Culture–Independent Diagnostics Forum

Charting a Path for Public Health

Meeting Summary

April 25 - April 26, 2012

Atlanta, Georgia

Marriott Atlanta
Buckhead Hotel and
Conference Center
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**Introduction**

The U.S. Centers for Disease Control and Prevention (CDC), the Association of Public Health Laboratories (APHL), and the Council of State and Territorial Epidemiologists (CSTE), organized an expert consultation on culture-independent diagnostic testing titled, “Culture-Independent Diagnostics Forum: Charting a Path for Public Health.” The two-day meeting was held April 25-26, 2012, in Atlanta, Georgia and was partially supported by the Marler Clark law firm.

The purpose of the Forum was to assemble subject matter experts representing various fields, industries, and agencies to discuss the complex issues involved with the increasing use of culture independent methods in clinical diagnostic laboratories. The two-day participatory meeting involved panel sessions and breakout sessions where participants presented, discussed, and brainstormed potential solutions to address the anticipated impacts culture independent clinical diagnostics will have on surveillance activities.

The focus of the meeting was on bacterial enteric (primarily foodborne) diseases and the challenges posed by the emergence of culture-independent methods and the anticipated impacts on public health surveillance programs. However, discussions also included similar surveillance issues that other areas of infectious disease (e.g. sexually transmitted diseases) have experienced or will experience in the future because of shifts in test technology.

The background for the organization of the meeting included the following:

- Surveillance of infectious diseases is an integral part of prevention and control programs.
- In the area of foodborne disease, programs such as PulseNet, FoodNet, OutbreakNet, FoodCORE, and NARMS have become essential components of our national food safety system.
- These surveillance systems are largely “isolate-based” systems, i.e. systems that depend on physicians ordering diagnostic tests that result in a bacterial isolate for definitive identification. This isolate is shipped to a public health laboratory for confirmatory testing and molecular subtyping.
- A new generation of clinical laboratory diagnostic tests is now entering the marketplace. These tests offer physicians faster results and in some cases provide more types of information than previously available (although in other cases less). Unfortunately, unlike culture, these new tests do not result in bacterial isolates being available for public health activities; in some cases, the tests are incompatible with culture. In addition, the new tests have widely varying performance characteristics.
- Lack of isolates will make public health follow-up problematic using current technology.
There are many potential strategies for addressing the issue of culture-independent diagnostics in a manner that supports both clinical diagnosis and public health needs. Each strategy has potential risk, varying benefits, and associated costs.

The meeting had five specific focus areas:

1) Regulatory requirements, test licensure, and reimbursement
2) Clinical practice guidelines
3) Laboratory methodologies
4) New technological approaches
5) Research funding and partnership opportunities

The meeting agenda may be found in Appendix A. Three-hundred sixty-one participants, including nineteen presenters, attended the meeting. The complete participant list is available as Appendix B.

Dr. Rima Khabbaz, Deputy Director for the Centers for Disease Control and Prevention and Director of the Office of Infectious Diseases (CDC), welcomed the meeting participants to kick-off the two-day Forum. Dr. John Besser, Deputy Chief of the Enteric Diseases Laboratory Branch (CDC), followed the Forum Welcome, providing an overview of the meeting.

Day 1 Proceedings

Dr. Rima Khabbaz, CDC: Welcome to the Forum

Dr. Khabbaz welcomed the participants and thanked the Forum sponsors, members of the planning committee, speakers, moderators, and attendees.

Dr. Khabbaz underscored the importance of the diversity of expertise among participants in coming together to bring awareness of culture-independent diagnostics issues and to provide effective strategies to overcome the public health challenges embedded in culture-independent diagnostics.

Robust surveillance systems, such as PulseNet, are the cornerstone of public health data and losing isolates used for surveillance compromises the ability to protect the nation’s health.

Dr. John Besser, CDC: Forum Overview

Dr. John Besser described the current landscape of culture-independent diagnostic testing and further defined the goals of the Forum: raise awareness, define the issues, generate ideas, stimulate applied research, start building consensus, and initiate post-meeting actions.
Bacterial culture has long been the standard for pathogen testing. As technology advances, new culture-independent methods are beginning to become the norm and represent a fundamental change and threat to current public health surveillance programs.

Although expensive, culture-independent tests are fast and require minimal infrastructure, expertise, and labor costs. However, the problems with non-culture tests include no present susceptibility data, specimens that are incompatible with culture, and concerns about false positives. Culture-independent diagnostics has the potential to improve patient management, but may cost the public health surveillance system important information gained from cultures.

Dr. Besser provided a history of public health surveillance of infectious diseases and the role it plays in disease prevention and patient management. Overviews of CDC’s surveillance system, PulseNet and investigations of various foodborne illness outbreaks, also were provided.

General strategies to address the impact culture-independent diagnostics have on public health surveillance were presented:
- Short-term: Preserve isolates
- Longer-term: Develop culture-independent pathogen characterization methods
- Very long-term: Paradigm shifting technologies

In order to identify and address the problems culture-independent diagnostics present, more work is needed; however, several activities are currently underway:
- The Culture-Independent Diagnostics Forum
- Workgroups (CDC, APHL, CSTE)
- CDC Genomics project
- FDA Genomics efforts
- DTRA/DOD/CDC Metagenomics project

Dr. Besser summarized that culture-independent diagnostics is a high probability, high impact issue. The risks of inaction and benefits of change are significant.

**Panel 1: Outbreak Detection and Investigation**

*Moderated by Dr. Rob Tauxe, CDC*

**Dr. Ian Williams, CDC: Foodborne Disease Outbreak Detection and Investigation Impacts**

Dr. Williams explained the changing landscape of foodborne diseases. More food is centrally produced and food trade occurs on a global scale; thus, the spectrum of food safety and foodborne disease outbreaks is important to consider broadly. In the past, foodborne illness outbreaks had numerous cases in a localized area; now, outbreak cases remain few but are spread over many jurisdictions. This change of
the nature of outbreak cases requires coordinated data collection from many states
to detect national outbreaks.

- PulseNet is the national molecular sub-typing network for foodborne disease
  surveillance. This system allows for better detection of multistate outbreaks as it
  allows analysis of historic data to determine “rare” or “common” cases as well as
  person, place, and time data. Additionally, PulseNet allows for real-time data on
  outbreak cases as they occur.

- In recent years, approximately 50,000 specimens annually have been uploaded to
  PulseNet. PulseNet adds specificity to case definitions and improves epidemiologic
  investigations by clarifying associations, thus increasing the opportunity to identify
  clusters and sub-types. By using PulseNet, 15 new food vehicles have been
  identified in U.S. multistate outbreaks since 2006. When resources are limited at
  state and local levels to conduct interviews as part of outbreak investigations,
  PulseNet provides cluster outbreak information to local partners.

- FoodCORE is a CDC program that aims to build capacity for laboratory surveillance,
  epidemiologic response, and environmental health assessment; develop
  collaborative surveillance and response programs; conduct rapid, coordinated,
  standardized investigations; and develop measurable performance indicators.
  FoodCORE operates in three core areas: laboratory surveillance, epidemiologic
  interviews and investigations, and environmental health.

**Dr. Joanne Bartkus, Minnesota Department of Health: Public Health
Impacts on Non-foodborne Diseases**

- Dr. Bartkus outlined the changing role in public health laboratories. Beyond
  traditional responsibilities of surveillance, reference, and response, public health
  laboratories are also providing routine diagnostic testing for pathogens of public
  health concern. Non-culture tests have variable levels of sensitivity and specificity
  and numerous types of tests are available. The limitations of diagnostic testing
  include issues such as false-negative/false-positive results, unknown virulence
  factors and antimicrobial susceptibility mechanisms, and an unmet need for
  archival strains for future research and method validation.

- In the example of gonorrhea testing, sentinel sites gather cultures from urethral
  and cervical swabs for surveillance purposes. However, as non-culture tests are
  being approved for many sample types, there is little incentive to continue urethral
  swabs. In legionella testing, recommended tests are urine antigen test as well as
  culture tests. Without clinical culture results, it is impossible to compare
  environmental culture results and thereby draw conclusions on a potential
  outbreak. Numerous “pseudo-outbreaks” have been documented as a result of
  determining an outbreak using non-culture test results rather than confirming with
  culture-based test results.

- Isolates allow for confirmatory testing on pathogens of public health importance.
  In the past five years, there has been enhanced surveillance of active bacterial core
pathogens and numerous isolates have been submitted to state-level public health agencies.

State public health laboratories have embraced molecular testing more than local public health laboratories. Ongoing challenges include decreased funding, evolving technology, workforce development, data privacy, informatics and bioinformatics, and health reform.

Dr. Dirk Werber, Robert Koch Institute: Toxin-based Surveillance of Shiga Toxin-producing E. coli Infection—The German Experience

Dr. Werber provided the German perspective on toxin-based surveillance of shiga toxin-producing E. coli (STEC). In Germany, STEC surveillance is comprised of case-based surveillance and electronically transmitted reports that include defined criteria. STEC and HUS have separate reporting categories. Many new methods of STEC detection use stool samples as test material. Serotypes have historically been identified; however, in the past couple of years serotypes have been missing because of the use of non-culture diagnostics. Most STEC outbreaks occurred in families and commonly occurred among kindergarten students.

Toxin-based surveillance provides useful epidemiological information irrespective of serogroup. Laboratory-based surveillance is currently neither timely nor complete with respect to serogroup. Complimentary surveillance of HUS is useful.

To enhance surveillance at the local level, toxin (gene)-based test procedures should simultaneously identify STEC and virulent serogroups.

Panel 1 Discussion

Dr. Werber and Dr. Bartkus, what are the greatest lessons learned from STEC regarding culture-independent diagnostics?

Dr. Werber and Dr. Bartkus provided insight on important lessons of STEC surveillance. Dr. Werber responded that more information is needed on non-culture methods. Reflux culture testing is also needed.

Dr. Bartkus added that the ability to get the specimens is necessary, whether or not the specimens can be cultured. Reimbursement for testing presents a challenge and test methods need to be standardized. Public health laboratories play a significant role in surveillance.

Dr. Werber, beyond the localized outbreaks seen in families and childcare centers, are there additional STEC outbreaks that could have been missed due to lack of sub-typing?

Dr. Werber explained that outbreak data could be missing due to a lack of sub-typing and since testing diarrhea is not common. A more systematic way of collecting data would be beneficial.
Dr. Williams, what is the public risk of not having sub-typing abilities for outbreak investigations and risk-based surveillance?

- Dr. Williams explained that sub-typing abilities are critical to identifying holes in the food safety system that could facilitate long-term disease patterns. Surveillance data is not only important to initiate food recalls but to identify gaps in processes. PulseNet and isolate-based detection helps with outbreak investigations.

Dr. Bartkus, how will the workforce be developed to address the changing landscape of diagnostics?

- Dr. Bartkus responded that public health laboratories and clinical laboratories are dealing with challenges regarding their ability to perform culture testing, and culture testing is not always financially supported. As funding decreases, public health laboratories stop doing culture testing.
- The current lab workforce is retiring and there is a need to maintain and develop a workforce who is knowledgeable about bioinformatics and microbiology. The workforce needs to retain the knowledge and skills to perform culture-testing as well as train new staff in culture-based testing.

Dr. Werber, is culture-independent diagnostics affecting other enteric bacterial pathogens beyond STEC, such as salmonella?

- Dr. Werber offered insight that culture-independent diagnostics have the potential to affect salmonella surveillance in a similar manner.

**Panel 2: Burden/Attribution/Trends**

*Moderated by Dr. Elaine Scallan, University of Colorado - Denver*

**Dr. Rajal Mody, CDC: Sporadic Enteric Disease—We are the 90%: Reducing the Burden of Disease in a Culture-independent World**

- Dr. Mody presented the current process for identifying and monitoring foodborne illness cases—a cyclical process of following trends and attributing illnesses.
  - Trends allow monitoring changes over time in the incidence of specific infections to prioritize and monitor prevention measures.
  - Attribution determines the proportion of illnesses due to specific sources or settings to guide prevention measures.
- Dr. Mody suggested that updated case definitions and the ability to differentiate between strains for some pathogens are needed for public health surveillance in a culture-independent world. Creating new case definitions is easy, but making sense of new definitions creates challenges since trends depend on stable surveillance methodology. Thus, public health may need to collect new types of data to adjust for these effects.
Sporadic infections account for 90% of total infections. Culture-independent diagnostics will hamper confidence in measured trends and may impede the ability to attribute certain types of infections to specific exposures.

**Dr. Jean Patel, CDC: Surveillance for Antimicrobial Resistance in the Absence of Culture**

Dr. Patel raised the issue of antimicrobial resistance in culture-independent diagnostics. Dr. Patel presented two possible solutions to a lack of isolates to perform antimicrobial susceptibility testing:
- Plan A: Use culture-independent methods to detect antimicrobial resistance
- Plan B: Figure out a way to obtain isolates for antimicrobial susceptibility testing.

Considering short-term solutions, Plan B is more feasible. Plan A could allow for rapid testing but could only detect known resistance. Antimicrobial susceptibility testing has led to development of new vaccines, recommendations, and policies surrounding pathogens and is thus essential to continue.

Dr. Patel anticipated that non-culture diagnostics are increasingly important for Campylobacter spp., Escherichia coli 0157, and Clostridium difficile. Among these pathogens, resistance is an issue garnering varying levels of concern.

Susceptibility surveillance is critical for formulating a public health response to the problem of antimicrobial resistance. Culture-independent diagnostics for antimicrobial resistance are not well developed.

Dr. Patel underscored the importance of identifying an alternative method to obtain cultures for antimicrobial surveillance.

**Dr. David Goldman, USDA/FSIS: Pathogen Testing in a Public Health Setting: FSIS Perspective**

Dr. Goldman provided insight on pathogen testing from the perspective of the USDA’s Food Safety and Inspection Service (FSIS). FSIS is the public health agency within USDA responsible for ensuring that the nation’s commercial supply of meat, poultry, and egg products is safe, wholesome, and correctly labeled and packaged.

Since 1996, FSIS has relied on culture-based methods and isolate subtyping for regulatory testing, baseline surveys, and foodborne illness investigations as well as policy and actions based on culture presence or absence. FSIS operates under the paradigm that methods must be dependable, results should be definitive, and actions must be defensible.

Culture-based methodology has flourished under this paradigm and has allowed FSIS to improve public health. Without clinical isolates, FSIS will have trouble detecting pathogens, enforcing laws and policies, and investigating outbreaks and clusters. For a non-culture approach, FSIS will require sound methodology and analyses that better understands virulence, adaptation mechanisms, and the complex ecology of food pathogens.
Dr. Eric Brown, FDA-CFSAN: The Importance of Cultures in FDA’s Regulatory Science Program

- Dr. Brown provided a case for the importance of cultures in FDA’s regulatory science program. Among the program’s goals are to establish science-based preventive control standards across the farm-to-table continuum and improve detection of and response to foodborne outbreaks and contamination incidents.
- The FDA relies heavily on cultures for microbiological methods development and validation; PulseNet reporting and responding to foodborne outbreaks; drug resistance monitoring in food, feed, and veterinary programs; and next-generation identification and typing programs.
- Clinical isolates are important for microbiological methods development and the isolates have served as surrogate strains in foods. Clinical isolates also play a critical role in microbiological methods validations, serving as inclusivity/exclusivity strains for food methods.
- Culture loss has implications for FDA’s Center for Veterinary Medicine. Without cultures, it will be difficult to link animal reservoirs to drug resistance in human isolates, determine zoonotic roles of specific pathogens, or identify animals that acquired pathogens with virulence factor implications.
- Development of metagenomic methods is a challenge but is feasible as metagenomic analysis provides one avenue for the potential typing of pathogens directly from complex high background sources.

Panel 2 Discussion

- Dr. Mody and Dr. Patel, how are laboratories evolving in calculating new burden estimates?
  - Dr. Mody described that beginning in January 2012, CDC implemented a new initiative as part of FoodNet and began to monitor practices in clinical lab settings. For certain pathogens, clinical labs are to answer a short list of questions about the type of test used and the circumstances under which they were used. These data will be collected every 6 months to find out what clinical labs are doing and what percentage of stool samples is tested based on established protocols. Dr. Mody raised the issue of needing to collect data on the volume of samples by test type.
  - Dr. Patel explained that surveys are conducted for antimicrobial susceptibility testing, and phenotypic methods are used in labs because susceptibility methods are not culture-independent methods. Until culture-independent diagnosis grows, it will only minimally affect anti-microbial susceptibility data collection at CDC.
- What are the challenges with attribution in an era of culture-independent methods?
Dr. Goldman outlined that FSIS is using outbreak data provided by CDC to look at the changes in attribution of pathogens. FSIS is examining the differences among estimates and how policies influence cases that are more recent.

Dr. Mody offered that the Danish source attribution model is worth considering for adaptation. In addition, it is interesting to examine how pulsed field gel electrophoresis (PFGE) patterns matchup with case control studies of sporadic illness. These are still dependent on culture.

**Panel 3: Stakeholder Perspectives**

*Moderated by Dr. Hugh Maguire, Colorado Department of Public Health*

**Dr. Marguerite Neill, Memorial Hospital of Rhode Island: A Physician’s Perspective**

- Dr. Neill highlighted the contextual factors present in diagnostics.
- The clinical drivers for testing in potentially infectious diarrhea include proof of a causative agent, treatment considerations, prognostic value (complications), prevention of irrelevant testing, and public health concerns. Other drivers for testing are possibility of helping versus hurting, use without prior approval needed, the newness of the test, perceptions of a test as “rapid,” and the cost of the test.
- There is a lack of homogeneity in knowledge base among the various medical professionals who order diagnostic tests (e.g. pediatricians, internists, nurse practitioners.)
- Dr. Neill discussed problems with the report format of non-culture reports, which are seen as reader unfriendly, as they often contain non-intuitive language and display results cryptically as “detected/not detected,” Sometimes the reference range is misinterpreted as the result, and physicians come to a wrong understanding of test results for the particular disease agent.
- To consider the clinician’s point of view in culture-independent diagnostic testing is to recognize the time constraints on clinicians and their limited time to review results. Report clarity in both content and format should be a priority in diagnostics. Additionally, information for clinical decisions that are based on the result should be moved closer to the result. Studies of the epidemiology of non-culture diagnostics need to occur in actual practice.

**Dr. Vicki Baselski, University of Tennessee Health Science Center: A Clinical Laboratory Perspective: Patient Benefit vs. Public Good**

- Dr. Baselski presented the practical considerations of culture-independent diagnostics that a clinical laboratory holds. The necessity of a test for patient management is the primary concern in a clinical setting. A test may have different procedural considerations during the pre-analytical, analytical, and post-analytical
phases of lab testing. False negatives and false positives can provide incorrect results and thereby inhibit proper patient care or rigorous public health surveillance.

- Dr. Baselski framed the public health aspect of culture-testing as that of an unfunded mandate. For example, confirmatory testing is not generally funded. Cultures are needed for surveillance purposes but there is no funding to continue to provide cultures.

- In clinical microbiology, there are “timeless battles” that beg the question of who is in control and who pays:
  - Pathogen vs. Host
  - Infectious diseases vs. Mankind
  - Private care vs. Public health
  - Patient benefit vs. Public Good
  - Laboratories vs. Administrators

**Dr. Robyn Atkinson, Utah Unified State Laboratories – Public Health: PCR, EIA, and MALDI: Oh My!!**

- Dr. Atkinson presented the public health laboratory perspective. In public health labs, organism isolation is critical. PulseNet differentiates bacterial strains by their unique patterns from pulsed-field gel electrophoresis. Public health laboratories, clinical laboratories, physicians, and industry must work together to ensure quality testing. Data from PulseNet and NARMS has been used to identify outbreaks. Poor data quality in these systems could lead to undiscovered foodborne illness outbreaks.

- Case definitions require culture confirmation. These definitions have implications for regulatory rules for food industry partners. In addition, clinical correlation is needed to link to infections.

- Public health laboratories rather than clinical laboratories are now becoming the primary entities in primary specimen culturing.

**Dr. Douglas Anders, FBI Hazardous Materials Science Response Unit: The ‘Culture’ of Forensic Science: Application of Microbiological Culture to Forensic Attribution**

- Dr. Anders presented the FBI perspective in culture-independent diagnostics. FBI is the lead federal agency for investigating crimes involving biological agents. As part of investigations, biological agents are collected as evidence.

- Cultures are often the logical connection between public health and law enforcement, and are necessary to support criminal investigations. Crimes involving biological agents may be overt, covert, or unintentional. The phenotype characteristics of cultures can provide clues to a criminal case. Cultures support attribution and also allow for determination of viability and cross comparisons.
between patients/victims and sources, making them a critical part of federal enforcement activities.

**Dan Rice, NY State Department of Agriculture & Markets: The Regulatory Food Safety Laboratory Perspective on Culture Independent Diagnostic Assays**

- Dan Rice offered insight on the regulatory food safety laboratory perspective. Regulatory action is not initiated until a culture confirmed isolate is generated. Delays in regulatory action may cause the potential for increased illness.
- Unlike other types of labs, food safety labs have specific methods, technologies, and assays to screen food for pathogens. If there is a reduction in the number of foodborne pathogen isolates, PulseNet may have greatly diminished utility.
- A key issue in the reduction of culture isolates is that food safety programs may lose ground in public health epidemiology and surveillance contributions. The lack of human isolates diminishes the value of food isolates, which in turn affects food-testing approaches.

**Dr. Barbara Kowalcyk, Center for Foodborne Illness Research & Prevention: The Consumer Advocacy Perspective**

- Dr. Kowalcyk offered the consumer advocate’s point of view on culture-independent diagnostics.
- Diarrheal disease is a global health issue and is a leading cause of child mortality and morbidity. This issue also burdens the U.S. with $78 billion in lost productivity and medical expenses. The vast majority of foodborne illnesses are not reported, and when they are, 58% of investigated outbreaks never find a source. For those that do find sources, molecular sub-typing was the method to identify the source.
- The benefits of implementing PulseNet outweigh its costs. PulseNet will be able to quickly and effectively identify gaps in the food system.
- Dr. Kowalcyk provided a vision for an integrated food safety surveillance system that tracks and links—through molecular methods—human, animal, environment, and food with the goal of being proactive and preventing foodborne illness and improving public health.

**Panel 3 Discussion Session**

- What can public health professionals do to lobby for receipt of culture isolates and sustain this technology across clinical lab and public health lab settings?
  - Dr. Baselski commented that awareness is necessary for these issues and that an unfunded mandate already exists. These issues require a collective sense of collaboration. Everyone wants to contribute and this has to be a shared responsibility. An example of the level of collaboration that is needed is evident in the recent prioritization of healthcare-associated infections. It will
be good to see similar directives that have been issued for the surveillance of healthcare-associated infections in hospitals extend to labs in the broader community.

A meeting participant from the audience offered an example, commenting that C. difficile infections remain a significant problem as a healthcare-associated infection. The lack of isolates available for C. difficile further complicates the problem. No one is culturing C. difficile infections, so it has become a tremendous challenge to obtain isolates, control, and reduce infections. It is agreed that there will be similar delays in outbreak investigations of foodborne illnesses because of the inability to culture and quickly secure isolates.

- There will be less acute care hospitals in the United States as years progress. Clinical microbiology labs are farmed out and shared if it is financially more beneficial. This issue has to be a shared responsibility.

What is the cost for clinical labs to perform back-up cultures for positive rapid tests?

- Dr. Neill added that commercial labs should be brought to the table as partners in this discussion.

From a test industry vendor’s point of view, where lies the most utility for development of new diagnostic products and offerings? What public health perspectives are needed in designing tests? Should broader pathogens or specific pathogens be considered?

- Industry develops new products based on sales and return on investment projections. Ninety-five percent of stool cultures are negative. The medical field wants diagnostic tests that improve patient care, reduce costs, increase stewardship, and conserves microbiology budgets. If the test industry develops a rapid assay-based test where results can be obtained in 1 hour, this test will help meet those goals.

- Stakeholders must be aware that financial resources are finite and everyone in the system must remain good fiscal stewards. Limited public health and clinical resources are significant issues.

- As molecular technologies become more widely available, there will be greater data available from small health care settings.

Today, few people have the time, skill, and/or resources to perform culture-based testing and secure isolates. The technology is aging and is over 20 years old. Because cultures are likely going away in the next few years, what will replace PulseNet?

- The key to the past success of PulseNet rests on the fact that so many partners use the same surveillance platform.

- New technology development has to focus on culture-independent diagnostics.

- One consideration of a new method is whole genome sequencing; however, this structure still needs to be further developed and will not address the issue by itself. Therefore, parallel methods are needed to address this issue.

- A step-wise shift away from PulseNet would be preferred, but changes may have to occur overnight.
The purpose of this meeting is to determine how to address these issues and how to respond.

State public health labs cannot adjust to changes and transition to new systems overnight. It will be a challenge to implement something quickly at the state public health level.

- CDC acknowledges these challenges fully.

- How do accrediting bodies function in this regard, where solutions require the adoption of new technologies, processes, and communication?

- Accreditation bodies may play an important role in requiring or at least suggesting follow-up culture-testing. The role they play should be incorporated in any discussion about solutions.

**Panel 4: Scientific, Legal, and Regulatory Perspectives**

*Moderated by Dr. Eric Brown, FDA-CFSAN*

**Dr. Nancy Miller, Boston Medical Center: Charting a Path for Public Health – Where is Technology At? Where is it Going?**

- Dr. Miller provided a perspective on technology’s role in culture-independent diagnostics. Assays span a diverse technological spectrum. Alternative technology is a component in many vendors’ product pipeline and new technologies are aggressively marketed to clinical laboratories. Sometimes a product-user mismatch arises when smaller labs do not have the capacity to use new technology products.

- Dr. Miller suggested standardizing the electronic laboratory reporting between diagnostic labs and public health labs. Standard workflows should be prepared and a plan for point-of-care culture-independent diagnostics should be implemented.

**Dr. Colin Stine, University of Maryland: Current State of Metagenomics: Diarrhea**

- Dr. Stine presented a case study of metagenomics in diarrheal diseases. Metagenomics allows for analysis of genetic material recovered directly from environmental samples. “Frequent and copious discharge” of sequences, sorting and filtering, and epidemiological relevance are all challenges to metagenomics.

- In low-income countries, diarrhea is the second leading cause of death among children less than five years old. Dr. Stine hypothesized that unrecognized bacteria cause diarrhea and sought to detect known pathogens by sequencing 16S from diarrheal and normal stools. 16S sequencing did detect known pathogens and numerous bacteria taxa were strongly associated with diarrhea.

- A conclusion is that deep sequencing does reveal the presence of bacterial taxa; however, more needs to be done with genetic characterization beyond 16S and phenotypic characterization.
Ms. Priya Rathnam, FDA-CFSAN: **Food Enforcement Perspectives**

- Ms. Rathnam provided a perspective from FDA’s regulatory arm. The regulatory considerations include whether the FDA has jurisdiction, if interstate commerce of food occurs, what is the violation, who is responsible, and the compliance history.

- Two charges that are enforced under the Food and Drug Cosmetics Act are:
  - 402(a) (1) (U.S.C. 342 (a) (1)), which holds an evidentiary burden on the charge, “if it bears or contains any poisonous or deleterious substance which may render it injurious to health…” This charge must be proven by laboratory confirmation that a substance shows presence of a pathogen and must demonstrate a reasonable likelihood of harm.
  - 402(a)(4) (U.S.C. 342(a)(4)), which states, “if it has been prepared, packed or held under insanitary conditions hereby it may have become contaminated with filth or whereby it may have been rendered injurious to health.”

- With the use of rapid testing tools instead of conventional culture methods, FDA enforcement is challenged by several aspects:
  - There is an absence of knowledge on the viability of a target pathogen. Even validated rapid test results need confirmation using a culture.
  - Rapid tests are less sensitive and specific than culture-based tests, which results in more frequent false negatives and false positives. The concern of false negatives and positives in a rapid test has high ramifications in the food industry, resulting in a decrease in consumer protection and confidence, unwarranted industry recalls and destruction, financial loss, and liability.
  - The FDA’s inability to support particular rapid testing methods limits the implementation of an integrated food safety system with other regulatory and public health partners.
  - A loss of culture may affect methods development, the ability to track foodborne disease, and impact pathogen surveillance programs.

Dr. Uwe Scherf, FDA-CDRH: **Clearance/Approval of Diagnostic Devices: Warnings/Limitations in a Package Insert**

- Dr. Scherf provided insight on the regulation of diagnostic devices and the use of package inserts in diagnostic devices. FDA regulates diagnostic devices and evaluates new products. Using a tiered-class system of risk (low to high likelihood of harm), FDA determines the likelihood of harm in devices and has procedural systems to mitigate these risks.

- FDA is challenged to determine if the diagnostic devices work. New devices and their results are evaluated against a “reference method” to evaluate performance in detecting a sample bacteria, virus, or fungi.

- The FDA regulation process allows the opportunity to create package inserts that include recommendations/limitations regarding culture testing for various devices.
Inserts contain language about culture testing for intended use of a device as well as a warning and limitation.

- Dr. Scherf suggested providing financial incentives to isolate and forward emerging/novel bacteria strains to CDC in addition to providing well-established follow-up procedures and protocols through the CDC website. Additionally, the participation of public health laboratories should be promoted.

**Panel 4 Discussion Session**

- Human disease surveillance is driving the issues at this meeting.
- Dr. Stine, since it is not always possible to identify every bacterial entity, will databases be able to keep up with technology as we move forward?
  - This depends on what level of genetic information is needed to use to answer the particular question of interest. If you were identifying the genus, then the answer is yes. If you were identifying the species, then you would need to specify. If you were considering the pathogen strain, it may be difficult to do because you will need the whole genome. It is more difficult to target the genome.

- Ms. Rathnam and Dr. Brown, when the FDA is prosecuting manufacturers for contamination violations, are culture-independent diagnostics accepted by courts? Will these methods be embraced as evidence?
  - For civil actions, the FDA has not yet prosecuted actions based on culture-independent methods. However, we may move in the direction of utilizing culture-independent methods in the years to come.
  - Culture-independent methods are considered presumptive results. The FDA would not move on an action with just these results. However, if the culture-independent results were part of a cumulative body of evidence, this would present a more compelling case.
  - The FDA relies on expert testimony to help present cases to the Department of Justice on how sample results are linked to illness. It would be a disservice if we do not explore samples from culture-independent methods if we are investigating an outbreak.

- For novel agents, how can one separate the cause from effect when looking at diarrheal infections?
  - You should go after the phenotype and set up monolayers to expose bacteria to, and try to assess cause and effect. You could also use longitudinal studies. However, one cannot use a case control study to determine cause and effect.

- How can one sub-type without cultures?
  - Sub-typing can occur through DNA sequencing.

- Dr. Miller, what are your thoughts about using lab-developed tests versus FDA-approved tests? Has there been a change in comfort level?
  - Yes. There are concerns with using lab-developed tests. There are issues with liability, verification of assays, and regulatory responsibilities for quality assurance and quality control. Economic challenges are also present. The
current environment is uncertain and clinical labs are having to deal with cost issues, expertise of staff, regulatory measures, and the maintenance of quality assurance standards for tests beyond what labs can actually support.

Dr. Scherf, what is the process to obtain warning/limitation language for a diagnostic device package insert? For example, for influenza that is unsubtypeable, language was added, “the sample should be forwarded to the Centers for Disease Control (CDC) in accordance with the MMWR notice.” The purpose is to determine whether unsubtypeable Flu A specimens represent emerging novel strains of influenza ....” How is this information added?

- The FDA collaborated with CDC to develop this language for the package insert to cover unsubtypeable influenza strains. CDC was included in the design and was brought on board early to have open and collaborative discussions about any potential problems that may occur and to develop solutions, which resulted in a very positive outcome.
- This same model can be followed for enterics as well. All partners involved should collaborate and develop solutions.

**Day 1 Conclusions**

**Proposed solutions**

- Need to integrate human, food, and environment systems and link trends.
- Attribution projects are needed in order to better inform trends.
- An entity to provide financial support for culture-testing is critical in addition to advocacy and awareness of these testing issues.
- Regulatory partners need to be closely connected with public health laboratories to have reliable evidence through isolate-based methodology.
- Industry partners should be engaged in more conversations about diagnostic testing so new diagnostic products and services can be developed that serve the needs of clinical and public health labs as well as public health surveillance stakeholders.
- Surveys of public health and clinical labs should be conducted to better assess their practices, understand the sensitivity and specificity of each test, obtain analyzable data on sociodemographic characteristics when using tests, and to understand the circumstances in which the isolates are obtained.
- In order to not miss any foodborne illness outbreaks, culture-test methods should be standardized.
- Obtaining cultures is important not only for identifying outbreaks and issuing food recalls but for understanding any weaknesses or pitfalls along the farm-to-fork continuum.
- The laboratory workforce is aging and close to retirement, so training new laboratory professionals in microbiology and culture-testing processes is critical to ensure culture-testing skills are not lost.
Cultures are required to uphold legal regulations of the food industry and to initiate legal actions for individuals and groups that are non-compliant with the law. Therefore, non-public health audiences should be aware of the far-reaching implications of culture-independent diagnostics.

- CDC should maintain up-to-date guidance on the CDC Web site regarding culture-testing follow-up procedures.
- The FDA should continue to provide package inserts with recommendations for follow-up culture-testing.
- Metagenomics and emerging technologies hold promise and are avenues worth further exploration.

**DAY 2 PROCEEDINGS**

**Breakout Group A: Regulatory and Device Industry Strategies**

**Moderated by Patricia Griffin**

- Group A offered suggestions for strategies that the medical diagnostics industry could take to modify its products and procedures to ensure that diagnostic needs are met but isolates are still available for public health activities.
  - Physicians must be involved in point-of-care test order decisions.
  - The FDA could ensure that language in a package insert would provide guidance on preserving the sample as part of the workflow of the kit.
  - Obtaining culture samples should be framed to the diagnostics industry as a collection issue rather than a test issue.
  - Current collection of stool samples by patients is problematic. Rapid tests can be used for a rectal swab sample and second samples may be collected during the patient visit.
  - Physicians could collect a culture sample if a test result was positive since rapid test results are less sensitive. This sample should be sent to a second lab for isolation then forwarded to a public health laboratory.
  - Physicians should be educated about laboratory testing requirements.
  - Government incentives should be provided to physicians to collect and forward appropriate specimens. A white paper could be used to advocate a mandate by HHS and FDA.
  - A system of sentinel sites that exclusively collect specimens should be established.
  - A cost-benefit analysis of PulseNet would be useful to provide support for its purpose to policymakers, especially for those who will see culture-independent diagnostic testing as a better option for patient care.
  - Moving towards a sentinel system may be less costly to society and may achieve more cultures.
  - Hospital emergency departments should perform culture testing.
Since individual states have different legal mandates, clinical labs submit different materials to public health labs. The different state laws do not allow CLIA to enforce regulatory requirements.

CMS was identified as a funder of lab tests through Medicare/Medicaid, but mandates could be enacted through the Social Security Act.

The hospital infections report from the Institute of Medicine could serve as a model for a report outlining the importance of culture testing and advocating for its implementation.

Since labs reference CDC-published best practices and instructions on confirmatory testing for culture-independent diagnostics testing, CDC can influence the guidance that labs follow. Not all labs have the necessary skill set in place to perform culture, and all labs do not properly verify results.

Financial incentives could prove effective in mandating culture after a rapid test is performed, since culture on its own is not necessary for the care of patients.

The majority of stool cultures do not have an identifiable pathogen. Whole genome sequencing and metagenomics provide useful information (not clear, in what regards to etiology of illness) and may find agents that culture may miss.

**Group B: Clinical and Public Health Practice**

**Moderated by Raj Mody**

- Group B offered strategies for clinical and public health laboratories, solutions for isolate preservation, and other considerations in the context of clinical and public health practice.
- Beyond conducting a cost-benefit analysis of PulseNet and outcome studies, such analyses should be timely and published in both peer-reviewed journals and publications with a broader cache of readers.
- Culture capacity should be the core capability for most states.
- Culture testing and sequencing responsibilities should be delegated. Local public health labs should analyze cultures and CDC should sequence.
- Microbiology education is deteriorating in university and medical school curricula. Microbiology training should be emphasized in education and science programs could even be developed in primary and high schools.
- Antimicrobial susceptibility could be surveyed via sentinel sites. Statisticians should ensure that the sentinel sites are properly chosen to serve at-risk populations.
- Recent isolates for new drugs should be maintained.
- The Bill and Melinda Gates Foundation could be a potential financial backer of culture testing requirements.
- Non-traditional partners could help with advocacy efforts (e.g. the American Association of Pediatrics).
- CDC should consider both clinical and public health contexts when drafting best practices.
Diagnostic test result reports should be formatted clearly and written succinctly.

CDC should develop enteric isolation information sheets for patients who receive positive test results. These information sheets would be similar to vaccine information sheets and would be housed on CDC’s website. Such fact sheets would facilitate two-way communication between the patient and clinician.

Regarding workforce development, a program similar to the EIS program should be developed for microbiologists to provide service to laboratories.

**Group C: Strategies 1—Culture-independent pathogen characterization assay development (strain, virulence, susceptibility, etc.)**

**Moderated by Efrain Ribot and Patti Fields**

- Group C provided recommendations on how to develop assays for culture-independent pathogen characterization. Potential strategies for conducting agent-specific surveillance in the absence of isolates, testing needs and new markets, and partnership ideas for needed research and development funding were considered.
  - Standards and metrics should be set to determine if isolates are still needed.
  - A better referral and lab system needs to be put into place for the forwarding of isolates.
  - A different funding mechanism is needed for culturing. Incentives are needed for the sending of isolates and specimens forward.
  - In order to understand the framework in which clinical labs and public health labs work, a workgroup should be convened to establish the framework.
  - Collaboration with industry partners and other partners is needed. Additionally, international perspectives should be considered. For example, China is moving to culture-independent diagnostics.
  - Test technology will continue to advance; however, culture will continue to be important. For this reason, public health programs may need to adapt more than clinical programs.
  - Public health surveillance is centralized but should be redistributed throughout states to better detect foodborne illness outbreaks.
  - Sentinel surveillance needs to be performed, versus passive surveillance. In addition, connections need to be made with clinical programs to allow information to readily flow from databases, despite the minimal personal information it may contain. The information from clinical databases could prove useful to surveillance programs.
  - Lobbying is needed and reimbursement for costs is a major challenge. Mandates may be needed to share cost burdens.
  - Investments should be made in bioinformatics to handle the large volume of data.
Databases should be interoperable. Other public health disease databases (e.g., HIV, influenza) could provide examples of best practices. Data privacy must be considered along with currently existing databases when developing a comprehensive database.

A genomic reference database should be developed in tandem with a committee to standardize subtype calls and algorithms.

Maintaining cultures while transitioning to metagenomics and whole genome sequences should be a priority.

Advocates and researchers could conduct a literature review on who is obtaining genomic information from isolates.

Sentinel labs should be part of one system and should include notifiable diseases beyond select agents.

A workgroup should come together and discuss best practices, gaps in knowledge, and funding issues across states.

A short-term solution to consider is to examine ways to maintain culture during periods of transition as well as how to ensure database systems talk to each other.

Group D: Strategies 2—Culture-independent pathogen characterization assay development (strain, virulence, susceptibility, etc.) plus strategies for susceptibility surveillance

Moderated by Barbara Mahon and Eric Brown

Group D focused on solutions for susceptibility surveillance and strategies for maintaining state and national susceptibility surveillance programs in the absence of isolates. Funding and partnership ideas for research and development were also considered.

Priorities for susceptibility include:

- Development of sentinel sites
- Development of methods for detection (e.g., proteomics, transcriptome themes)
- Prioritization of drug-bug combinations
- Support for universal transport media for sample to facilitate culture testing

Susceptibility surveillance should take a multi-pronged approach by preserving the ability to perform cultures and phenotypic testing, while other methods such as microarrays and transcriptomic and proteomic applications are developed.

A sentinel site approach should be careful to avoid intense sampling for some sites but not others.

When structuring databases, it is important to consider different audiences since they will use the information differently.

The focus should remain on the functionality of resistance genes rather than the subtypes.
Targeted molecular tests may not detect pathogens with mutations.

Partnerships among FDA, CMS, CDC, and industry companies are necessary.

Solutions were prioritized for those that should be implemented now, soon, and later.

- **Now:** Culture needs to be maintained and the techniques simplified.
  - This involves referring clinical materials to a central location, carefully selecting bug-drug combinations, archiving and curating isolates where government involvement is key for preservation, and establishing references.

- **Soon:** Genomic and metagenomic approaches are rapidly developing.
  - It is currently possible to target many known resistance determinants; however, it is not possible to detect these determinants without the capacity to evaluate the phenotype. Long-read DNA sequencing may help with problems in linking resistance determinants to pathogens, but these techniques have some quality issues. Until a comprehensive metagenomic approach is developed, a back-reference to existing technologies is needed.

- **Later:** Transcriptomics and proteomics are also developing rapidly.
  - Proteomic prediction work is ongoing and the “link to biology” need implies that culture must be maintained, at least for validation purposes.

**Group E: Novel approaches, known but unproven technologies or processes**

**Moderated by Joanne Bartkus and Peter Gerner-Smidt**

Group E focused on solutions that could be feasible due to emerging technologies and processes. The outlook for diagnostic technologies and novel approaches that could potentially be exploited for surveillance in a culture/isolate-free world was considered.

- Four primary solutions were raised:
  - Reflexive culture of patients with specific exposures
  - Metagenomics
  - Species-specific targets
  - Proteomics

- Reflexive culture is a short-term solution to use since culture-independent diagnostics do not provide needed surveillance information and necessitates going back to the patient for sampling.

- Metagenomics is a long-term solution. Metagenomics is possible for different pathotypes. Interactions between pathogen and host will be seen with metagenomics, which can help with outbreak investigation and will be of public health value.

- Sequencing may be the most useful approach; however, this is a long-term approach as well and intermediary approaches are needed.
Most physicians who order diagnostic tests only want very basic information (i.e. what is the pathogen and what are the AST results) in order to help patients. Some physicians will have sophisticated demands and may want to know interactions between pathogens and host that can be derived from metagenomics. A combined approach that provides epidemiological data linked to clinical lab data may be needed.

Whole genome sequencing is suggested in order to assess where important targets may lie, followed by the use of targeted de novo sequencing for those important regions. This will reduce the need for sophisticated bioinformatics.

Data access and data management issues will be major obstacles. Standards should be set by well-curated databases and specimen banks. The FDA should begin considering these standards now before requests are made.

An integrated and standardized system is warranted, with the needs of clinical labs, public health labs, and regulatory agencies all considered.

Multiple infections will continue to be challenging for diagnostics. Food testing cannot use a clinical system as a model. Metagenomics approaches will help food microbiologists.

A long-term genomic database is needed and NCBI and Genbank could be a site for storage and data analysis.

Even though data privacy should be maintained in databases, a wide variety of global audiences should be able to access the information.

Public health surveillance needs access to information stored in databases that would not be public and can be linked back to patient records. A consideration for storing this information “in the cloud” is suggested.

Standards should be set so that data generated on different platforms can be comparable.

Workgroups around databases and data collection should be developed.

Healthcare informatics skill sets are critical to developing new data solutions.

Exposure assessment should be improved.

Metagenomics should be performed by PulseNet labs, not at the clinical level.

Vendors, health care informaticians, and information technology specialists should be engaged in conversations to ensure compatibility of metadata.

Continued discussions are needed between public health, industry, regulatory agencies, and bioinformatics groups.

**Day 2 Conclusions**

**Proposed solutions**

- A comprehensive genomic reference database is needed with functionality that serves the needs of diverse audiences. Data privacy should be maintained without affecting accessibility.
- Responsibility for public health surveillance should be redistributed to the state-level.
Metagenomics and proteomics should be explored as possible long-term solutions for use in surveillance and outbreak investigations.

Whole genome sequencing and the identification of biomarkers should be pursued.

- Whole genome sequencing can also help inform the development of new test technologies.

Susceptibility surveillance should take a multi-pronged approach by preserving the ability to perform cultures while other methods such as microarrays and transcriptomic and proteomic applications are developed.

Guidance on culture-testing and preserving a sample should be continued to be placed in diagnostic device package inserts. This guidance should be part of the workflow of kits.

CDC should streamline their guidance on culture-testing and distribute this information to stakeholder audiences.

- An information sheet should reside on CDC’s website that clinicians can use to communicate with and distribute to patients.

Culture-independent subtyping tests, or “CIST,” were proposed.

A study should be implemented that assesses the actions clinicians take based on laboratory results.

A PulseNet scenario modeling study was proposed.

Broad consensus among all stakeholders is a priority need to ensure culturable material is present for immediate public health purposes until other solutions can be implemented.

A service tiered approach among clinical, and local, state, regional, and national public health surveillance and outbreak detection agencies is proposed as a priority solution to capture information needs for isolates as well as quantities of isolates.

- Cost needs can be split across tiers.
- CDC can aggregate the data and identify trends.
- Each service tier will have its own area of expertise.

Several technological recommendations were made as interim and long-term solutions:

- Support whole-genome sequencing projects to provide the information needed to identify suitable assay targets.

- Consider various options for characterizing Shiga toxin-producing E. coli (STEC) directly in stool.

- Prevent the need for manual uploading of diagnostic results to surveillance national databases by considering the mechanics of future molecular subtype-based surveillance (e.g. real-time “cloud” analysis directly from sequencers)
Areas of Disagreement & Parking Lot Issues

Areas of Disagreement

- Several partners in culture-independent diagnostics have different and conflicting goals in their laboratory testing.
  - Industry partners are limited to profitable services and offerings that are dictated largely by the markets they serve, not necessarily public health needs.
  - Cultures remain critical for public health audiences and federal agencies such as CDC, FDA, and USDA, yet these agencies are unable to provide financial support to laboratories to receive needed cultures. These agencies offer guidance and direction to encourage culture-testing, but without a federal or industry mandate or financial incentives, these public health bodies are at a loss.
  - The bottom line for physicians is patient care and management. While clinical labs have expressed interest in supporting public health surveillance of foodborne illness, oftentimes obtaining the needed cultures conflicts with the ability to provide high patient care.
- Culture-dependent methods are tightly woven in FDA and USDA regulatory controls and actions. Moving away from isolate-based approaches would cause setbacks and agencies would lose the ability to identify and investigate outbreaks effectively. There is a level of disconnect with the regulatory process and the challenges public health and clinical labs face.
  - The public health system is in flux and is tasked to maintain traditional technology alongside new technologies.
- A blend of culture-based methods and culture-independent methods seems inevitable. This is understood; however, what remains to be clear are the steps to take to best achieve this outcome.
- Some feel sentinel sites where only a set number of isolates are submitted should be established as a surveillance solution, while others believe sentinel systems are not an ideal model.

Parking Lot Issues

- Is culture-testing going away completely?
- What are long-term strategies for surveillance without cultures?
- What will replace PulseNet?
- Will evolving molecular epidemiology be back-compatible with current epidemiological information?
Recommendations and Next Steps

Recommendations for future research and collaborations

- Publish a cost-benefit analysis of PulseNet to provide evidentiary support to policymakers on the issue of culture-independent diagnostics.
- Consider collaborating with the Social Security Administration.
- Learn best practices on how to make health care delivery changes from issues of healthcare-associated infection control, such as in hospitals.
- Develop guidance on workforce development for microbiology and culture-testing skills.
- Identify organizations that could provide financial support for culture-testing (e.g., Bill and Melinda Gates Foundation).
- Engage non-traditional partners in issues of non-culture diagnostics (e.g. American Association for Pediatrics).
- Engage health care informatics personnel and information technology specialists to ensure compatibility of metadata.
- Conduct a literature review on who is obtaining genomic information from isolates.
- Establish communication between CDC and the FDA device licensure group to ensure awareness of emerging test devices for approval and comment, and to promote collaboration for development of product insert language that is consistent with public health needs.
- The needs and lessons learned from others should be considered. Collaboration and consensus-building on the best ways to address and incorporate culture-independent diagnostics from public health institutions, regulatory agencies, scientific and medical device industry, physicians, and laboratories is important to pursue.

Next Steps

- Organize and convene suggested work groups:
  - Test technology workgroup
  - Regulatory collaboration & needs workgroup
  - Industry & clinical partners workgroup
  - “Setting a framework” among clinical labs and public health labs workgroup
  - Funding streams, gaps, and best practices workgroup
  - Use of metagenomics workgroup
  - Database and data management issues workgroup
  - Ethics workgroup
- Continue the discussions held at the Forum among various work groups as well as among different stakeholders.
- Develop a white paper about the implications of culture-independent diagnostics.
List of Appendices

Appendix A: Meeting Agenda
Appendix B: Meeting Participant List