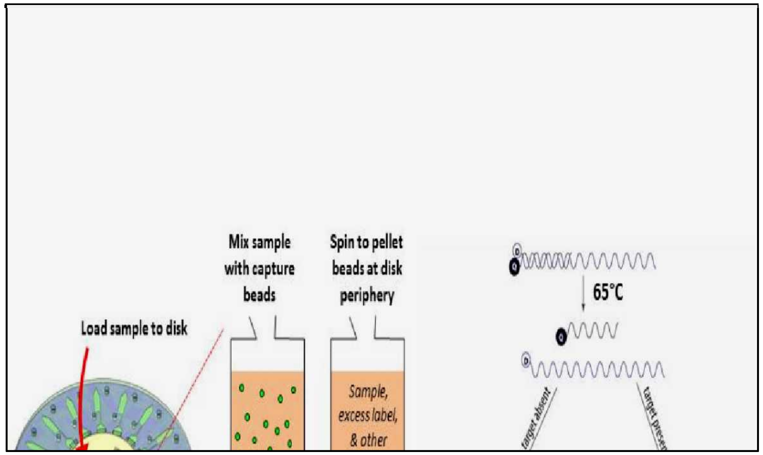


- Use NCBI blastx to identify potential pathogen sequences
- Align pathogen sequences to reference genomes for confirmation
- Perform phylogenetic analysis on pathogen sequences and monitor drug resistance mutations in a population
- Develop rapid PCR and antigen-based screening assays to monitor transmission

Advantages to RapTOR disease surveillance platform

- Characterize all known eukaryotic pathogens circulating within a given population
- Use as a clinical diagnostics tool for human samples with unknown disease etiology
- Identify regional and local disease “hot spots” to focus public health resources where it is most needed.
- Mitigate disease in affected population(s), if therapeutics and/or control measures are available
- Use pathogen sequence information to develop rapid diagnostic assays for surveillance

SpinDx™: Lab on a CD for disease surveillance



- Microfluidic platform
- Inexpensive diagnostic/surveillance assay
- Immunoassay (Ab/Ag) or nucleic acid (DNA/RNA)
- total sample-to-answer time of < 20 minutes
- No sample preparation necessary (sample-to-CD)
- Multiplexing capabilities

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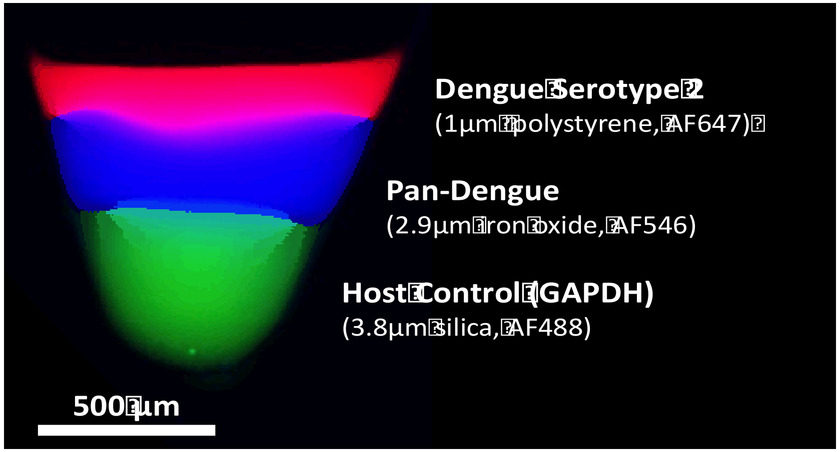
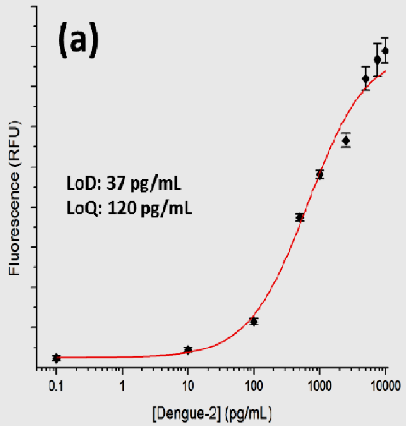
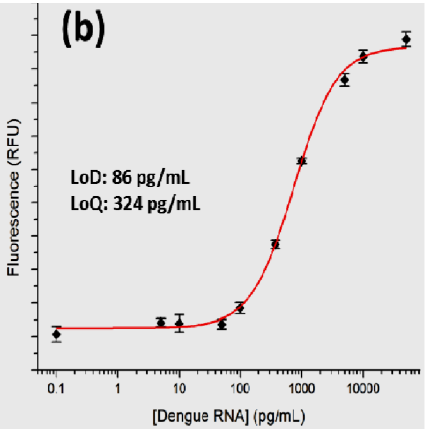
Dengue virus SpinDx







- Identifies all DENV serotypes (1-4) in a single multiplexed assay
- Detects multiple conserved DENV NA signatures using fluorescent DNA probes
- Sample nucleic acid integrity evaluated
- Up to 50 samples per CD

Acknowledgements

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DOE LDRD Pathogen detection