PUBLIC HEALTH AGENCY of CANADA
AGENCE DE SANTÉ PUBLIQUE du CANADA
The Untold Stories Of The National Microbiology Laboratory:

Innovations to keep ahead in the evolutionary struggle with the microbial world

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Distinguished Professor, University of Manitoba
2017 Gairdner Wightman Lecture
Emerging and Remerging Infectious Diseases

- Emerging infections are those that are new or newly discovered in humans – mainly come from animals (H1N1, measles, plague, tuberculosis, influenza, HIV, SARS)

- Infections re-emerge when old microbial foes acquire new weapons through genetic exchange or mutation – resistance to drugs or vaccines, escape from the human immune defences
# Emerging and Re-emerging Infectious Disease Over My Career

**Bacteria**

- Legionnaire’s disease
- E.coli H7:O157
- *Clostridium difficile* colitis
- *Helicobacter pylori*
- *Chlamydia trachomatis* and *C. pneumonia*
- *Staphylococcus* toxic shock
- Flesh eating disease
- Methicillin resistant *S. aureus*
- Penicillin resistant gonorrhea and *Hemophilus influenza*
- Extremely drug resistant tuberculosis
- Vancomycin resistant enterococcus

**Viruses**

- Ebola virus
- HTLV-I
- HIV-1
- HIV-2
- Nipah virus
- Borna virus
- West Nile virus
- SARS
- H5N1 Avian influenza
- H1N1 pandemic influenza
- Hepatitis B & Hepatitis C
- Delta agent
- Prion disease (mad cow)
- NERS
Are Infectious Diseases Threats Increasing?

- Probably “yes”
- 35+ “new” diseases over the past 40 years
- Of all microbial species, we have characterized less than 1% and the unknown 99% represent constant source of new threats.
- Most new infections come from animals
- Organisms mutate in response to human tactics: drugs, vaccines, disinfectants ...
Why Is This Happening?

- Ecologic changes
- Human demographic/behavioural changes
- Globalization
- Rapid growth in technology
- Microbial adaptation and change
- Gaps in public health programs/infrastructure
Anticipating the Puck

The Katrina Lesson
Canada’s Response To These Threats – Build The National Microbiology Laboratory In Winnipeg
NML Fast Facts

- Announced 1987
- Construction began 1992
- Official opening 1999
- Only operational Level 4 lab in Canada
- First facility with human and animal CL 4 labs
- 31 metres high
- 29,300 sq. metres
Recent Expansion

◈ 3 story expansion funded by the Economic Action Plan ($24 million)

◈ Completed March 31, 2011

◈ Expanded specimen receiving, shipping and receiving, bio-repository and media preparation areas.
Most CSCHAH labs are CL2 (60.8%) 
Similar to laboratories in hospitals and medical clinics
Work done in a biosafety cabinet with controlled air flow (at right)
Treatment and preventive measures are available

Examples:
- E-coli
- Whooping Cough
- Hepatitis C
Containment Level 3

- 35.5% of total lab space
- Can cause serious disease in humans or result in serious economic consequences (animals)
- Diseases that do not ordinarily spread by casual contact or they are treatable
- Staff wear laboratory clothing and shower out (most areas)
- Air is filtered; waste is treated

Examples:
- Foot-and-Mouth disease
- Tuberculosis
- West Nile virus
Containment Level 4

- **3.7%** of lab space (1.1% of building)
- Dangerous agents that usually produce very serious and untreatable diseases
- Staff wear biosafety suits; chemically treated each time
- Each department has one CL4 suite which provides back-up during annual recertification
- Suites are air tight
- All air and waste sterilized

**Examples:**
- Ebola virus
- Nipah virus
- Marburg Virus
Air pressure is tightly controlled in and around high containment labs.

Doors are interlocking; bioseal (submarine) doors in key locations.

Progressively lower pressure going deeper into lab space dropping by 50 pascals between rooms ensures air flows in toward lab and out through HEPA filters.
Some Important Public Health Innovations From The NML
Innovation 1:
Rapid Detection & Alerting of Infectious Disease
New Tools to Increase Speed of Detection and Alerting

• Previously: Countries reported new & emerging diseases to WHO – take weeks

• Now: advanced computer based technologies
  – Canadian Network for Public Health Intelligence
  – Monitors news, internet etc.

• Examples: SARS, H1N1, Listeria
Canadian Network for Public Health Intelligence

Fostering collaboration and consultation through innovation in disease surveillance, intelligence exchange, research, and response to protect, promote and support public health

Dr Shamir N Mukhi
Chief Engineer
Background

• An innovative scientific public health informatics platform developed and managed by PHAC-NML.

• Includes technologies for collaboration, surveillance, alerting, knowledge management, lab systems, and event management supporting large number of F/P/T public health professionals in human, animal and environmental health domains

• Recognized as trusted platform providing key foundational infrastructure for public health surveillance in Canada.
What is CNPHI?

A secure public health intelligence cloud
What is CNPHI?

- CNPHI is an innovative, versatile informatics platform that has been custom built for public health needs
- CNPHI platform is not static; constantly to meet current and future needs of dynamic public health programs
- Respects jurisdictional boundaries
- Helps transform program to structured centralized data collection and analysis
- Innovative current technology
- Six focus areas: Knowledge Management, Collaboration, Alerting, Surveillance, Event Management, Laboratory Systems
Benefits

• Provides capability to directly link F/P/T epidemiologists and laboratories, enabling bi-directional and close to real-time data and intelligence sharing between partners while respecting jurisdictional boundaries

• Innovative reporting and data entry/collection tools supporting increased data quality, interactive data analysis

• Provides initiative specific sponsors control to manage access to applications within their platform

• Easy sharing with all participants of discussions
CNPRI at a Glance

Knowledge Management Resources
- Protocols
- Training Materials
- References
- Resource Inventory

Decision Support Resources
- GIS
- Modeling
- Statistics
- Algorithms

Inter-Jurisdiction Case Management

Intelligence Exchange Resources
- ETEAM
- Discussion Forum
- News Board
- Document Manager
- Group Chat
- Scheduler
- Web-cast
- Other
- Web Surveys

Outbreak Summaries
- Phone
- Fax
- Email
- Pager

Public Health Alerts
- STD
- Nosocomial
- Zoonotic
- CBRN
- Enteric
- GPHIN
- Respiratory
- Travel

Program Specific Surveillance
- NESP
- CBRN Watch
- WNV
- FluWatch
- CNISP
- Other
- Syndromic Surveillance

Inter-Jurisdiction Case Management

Data Collection/Exchange
- Web-Data
- Manual Data Entry
- Automated Data Collection
- Web-Data
- Prov/Terr Epi
- Labs
- Schools
- Hospitals
- OTC
- Telehealth
- Others

Surveillance/Program ‘Watches’
- Intelligence presentation using maps, charts, etc.
- Supported by algorithms and other decision support tools
- Program driven; configurable and flexible

Alerting
- Targeted alerting
- Role based
- Respect jurisdictional accountabilities
- Program driven; configurable and flexible

Event Management
- Command and control
- Real-time data collection and integration
- Intelligence organization, display, and decision making tools
- Integration of organic and external expertise
- Connectivity of external command centres and capabilities
- Data recovery and long-term analysis

Program Management
- Program/Business centres
- Communication and coordination
- Program driven; configurable and flexible

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Canadian Integrated Outbreak Surveillance Centre (CIOSC)
Public Health Alerts

Alert Modules
- Enteric (launch Apr 2001)
- Respiratory (launch Dec 2004)
- Travel (launch Apr 2005)
- Zoonotic (launch Apr 2005)
- General* (launch Apr 2005)
- First Responder (proposed)

Other Federal Agencies
- Epi-X

Alert Modules
- Targeted alerting
- Role based
- Respect jurisdictional accountabilities
- Program driven
- Configurable & flexible
- Secure web-technology

First Responders
- FNIB health care professionals
- Custom Officers
- Others
- ER physicians
- General practitioners
- Military
- Law Enforcement
- Laboratorians
- Paramedics
- Veterinarians
- Social Workers
- Nurses

Provincial/Territorial Authorities

Phone
Fax
Email
PAGER

*General Alerts will accommodate disease areas not specifically addressed in other modules until program areas define disease specific user requirements
Laboratory Feature of CNPHI

PFGE tiff file

Patterns entered into Bionumerics and analyzed

Dendrogram created in Bionumerics

Each lab analyzes the image and replies to listserv:
Any pattern matches?
Any known sources of infection?
What is known about the pattern?

Clusters identified
Is this a new pattern?
Is this a common pattern?

Patterns designated
How DNA fingerprinting* was used to identify and investigate the 2008 listeriosis outbreak, example:

<table>
<thead>
<tr>
<th>Source</th>
<th>Listeria DNA Fingerprint</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 3</td>
<td></td>
<td>not outbreak strain</td>
</tr>
<tr>
<td>Patient 4</td>
<td></td>
<td>not outbreak strain</td>
</tr>
<tr>
<td>Patient 5</td>
<td></td>
<td>outbreak strain</td>
</tr>
<tr>
<td>Food Product 1</td>
<td></td>
<td>outbreak strain</td>
</tr>
<tr>
<td>Food Product 2</td>
<td></td>
<td>outbreak strain</td>
</tr>
<tr>
<td>Patient 6</td>
<td></td>
<td>outbreak strain</td>
</tr>
<tr>
<td>Patient 7</td>
<td></td>
<td>not outbreak strain</td>
</tr>
<tr>
<td>Patient 8</td>
<td></td>
<td>not outbreak strain</td>
</tr>
<tr>
<td>Patient 9</td>
<td></td>
<td>not outbreak strain</td>
</tr>
<tr>
<td>Food Product 3</td>
<td></td>
<td>not outbreak strain</td>
</tr>
<tr>
<td>Patient 10</td>
<td></td>
<td>not outbreak strain</td>
</tr>
</tbody>
</table>

* Pulsed-field gel electrophoresis (PFGE)
Listeria monocytogenes DNA fingerprints analyzed by the National Microbiology Laboratory (NML), June – October, 2008

Includes all human, food, and environmental samples from the 2008 national Listerialis outbreak investigation.

Outbreak strain
LMACI.0040/LMAAI.0003
Outbreak strain
LMACI.0040/LMAAI.0001
Outbreak strain
LMACI.0001/LMAAI.0001
NOT Outbreak strain

Listeria monocytogenes DNA fingerprints analyzed by the National Microbiology Laboratory (NML), June – October, 2008

Includes all human, food, and environmental samples from the 2008 national Listerialis outbreak investigation.
Innovation 2:
Rapid Containment - Sending the Lab to the Specimen!
Microbiologic Emergency Response Teams

- use of portable CL3 units to create safe work environment
- isolator for basic microbiology
- isolator for specialized techniques
- equipment needed to perform testing
Arrival In Uige

Mobile Laboratory Equipment

Uige Airfield
Second team to new location → breakdown lab and transport, second team sets up again.
High Containment in the Bush
Perfectly Functional Laboratory
Innovation 3:

Using Viruses to Fight Viruses!
### Viral Hemorrhagic Fevers

#### Scary Viruses!
- Ebola
- Marburg
- Lassa
- CCHF
- Machupo

#### Why Feared?
- Zoonotic
- Mortality as high as 80%
- No treatment, no vaccines
- “A list” of bioterrorism threats
Ebola Vaccine Development

- Uses a Vesicular Stomatitis Virus to fool the immune system into thinking it’s Ebola.
- Effective in non-human primates, seemingly proved effective for human use in West Africa
Non-human primates

Immune Parameters Correlate with Protection Against Ebola Virus Infection in Rodents and Nonhuman Primates
Gary Wong et al.
Sci Transl Med 4, 158ra146 (2012);
DOI: 10.1126/scitranslmed.3004582

Protecting Against the Zombie Apocalypse
A not so brief history of VSV-EBOV

Ebola vaccine developed in Winnipeg is headed for Africa
Canada is donating 800 to 1,000 doses of the vaccine, which was developed at the National Microbiology Laboratory

Ebola vaccine efficacy trial ready to launch in Guinea
Joint news release WHO/MSF/NIPH

5 MARCH 2015 | GENEVA - Based on promising data from initial clinical trials in late 2014, WHO with the Health Ministry of Guinea, Médecins Sans Frontières (MSF), Epicentre and The Norwegian Institute of Public Health (NIPH), will launch a Phase III trial in Guinea on 7 March to test the VSV-EBOV vaccine for efficacy and effectiveness to prevent Ebola. The vaccine was developed by the Public Health Agency of Canada. A second vaccine will be tested in a sequential study, as supply becomes available.
A humble history of VSV-EBOV

Ebola virus disease

Learn about Ebola virus disease, its causes, symptoms, risks, treatment and prevention. Also find information on surveillance and guidance for health professionals.
Emergency vaccination

A. Ring vaccination

B. Post-exposure vaccination

http://www.vaccineinformation.org/rabies/photos.asp
http://www.tabletsmanual.com/wiki/read/human_rabies
Phase III vaccine trials

- **VSV-EBOV**
  - NewLink Genetics & Merck Vaccines
  - USA
  - Phase I by WHO & MoH Guinea in Conakry, Guinea
  - Spring 2015 – ring vaccination trial design

- **ChAd3-ZEBOV & VSV-EBOV**
  - GlaxoSmithKline & Public Health Agency of Canada
  - Phase III by US NIH & MoH Liberia in Monrovia, Liberia
  - Spring 2015 – randomized control trial design

- **VSV-EBOV**
  - NewLink Genetics & Merck Vaccines
  - Phase III
  - By US CDC & MoH Sierra Leone in Freetown, Sierra Leone
  - Spring 2015 – unblinded trial design

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**Concerns and future development**

- Adverse effects: higher attenuated vectors
- Durability: study and improve long lasting immunity
- Livestock pathogen: study impact on livestock and wildlife species
Acknowledgements

- Government of Guinea
- Government of Sierra Leone
- Pierre Formenty (WHO)
- Laurent Kaiser (HUG)
- Heinz Feldmann (NIAID)
- Dr. Jimmy, Prof Muyembe, Dr. Kebela (DRC)
- Special Pathogens (Winnipeg)

National Institute of Allergy and Infectious Diseases

U.S. Army Medical Department
U.S. ARMY MEDICAL RESEARCH INSTITUTE OF INFECTIOUS DISEASES
These Vaccines Could Help Save the Great Apes
Innovation 4: Monoclonal Treatment For Ebola Virus Infection!
Therapeutic options

- Coagulation regulators (e.g. MAPc2)
- Convalescent plasma
- Monoclonal antibodies (e.g. ZMapp)
- PMOs, siRNA
- Small drug molecules (e.g. BCX4430, T705)
- Interferons
Binding sites of mAbs

1H3
Escape mutation

2G4, 4G7
Escape mutation

1H3
aa 1 33

4G7 2G4

501 508 651 671 676

NH2-
sp
sGP

1H3

274

TM

-GOOG
• ZMapp in Sierra Leone; Dr. Khan.
• ZMapp in Liberia; Jimmy.
• Zmapp versus Zmab and sleep deprivation.
• Compassionate use in emergencies and the law.
• What do we need to believe.
Antibody Therapy

• The initial use of antibodies (in the form of serum containing polyclonal antibodies) to treat infectious diseases can be dated back to the late 19th century.

• Prior to the availability of antibiotics and most vaccines, immune serum containing high titered polyclonal antibodies was the only and most effective way to prevent a variety of viral infections: Measles, hepatitis A, rabies, smallpox, diphtheria, tetanus, botulism as well as pneumococcal and Haemophilus influenzae B infections.

• Antibody therapy was essentially sidelined in the late 1930s with the discovery of antibiotics.


• Russia got the world’s first communist government, lead by Lenin.
• US declares war on Germany, Jerusalem falls to Britain

• NHL forms with Montreal Canadiens, Montreal Maroons, Toronto Arenas, Ottawa Senators & Quebec Bulldogs. 1st NHL championship game ever played, Toronto Arenas beats Montreal Canadiens 7-3 in 1st of 2 game set.

• Secret Service extends protection of president to his family
The introduction of hybridoma technology in 1975 made possible the generation of one antibody or monoclonal antibody (mAb) produced from one B-cell clone, specific for one antigenic epitope.

The technique was initially developed in mice and later mAbs were partially or fully humanized.

There are currently around 350 mAbs in clinical development, with most in early developmental stages.

The majority (~90%) of these mAbs target antigens relevant either to cancer or inflammatory or immunological disorders.
Innovation 5:

Using High Throughput Machines To Understand Genetics

H1N1
Mexican Health Officials Request Assistance from NML

April 17

Dear Dr. Plummer:

I hope this mail will find you very well. I am bothered by you to comment on a situation regarding some confirmed and probable cases of influenza with rapid evolution to interstitial pneumonia requiring mechanical ventilation that we are having in México right now. I would appreciate any comment and help for other possible diagnoses.

The attack rate among health workers seems to be higher than normal. We do not have the entire picture because under notification is still a problem in México.

So far I can tell you we have seen a late peak in March and April of probable influenza and confirmed cases, mostly adults 17-45 years old (we do have vaccination programs for 65 years old and small children). We detected several outbreaks in three different states with fatalities, in the last two months. One of these outbreaks, in Tlaxcala, central part of Mexico, with almost 60 probable cases and we confirmed 35 of them with both A and B influenza virus. Other outbreak in a small town in Veracruz (gulf coast) with a clinical picture “influenza like” with an attack rate of 30%, almost 400 probable cases, no fatalities, but we only confirmed influenza in 4 (three A and one B, un SRV, 3 Parainfluenza and 2 adenovirus). The most of the samples is late after 5 days then we lost sensitivity. However since the last 2 weeks one of the biggest National Institutes of Health in México (NIH), National Institute of Respiratory Diseases (INER) reported us Tuesday almost 50 cases of Probable influenza with 10 cases of severe pneumonia, 2 death in small children and 1 physician (transferred from another hospital), only 5 of these cases were positive for influenza using a commercial real time PCR kit at the clinical lab in the hospital. We confirmed 3 of these cases (two of the deaths), unfortunately the other 2 were secondary samples 2 or 3 days later in patients already receiving Oseltamivir and they were negative for us. These virus were 2 influenza A (H1N1) and 1.5. The physician death was 59 years old and of his daughters had the same clinical manifestation with pneumonia, both of Down syndrome one of them died a week before and the other one is hospitalized recovering. In these cases they have a high attack rate within hospital workers, physicians and nurses mainly, not severe pneumonia in them only severe myalgias, arthralgias, fever, and so on. The physician is one of the positive for influenza A at the hospital clinical lab but negative for us.

The personnel concern allowed us to find this and we started our investigation. Other big NIH Hospital reported 2 cases with rapid evolution with severe pneumonia with the requirement of mechanical ventilation and one is an Anesthesiologist of that hospital. The confirmed Influenza in the “Outpatient” but the fellow was negative, both of them receive immediately oseltamivir and they are recovering now. Oaxaca state reported a 37 years old diabetic woman with the same clinical picture with rapid evolution to severe pneumonia and she died after 4 days of hospitalization no more cases are reported, no outbreak of respiratory diseases in the area. I got bronchoscopy fluid, nasopharyngeal swab, serum, lung and liver biopsy of this death patient. Autopsy was not authorized by the family. So far all the samples including lung tissues are negative for influenza, parainfluenza type 3-5, adenovirus, pneumovirus, coronavirus, Hepatitis in serum, etc. However in a private clinical laboratory in Oaxaca they ran some bronchoscopy swab and the report was positive for coronavirus. We have tested this twice in two different places here in Mexico city and they are negative for coronavirus. Today we detected that there is another fellow hospitalized in a City near Mexico City with severe pneumonia and mechanical ventilation, they never notified and we do not have samples. In the central part of Mexico San Luis Potosí a Private ED physician called us to say he received 30 cases of severe respiratory diseases 3 of them with severe pneumonia previously healthy and one death, we checked in the area and we found one severe pneumonia case in another hospital and the antecedent of another one death all of them are between 19 and 47 years old. They will send me autopsy tissues of one of the deaths and biopsy and samples of the other one by Monday.

All the cases are interstitial pneumonia, no hemorrhagic data, some of them with shock in the beginning. Laboratory suggesting viral diseases, some of them with longer hospitalization suggest bacterial infection added.

In addition to this, I can tell you that influenza surveillance is improving in México, is limited, but so far in this season we have tested a little bit above 4000 probable cases and we confirmed 315, 37% B (increased amount in comparison to last season and before, less than 35%) and even we have not subtype all the A isolations the most of them are H3N2 and H1N1 including those from Tlaxcala outbreak and the recent 2 A isolations from INER.

After all the analysis we consider we have a late peak of influenza season with more severe presentation because of the confirmation in some of the cases and they are not confined to specific areas but there are association among some of these cases, we are concern regarding the health care workers attack rate, but we found no matter vaccination for them is free the vaccination coverage in them is only 20-40%, we are using late vaccination now to improve coverage in health care workers, we reinforced all precaution measurements including high efficiency mask for health care workers in dose contact with probable cases in hospitals and health promotion regarding respiratory diseases campaign for public, in general we did a press conference today without panic pointing these issues.

I would really appreciate any comment about this situation and advice for more diagnosis and if it is possible to send some of the tissues or samples to NML.

Best regards

Celia

Dire. Celia M. Alpuche Areana
Dirección General Adjunta
Instituto de Diagnóstico y Referencia Epidemiológicos (InDRE)
MX contacts NML requesting assistance for SRI cases

PHAC and CDC Senior Management discussions

NML Operations centre activated

Results indicate MX samples correlate to swine influenza

First Canadian cases of H1N1 human swine influenza confirmed

MX sends additional 200 samples & deploys 2 more scientists to MX

NML reports all results to MX

WHO: Alert Level 5

MERT deployed to MX

April
17 18 19 20 21 22 23 24 25 26 27 28 29 30
May
1 2 3

NML ships primers for H1N1 to Provincial labs

Provincial samples sent to NML

51 samples received from MX
Preliminary results show influenza A
P/T alerted to situation

2 cases in California

Trilateral (CAN-USA-MX)
C IOSC postings (MX SRI and CA swine flu)

CDC contacts PHAC to discuss human swine flu cases in California

NML receives 200 samples from MX

NML reports Results to MX
NML determines outbreak in Mexico is **H1N1 Influenza A** (human swine flu)
North America (A/Mexico/ 2009 [H1N1]), Influenza A virus, April 2009:
- Reassortment H1N1: An unusual mix of genetic sequences
- 4 unique virus sources

North American Human Origin
North American Swine Origin
Eurasian Swine Origin
North American Avian Origin
April 29

200 clinical samples

Mexico City direct to Winnipeg
Innovation 6: Using Systems Biology to Understand Infectious Disease

Solutions for the HIV Pandemic
# HIV Prevention With The Old Science

<table>
<thead>
<tr>
<th>Finding</th>
<th>Time Lag to General Acceptance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women were readily infected with HIV through sex</td>
<td>2 years</td>
</tr>
<tr>
<td>Other STD promote HIV transmission</td>
<td>5 years</td>
</tr>
<tr>
<td>Breast feeding is a major route of mother to child HIV transmission</td>
<td>5 years</td>
</tr>
<tr>
<td>Male circumcision reduces HIV susceptibility</td>
<td>19 years</td>
</tr>
<tr>
<td>Hormonal contraception enhances susceptibility to HIV</td>
<td>?</td>
</tr>
<tr>
<td>Behavioural interventions targeted at “core groups” reduced HIV in the general population</td>
<td>?</td>
</tr>
</tbody>
</table>
Resistance to HIV-1 Infection

Highly-exposed persistently seronegative.

3 years follow, HIV-1 serology and PCR negative, Active in sex work.

10% of highly exposed sex workers resistant to HIV-1.

Decline in HIV-1 Incidence with follow up in the Pumwani Cohort.

Adapted from Fowke et al Lancet 1996; 348: 1347–51
Gene expression profiling in HIV Resistant Women

CD4 T cells

Whole Blood

Affy Pval < 0.01 and FC > 1.5

Res
Negs

Low
Neutral
High
Conclusion

- Microbial threats are growing and ever changing
- The National Microbiology Laboratory has become a key global institution in innovation for response to emerging infectious diseases.
- The importance and achievements of the National Microbiology Laboratory are relatively unknown by Canadians.
Next Steps

• In general existing bioinformatics has yielded limited insights into the basis for resistance to HIV infection and other complex data problems.

• In collaboration with a machine learning company we are exploring the utility of artificial intelligence for understanding these kinds of complex data.