Forward genomic surveillance advances DoD biomedical research toward combating high-consequence emerging infectious diseases

Innovations from a Global Health Engagement and Rapid Response during the 2013-2015 Western African Ebola virus outbreak

Opinions, interpretations, conclusions, and recommendations are those of the author and are not necessarily endorsed by the U.S. Army.
USAMRIID increases Liberia’s capacity to combat the Ebola Virus
Liberian Institute of Biomedical Research (LIBR)

**PURPOSE:** To build country capacity by establishing a permanent and sustained Ebola diagnostic laboratory and a high-throughput sequencing capability at LIBR

We were postured to respond:
- 8 filovirus diagnostic assays with pre-emergency use authorizations (EUA) approved by FDA since 2013
- Depth of expertise in full genome sequencing and analysis methodologies for filoviruses

We responded:

1. Diagnostic Capacity built beginning in April 2014 and continues today
   - To assist patient triage and isolation guidelines for ETU
   - 1 of 10 labs in country; < 3 exist today
   - First EUA in U.S. for Ebola with CLIP certification for testing of American Citizens and U.S. Military personnel supporting Operation United Assistance
   - Capacity today transitioned to EID diagnostics – Lassa fever (CDC-ACCEL)

2. Sequencing Capacity built December 2014 and continues today
   - Risk of target erosion of diagnostics and sequence-based therapeutics
   - Only Sequencer in Liberia
01 SEP – 6 DEC 2014:
~3000 samples tested by diagnostics

~200 complete sequenced genomes

IMPACT:

- Largest collection of samples and genetic data for variants that circulated in Liberia for this outbreak

- 8 lineages circulated in Liberia,
  - 7 of which in Monrovia;
  - lineages are geographically associated

- Calculated rate of evolution consistent with neighboring countries
  - $9.17 \times 10^{-4}$ substitutions/site/year

- Target Erosion Confirmed but low risk to efficacy:
  - 26 mutations to epitopes recognized by immunotherapies
  - 5 mutations in siRNA therapy binding sites
  - 2 mutations in diagnostic primer binding sites (binding not impacted)
Lesson Learned: Mapping diagnostic and sequencing data reveals probable viral escape event missed during mission

- Sequenced samples reflect the distribution of EVD positive patients confirmed during diagnostic testing.
- Sequencing covered regions with indeterminate results except for one region (circled) which could indicate mutation of virus that escapes diagnostic testing assays.

** Produced by the National Geospatial Intelligence Agency – Experience Directorate**
USAMRIID provides molecular evidence for sexual transmission of EBOV

- **March 20, 2015** – *2 New EVD Case* Identified 30 Days into “the count”
- **April** - USAMRIID confirmed source was a male survivor who had a persistent infection for 179 Days
- **May** – Change in health policy and infection control measures
- **July** – Men’s Health Program opened to permit

Sequencing confirmed:
- Variant had circulated in Liberia
- Variant from semen was nearly identical to the new infection
- Both variants exhibited unique substitutions never seen before
- Variants exhibited a reduced rate of evolution = persistent infection & reservoir
Evolutionary analysis revealed:

- Patients were not infected by EBOV that circulated in Liberia
- Closest to variants from Guinea
- Reduced evolutionary rate was consistent with the source for the flare-up in Guinea, a persistently infected Survivor.

Cases were nearly identical to variants from flare-up in N’Zérékoré, Guinea

4 Flare-ups in Liberia & Source
ST = Sexual Transmission
CB= Cross-Border transmission
Persistence in immune privileged tissues: Ebola outbreak largest impact to public health knowledge and continues to be a public health concern.
USAMRIID is now applying the same **Genome Surveillance Strategy** to combat Zika on the Homeland

Reports demonstrate sexual transmission and persistence of Zika virus.

Different Virus- Same questions for molecular epidemiology

- When did local transmission actually begin?
- How many introductions have contributed?
- Which cases are epidemiologically linked?
- Reduced rates of evolution signify persistence?

*We are already assisting public health officials and increasing public knowledge*
References

Publications by USAMRIID Investigators:


Other Publications cited: