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Culture-Independent Diagnostic Tests

Laboratory culturing of bacteria represents a technique dating back over a century. Recent availability of additional non-culture testing methods provides both opportunities and challenges to public health agencies in detecting and responding to communicable disease cases and clusters.

Culture Dependent Methods

Fanny and Walter Hesse
Ihm.nhl.nih.gov

In his ground-breaking microbiology work, Robert Koch grew bacteria using liquids, potato slices, and gelatin as growth media, but none of these proved ideal. In 1882, his assistant Walter Hesse and assistant's wife Angelina Fanny Hesse developed agar as a bacterial growth medium. That technology has persisted in microbiology laboratories to the present day.

Culture methods became the main diagnostic method for enteric infections with bacteria such as *Salmonella*. Selective medium that grew only certain bacteria, biochemical tests, and antisera were used to culture and further identify specific bacteria. Beginning in the 1990s, pulsed-field gel electrophoresis and other molecular methods for strain typing and subtyping of isolates became increasingly important to identify outbreaks. A pure culture of an organism was also needed for subtyping or testing for antibiotic resistance. More recently, whole genome sequencing is being utilized for subtyping. Public health agencies, including Washington State Department of Health, require submission of isolates from clinical laboratories for a range of organisms including enteric bacteria, bacterial vaccine-preventable conditions, and bacterial agents of bioterrorism.

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Culture-Independent Diagnostic Tests

In parallel with culturing, laboratories have been using a variety of other methods to detect or characterize pathogens. Such culture-independent diagnostic tests (CIDTs) include antigen-or molecular-based tests (such as nucleic acid amplification testing [NAAT], polymerase chain reaction [PCR], and enzyme immunoassay [EIA]). Diseases commonly diagnosed by non-culture methods include:

Campylobacter – EIA
Gonorrhea – NAAT
Legionellosis – urine antigen (*L. pneumophila* serogroup 1)
Pertussis – PCR
Shiga toxin-producing *E. coli* – EIA

Utililization of CIDT tests have steadily increased. There are now multiplex molecular panels that simultaneously detect multiple pathogens associated with particular syndromes (e.g., respiratory, enteric, or bloodstream infections). CIDTs can be classified into widely-used commercial test kits that receive clearance from the Food and Drug Administration (FDA) or laboratory-developed tests (LDTs) used within a single laboratory. Available CIDT products have varying sensitivity and specificity. Each CIDT product has its own pathogen coverage, varying in which agents are tested.

www.cdc.gov

Public health agencies prefer cultures because they generate an isolate that can be used for additional testing such as subtyping (e.g., by pulsed-field gel electrophoresis) or whole genome sequencing. Cultures are more time intensive for the diagnostic laboratories, must be done individually for specific bacterial pathogens, and do not detect parasites or viruses. Clinicians and diagnostic laboratories tend to favor culture-independent methods which are rapid, are less expensive, require less training, and can test multiple agents for a syndrome including parasites and other agents that are not cultured. CIDTs may give results even after antibiotic therapy has been initiated.

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National case definitions for notifiable conditions may change to include newer CIDT methods. *In 2015, d*etection of *Campylobacter* spp. in a clinical specimen using a CIDT was added to support a Probable case classification. In the next few years, similar criteria may be instituted for other enteric bacteria.

Tests for Detecting Foodborne Illness

	Culture-Dependent	Culture-Independent
Uses specimens from patients (e.g., stool, blood, urine, etc.)	✓	✓
Has high accuracy rate	High	Low to High
Produces fast results		✓
Requires special knowledge to run	✓	
Produces pure cultures for subtyping	✓	
Produces pure cultures for antimicrobial susceptibility testing	✓	
May test for bacteria, viruses, and parasites at the same time		✓
May be done at physician's office		✓

Future Impact of CIDTs on Public Health

CIDTs have the potential to improve surveillance because 1) they may be more sensitive than cultures, 2) their relative ease of use may increase the number of patients tested, 3) they may detect organisms without existing practical laboratory tests, and 4) they may better detect polymicrobial infections even if multiple agents are not suspected.

In contrast to the effect on improving surveillance, CIDTs may affect disease investigation by reducing the ability to detect outbreaks. Without isolates, various characterization methods such as strain typing and antibiotic resistance determination cannot be performed. Preliminary national data suggest that clinical laboratories often do CIDT instead of cultures, including for *Salmonella*.

CDC has encouraged clinical laboratories to do reflex culturing, or culturing a specimen when there is a positive CIDT result. Another option encouraged by CDC is to send the specimen to public health laboratories for culturing, but capacity and support for handling the volume of specimens are not yet available at Washington State Public Health Laboratories. Developing non-culture methods for identifying subtypes, conducting whole genome sequencing, and testing antibiotic resistance are ongoing activities that may eliminate the need for pure cultures, but such methods are not yet standardized and available. Washington State Public Health Laboratories is working on a plan to implement this recommendation. Until then we encourage laboratories in Washington State to do reflex cultures and to submit isolates for further characterization.

Use of existing CIDTs is expected to increase and new test options are likely to be developed. Public health laboratories will be adjusting to the changing face of clinical diagnostic testing to continue providing support for public health investigations.

Resources

FoodNet results:
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6409a4.htm?s_cid=mm6409a4_e

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6409a4.htm

http://wwwnc.cdc.gov/eid/article/21/9/15-0570_article

http://www.cdc.gov/pulsenet/next-generation.html