Public Health Laboratories Research: Success and Strategies

From the Perspective of the City of Milwaukee Health Department Laboratory

Sanjib Bhattacharyya, PhD
Deputy Laboratory Director

Adjunct Faculty- UW- Milwaukee
ZSPH & Biomedical Science

Think Health. Act Now! • CITY OF MILWAUKEE HEALTH DEPARTMENT • www.milwaukee.gov/Health
Content in this presentation may not be duplicated, copied, or reproduced without permission.

APHL Annual Meeting- 2014
Outlines

* MHD Laboratory-at-a-glance
* Research Areas and Institutional Positions
* Community Engagements and Systems Partnerships
* Success and Challenges in PHL Research
* Future Directions
City of Milwaukee Health Department

City - 7,200 :: ~$1B

MHD – 275 :: ~$15M (1/2 grant)

MHD Lab :: ~$3M (1/4 grant)

MHD Divisions

- Disease Control & Environmental Health
- Family & Community Health
- Laboratory

3-Health Centers- STD Clinic Laboratory
### Disease Control and Environmental Health

#### Home Environmental Health
- Lead, Asthma, Injury Prevention

#### Consumer Environmental Health
- Food Inspections *(Food Safety & Security)*
- Weights and Measures
- Tattoo and Body Piercing Inspections

#### Communicable Disease & Emergency Preparedness
- Communicable Disease Surveillance and Control
- Milwaukee County CD Statistics *(SurvNet)*
- Immunization Programs
- Emergency Preparedness and Response

#### Community Environmental Health and Safety
- Air Quality
- Animal Health
- Hazardous/Toxic Materials *(Ozone, pesticides, tobacco, etc.)*
- Water Quality *(Potable/Recreational)*

#### HIV, STD, and Tuberculosis Prevention
- Tuberculosis Surveillance, Clinic and Control
- Refugee Health Screening
- STD & HIV Clinic Services
MHDL History - Legacy of PH Research
Est. 1872

The Early Years .......

Milk Testing - 1910

Dr. Henry Wisniewski
Chief Virologist & Lab Director (1952-1988)

1953- Diagnostic Virus lab

1955- Polio Foundation supported research on Polio vaccine

1955- NIH-supported Rickettsial Disease Research

1955- NIH-supported Polio vaccine work

1956- NIH-supported Q-Fever research

1958- Nobel Laureate Dr. Albert Sabin visited MHD-Polio vaccine work
City of Milwaukee Health Department

Today’s Public Heath Laboratory

~ 100,000 tests/year

- 13,000 sq. ft.
- Totally rebuilt 1957 → 2000
- Dedicated one pass air: HEPA-in
- Dedicated exhaust: HEPA-out
- TB-designed BSL-3 Lab
  - Renovated 2003: added BSC/room
- STD Clinic Lab offsite (2 MLTs)
City of Milwaukee
Public Health Laboratory Strength

23 Staff

18 Scientists

- Laboratory Director
- Deputy Laboratory Director
- Laboratory Operations Manager

Clinical & Environmental Microbiology (BSL-3 facility)

- 5 Microbiologists
- 2 MLTs (STD Clinic Lab)

Virology, Chemistry & Molecular Science

- 5 Chemists
- 3 Virologists

1 LIS Coordinator
1 Lab Support Staff

2 Office Staff
1 Custodian
### MHD Laboratory Programs

#### Sexually Transmitted Disease
- Resistance surveillance: NAAT, GS-AST-CDC

#### Foodborne Disease

#### Emergency Preparedness

#### Molecular diagnostics
- Real-time PCR (Bacterial and viral pathogens)
- Luminex (Respiratory virus surveillance; enteric pathogens)
- Molecular sequencing- Sanger & Pyroseq (ref. bacteria and fungus ID, TB, anti-viral resistance)

#### Communicable Disease
- Microbiology: Ref- Clinical, Env. & TB
- Virology: culture, NAAT & serology
- Surveillance programs: CDC, Wisc., WHO

#### Waterborne Pathogens
- Cryptosporidium/Giardia/ Culturable Viruses- EPA

#### Water Quality – Recreational and Potable- Colilert, qPCR

#### Chemistry- Analytical and Clinical
- Env. & Blood lead, Heavy metals, Asbestos, Household allergens- ELISA, MARIA
- AA’s, GC/LC-MS- VOC/SVOC/Env. tox
Outlines

* MHD Laboratory - at-a-glance
* Research Areas and Institutional Positions
* Community Engagements and Systems Partnerships
* Success and Challenges in PHL Research
* Future Directions
PH Research Projects
APHL Priority Areas

* Infectious Disease Detection and Technology Development
* Genetics & Newborn Screening
* Communicable Disease and Epidemiology
* Chronic Disease Detection and Prevention
* Health Research and Policy Development
* Primary care and Outcome-based Research
* Community Health
* Laboratory Information Systems and innovation in IT
MHD Supports to PH Research

MHD perspectives
• PH Surveillance and Preparedness Support
• Diagnostic Development- Program support & Revenue generation
• Academic Health Department- Partnership Grants & Publications
• Research committee- IRB (human subject research) & IBC (general bio-safety and recombinant DNA work)

Resources
• Leadership supports and promotes research- basic, applied & translational
• Funding availability- operations budget, grants & collaborations
• Qualified staff and state-of-the-art technology platforms
Outlines

- MHD Laboratory- at-a-glance
- Research Areas and Institutional Positions
- Community Engagements and Systems Partnerships
- Success and Challenges in PHL Research
- Future Directions
L-SIP actions have focused on responding to system gaps in Workforce Development and Research:

• Convened the Milwaukee Laboratory Advisory Committee (MLAC) to guide strategic planning efforts
• Selected Community Co-Chairs and Subject Matter Experts
  • Research sub-committee – Clinical & Environmental Health (areas of basic, applied and translational)
**PHL Research Improvement Strategies**

*An Innovative System’s Approach*

- **Diverse group of partners**
  - Diversity in research areas & innovations
  - Expanded research capabilities, themes, and collaborations

- **Identify laboratory systems research need & priorities**

- **Create an LPHL system research inventory**
  - Current research
    - Research methods (e.g., chemical, biological, microbial, engineering), biological systems, modeling, and surveillance
  - Research interests
    - Linking to other disciplines (outreach & interdisciplinary)- microbiology, genomic, molecular biology, environmental-toxicology and immunology
  - Resources
    - Models/centers of excellence, databases, specimen/sample repositories, instrumentation, students/interns and support staff
Research and Academic Partners

* CDC- Influenza, Picornavirus, STD and DPDx laboratories
* Environment Protection Agency (EPA)
  * Potable, Recreational water (E. coli, Crypto/Giardia) & waterborne viruses, env. toxins
* Department of Natural Resources (DNR)
  * Beach monitoring (in partnership with EPA and UW-Milwaukee School of PH)
* Milwaukee Medical Examiners- Infant death related
* Medical College WI (MCW)- CTSI, HWPP; Children's Hospital of WI (CHW)
* Milwaukee Water Works (MWW)
* WI State Lab and Racine Health Department
* Blood Center of WI, FDA and NIH-
  * Influenza Immunology (donor population) and herd immunity
* Tufts University, MA- InForMID- Influenza Seasonality
* UW-Milwaukee: School of PH; Biomedical Science; School of Freshwater Science-Milwaukee Water Council- Env. monitoring
* Biotech industry (Luminex, Cepheid, Life Tech; Hologic- GenProbe; Longhorn vaccine)- NGS
* Milwaukee School of Engineering- BioE, and Bio-Modeling (SMART program)
* Concordia University if WI (CUW)- TB MIC, adverse birth, nanotechnology (with UWM)
* University of Lagos, Nigeria (with UWM- Biomedical Science)- E. coli & AST
Diversity in Partnerships and Areas of Multidisciplinary Research

BASIC
- BCW
- FDA
- CUW

Global Health
MDR TB
Univ. Lagos
E. coli AST

Policy Research
- Community Partners
- Genomic education

MHD Research Diversity

APPLIED
- Industry
- MSOE
- EPA
- UWM

TRANSITIONAL
CTSI, MCW
Tufts, HWPP

Innovative
- NGS
- Nanotech Environ.
Technology Advancement

- Evaluation of new platforms/technology
  MHD lab uses and evaluates new instruments and provide input on the next generation of products

- Training on new technology
  ◦ Develop joint training courses (bio-safety)
  ◦ Provide opportunities for Corporate members to learn about PH preparedness and response capabilities at MHD/L

- Work together with partners for understanding the testing priorities (e.g. Clinicians, Epidemiologists, Law Enforcement, FBI-BioWatch, H1N1 and PH emergency)
1. **Community involvement** in PH research practice
2. **Communities feedback** in practice and priority of research topic
3. **Engage community partners** at different stages of research
4. **Celebrate community-PH research success-visibility** by community members and leaders
Outlines

* MHD Laboratory- at-a-glance
* Research Areas and Institutional Positions
* Community Engagements and Systems Partnerships
* Success and Challenges in PHL Research
* Future Directions
Anti-picornaviral drugs not available, but early reporting of confirmed cases using molecular approach can help build the case for need
SIDS in Wisconsin: 1987-2004

- Autopsies in 1263 unexplained deaths of children ≤ 2 y
  - Median age, 2-3 mo
  - Virus isolates in 445 cases
    - 40% Enterovirus
    - 22% Adenovirus
    - 20% Rotavirus
    - 5% CMV
    - 5% Parechovirus
    - 2% Rhinovirus
    - Others: HSV, RSV, flu, HPIV, reovirus

- Specimens: NP swab, colon swab, lung tissue from all; some others
  - 47% picornavirus (+)


Think Health. Act Now! • CITY OF MILWAUKEE HEALTH DEPARTMENT • www.milwaukee.gov/Health

Content in this presentation may not be duplicated, copied, or reproduced without permission.
Multi-lab, Multi-jurisdictions
EPA Validation Study of Rapid Method “qPCR”
Water Quality - Milwaukee Beaches

Real Time PCR vs. Culture Based Fecal Indicator Bacteria Measurements
to Determine Beach Water Quality

Pathogens too diluted & varied to measure at beach. Indicator bacteria still measurable.

Enterococci:

Content in this presentation may not be duplicated, copied, or reproduced without permission.
Spotlight on Member Research

Milwaukee Lab Investigates Beach Water:

Same-Day Direct Detection and Quantification of *Escherichia coli* from Recreational Water by Rapid Quantitative Polymerase Chain Reaction Assay at the City of Milwaukee Health Department Laboratory

By Sanjib Bhattacharyya, PhD, Chief Molecular Scientist; Manjeet Khubbar, MS, Microbiologist III; Valdis Kalve, MS, Microbiologist II; Steve Gradus, PhD, D(ABMM), Laboratory Director, City of Milwaukee Health Department Laboratory

polymerase chain reaction (qPCR) assays might allow faster public health actions. This article highlights the results.

As per the Beaches Environmental Assessment and Coastal Health Act of 2000 and Section 303(a) of the Clean Water Act, MHD adopted EPA water quality criteria and standards to issue public notifications on recreational water quality within 24 hours of water sampling using Colilert. The Beach Protection Act of 2008 now allows EPA-approved labs to use a rapid-testing method.

MHDL staff Valdis Kalve filtering beach water samples.

---

Bridges
Connecting the Nation’s Environmental Laboratories

Issue 8: Summer 2011

Think Health. Act Now! • CITY OF MILWAUKEE HEALTH DEPARTMENT • www.milwaukee.gov/Health

Content in this presentation may not be duplicated, copied, or reproduced without permission.
Research Partnership with EPA (since 2006)

Same-day Beach Closure Decisions Using Real-time Quantitative PCR Assay: Detection of E. coli in Milwaukee Area Beaches

Sanjib Bhattacharyya, Manjeet Khubbar, Valdis Kave, Terri Linder, Anupa Gandhi, Steve Gradus

City of Milwaukee Health Department Laboratory, Disease Control and Environmental Health, Milwaukee, Wisconsin

Abstract

Objective: To evaluate the real-time quantitative PCR (qPCR) assay as a practical, low-cost, portable alternative to traditional culture methods for rapid detection of pathogenic bacteria in raw and treated water.

Study Design: qPCR analysis was conducted on water samples collected from 16 beach areas in Milwaukee County, WI. Water samples were collected at 48 beach locations, and the samples were analyzed for E. coli using qPCR.

Results: The qPCR assay was able to detect E. coli in all samples, and the results were comparable to those obtained using traditional culture methods. The qPCR assay was able to detect E. coli in samples collected from 48 beach locations, and the results were comparable to those obtained using traditional culture methods. The qPCR assay was able to detect E. coli in samples collected from 48 beach locations, and the results were comparable to those obtained using traditional culture methods. The qPCR assay was able to detect E. coli in samples collected from 48 beach locations, and the results were comparable to those obtained using traditional culture methods.

Conclusions: The qPCR assay is a rapid and sensitive method for detecting E. coli in raw and treated water and can be used as a practical alternative to traditional culture methods for rapid detection of pathogenic bacteria in raw and treated water.
Control of Influenza Virus by Immunity

NIH-funded study with BCW, Tufts Univ. & FDA

♦ High rate of natural variation due to mutations, reassortment

♦ Current vaccine system: world-wide surveillance, strain predictions
  ♦ Strain-matched vaccine lacking when predictions are wrong, or a pandemic emerges-
    Takes about 6 months to make available

● Can that public health gap be filled?
● Association with seasonality
● Universal influenza vaccines: based on cross-protection
  ■ For cross-protective vaccines, immune response (antibody, T cell) to conserved
    antigens, not HAI, might provide correlates

Individual Blood Donor Responses to Antigens

Reflections to the Herd Immunity?


Milwaukee Healthy Homes Program
Developed Indoor Allergen Testing Capability
- Partner with Indoor Biotech- ELISA, MARIA

Started: Oct 2003:

Funded by HUD
April 2009 – 2012

PURPOSE:
reduce indoor asthma triggers
improve asthma control

PARTNERS:
Dominican Center For Women,
Children’s Hospital of Wisconsin, Fight Asthma Milwaukee

Outcomes:
Routine monitoring of allergen concentration along with nurse case management and home environmental intervention

• decreases the dust load,
• reduces children’s exposure to allergens

Manuscript under prep. J. Asthma
Technology Development:
Multiplexing Approaches for Microbial Identification & Real-time Disease Surveillance

1. Respiratory Virus Surveillance
2. Gastric pathogens (bacteria, virus and parasites)
3. Salmonella serotyping
4. Fungal identification (in progress)

Partners:
- Luminex Corporation, Canada; and Austin, TX
- Eragen Bioscience, Madison, WI
- Le Boehner Hospital, TN


Clinical Relevance of MOTT and MDR TB

Average annual prevalence of non-AIDS pulmonary non-tuberculous mycobacteria–associated hospitalizations by age group, sex and corresponding MDR TB ID

| Project Title: Growing Healthy Soil for Healthy Communities |
| HWPP Project #: 2013I-06 |
| Award Amount: $749,999 |
| Start Date: 1/1/2014 |
| End Date: 12/31/2018 |

| Project title: Science Awareness Genomics & Ethics- Building SAGE Communities |
| Partners: MCW-HWPP, MSOE, Community Partners |
Addressing Global Health
Expanding the PHL Research

* Characterization, Antimicrobial Resistance and Molecular Profiling of Clinical and Environmental *E. coli* Isolated from Lagos, Nigeria and Milwaukee, WI (PhD student from Univ. of Lagos- with UW-Milwaukee)


* Responses to Global Multi-drug Resistance TB- Use of Next-Generation Sequencing for Identifying Pyrazinamide Resistance in *M. tuberculosis* (with Longhorn Vaccines, TX; Univ. of Pretoria, & South African Medical Research Council, South Africa)

Challenges in PHL Research

Potential Roadblocks

1. Leadership buying
   - Perception
   - Legal issues- sharing clinical materials, safety and patient confidentiality

2. Admin support
   - Justifying the need
   - Research areas

3. Sustained funding
   - Limited operations cost
   - Challenges in obtaining grant

4. Personnel
   - Staff Vs. Researcher
   - Motivation & expertise

5. PH routine response & emergencies
   - How do you manage and sustain the demands of day-to-day service and surges while also continuing research projects?
Outlines

* MHD Laboratory- at-a-glance
* Research Areas and Institutional Positions
* Community Engagements and Systems Partnerships
* Success and Challenges in PHL Research
* Future Directions
Potential Research Areas

...but not limited too...

* Nanotechnology- Impact of Human and Environmental Health-
  * TEM study to analyze the nanoparticle in water (with UW-Milwaukee)
  * Public health impact and understanding

* Microbiome approach- Complex matrix analysis for potential microbial impact on chronic diseases- Use of NGS for WGS
  * Fecal transplant and biome analysis- pathogen ID & interactions
  * Impact of pathogen load in gut microbiota & obesity
  * WGS for MDR- TB, MRSA (mechanism of resistance during photo-therpy)

* Environmental Health Genomics- New Paradigm to address children’s environmental health- NIEHS priority areas

* Immune Protection in HIV Disease- Partner with UW-Milwaukee and University of South Africa

* Genomic and Society- Community understanding of genomic application-
  Scientific citizen and Citizen Scientists- Partner with MCW, CTSI and HWPP

Nature, 2014
Quality Control and Critical Workforce for PHL Research

1. Adhere to the LEAN and Quality Control Practices
2. Workforce development- students, interns and faculty development
3. Partnership with industry, academic- explore non-traditional partners
4. Sustained funding
5. Publication, seminars

Students & Workforce Development

Collaborations for Applied Research: Developing Public Health Tools

ASQ – LEAN Tools
Characterization of Multi-drug Resistant Mycobacterium tuberculosis
from Immigrants Residing in the United States using Next Generation Sequencing

L. Daum, G. Fischer. Longhorn Vaccines & Diagnostics, San Antonio, TX
S. Bhattacharyya, M. Khubbay, J. Sromek, P. Hunter, S. Gradus: City of Milwaukee Health Department Laboratory, Milwaukee, WI

Abstract

Objective: Drug-resistant Mycobacterium tuberculosis (MTB) is spreading worldwide. While this global threat is real, there is a growing belief that MTB cases are from foreign-born persons currently residing in the United States. The use of next generation sequencing (NGS) can be a powerful tool to identify new drug-resistant strains and potentially provide a more meaningful characterization of drug-susceptible strains.

Study Design: The City of Milwaukee Health Department's Laboratory studied the MTB-reactive strains from foreign-born, testing and/or immigrating residents in Milwaukee. We ran hormone manipulate sequencing and applied 72 isolates on the Illumina MiSeq platform, identifying 53 in silico-confirmed drug-resistant MTB strains.

Results: Genotypic characterization was used. Full-length nucleotide and protein sequences were used to establish drug-resistance mechanisms. MDR (multi-drug resistant) MTB were identified in 53 of the 72 isolates. Genotypic sequencing was consistent with phenotypic testing, allowing for rapid identification of resistance profiles.

Conclusions: Our study demonstrated that NGS was an efficient method for detecting drug-resistant MTB in foreign-born residents.

Introduction

Increasing rates of multidrug-resistant (MDR) and extensively drug-resistant (XDR) MTB cases are a threat to public health. The World Health Organization (WHO) has estimated that 450,000 new MTB cases are drug-resistant, with 30,000 having XDR-MTB, globally. The United States has seen an increase in drug-resistant MTB strains, with the Centers for Disease Control and Prevention (CDC) reporting a 5% increase in the number of cases in the last decade.

Methods

MDR and XDR MTB strains were tested at the University of Wisconsin-Madison. Real-time polymerase chain reaction (PCR) was used to detect MDR strains. Next generation sequencing (NGS) was used for genotypic resistance testing, which allowed for the identification of resistance mechanisms.

Results

PCR was performed using standard protocols. Full-length nucleotide and protein sequences were used to establish drug-resistance mechanisms. NGS was consistent with phenotypic testing, allowing for rapid identification of resistance profiles.

Conclusions

Our study demonstrated that NGS was an efficient method for detecting drug-resistant MTB in foreign-born residents.
Thank You
www.milwaukee.gov/healthlab

Contact:
Sanjib Bhattacharyya, PhD
Tel: 414.286.5702
sbhatt@milwaukee.gov