AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology®

EDITORIAL

Unforeseen Consequences: Culture-Independent Diagnostic Tests and Epidemiologic Tracking of Foodborne Pathogens

Alexander J. McAdam, Editor in Chief, *Journal of Clinical Microbiology*

Department of Laboratory Medicine, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts, USA

KEYWORDS culture-independent diagnostic tests, epidemiology, foodborne pathogens

The increasing use of culture-independent diagnostic tests (CIDTs) to detect enteric pathogens, driven in large part by the desire to improve clinical service, is having unexpected consequences for epidemiologic studies of foodborne pathogens in the United States. CIDTs detect pathogens without isolation of the organism in culture. These tests include microscopy, immunoassays, and nucleic acid amplified tests (NAATs), among others. Advantages differ for specific CIDTs but include short turnaround times, limited requirements for technical expertise, simplified workflow, and high sensitivities and specificities. Prominent among the CIDTs are FDA-approved multiplex NAATs, often called "syndromic panels," for detection of several different pathogens associated with similar manifestations. The reduced turnaround time and diversity of pathogens detected have led many labs to offer these tests because of a desire to improve patient care.

There are several CIDTs for intestinal pathogens that cause diarrhea and other manifestations. Among the more commonly used of these are immunoassays for *Campylobacter* species (1) and for toxins produced by Shiga-toxin producing *Escherichia coli* (STEC) (2) as well as several multiplex NAATs for detection of several pathogens in one test (3, 4). Some important, and perhaps unexpected, consequences of the increasing use of CIDTs for intestinal pathogens are evident in a recent report, by Marder et al., about the epidemiology of pathogens commonly transmitted in food in the United States (5). When authors of an article in the *Morbidity and Mortality Weekly Report* call out "...the Effect of Increasing Use of Culture-Independent Diagnostic Tests on Surveillance..." in the title of their report, the spotlight is on the clinical microbiology laboratory!

Marder et al. note two important effects of the increasing use of CIDTs for enteric pathogens on the ability to conduct epidemiologic investigations into foodborne pathogens (5). First, changing the method by which a pathogen is detected can change the apparent or measured incidence of infections caused by the pathogens. Useful comparisons between the incidences of an infection at different times require that the same fraction of true infections be detected at those times. If the rate of detection of an infection doubles when the number of infections is constant (and the population size is unchanged), the incidence will appear to double when it really has not changed. Does that sound like an exaggeration? Consider this: Marder et al. found that the change in incidence of Shiga-toxin producing *E. coli* from 2013 to 2015 (combined) to 2016 was 21% when estimated using culture-confirmed results, but it was 43% when culture-confirmed results and CIDTs were both used for the estimate (5). Another possible effect of CIDTs is that false-positive results can lead to an erroneous apparent

Accepted manuscript posted online 3 May 2017

Citation McAdam AJ. 2017. Unforeseen consequences: culture-independent diagnostic tests and epidemiologic tracking of foodborne pathogens. J Clin Microbiol 55:1978–1979. https://doi.org/10.1128/JCM.00678-17.

Editor Karen C. Carroll, Johns Hopkins University School of Medicine

increase in the incidence of disease. This is of particular concern for detection of infections with *Campylobacter* species, for which CIDTs, specifically immunoassays, have been found to have positive predictive values around 50%, meaning that half of the positive results are incorrect (6). This is to be expected; if a test has good, but imperfect, specificity, the positive predictive value will be low if the prevalence of disease is low. In the report by Marder et al., only 52% of specimens that were positive for *Campylobacter* by a CIDT had detectable organism when culture was performed. It will be very difficult to determine how the incidences of foodborne infections are changing over time if increasing use of CIDTs significantly changes the rate at which infections are detected and provides incorrect results that bias the results.

A second important effect of increasing use of CIDTs is the loss of bacterial isolates if reflex culture is not performed on specimens that are positive for a bacterial pathogen in a CIDT. These isolates are needed for investigations that yield data which are critical for public health investigations. These include determination of antibiotic susceptibility for detection of changes in resistance patterns and bacterial typing for detection of emerging subtypes of bacteria or detection and investigation of foodborne outbreaks (7). Some CIDTs for enteric pathogens include recommendations to perform additional tests, such as culture, to confirm positive results, and some do not. Some labs follow recommendations to perform reflex testing, and some do not. In the study by Marder et al., the number of infections detected by CIDTs for which a reflex culture was not performed steadily increased for the years 2013 to 2016 (5). In 2016, a reflex culture was performed for only about 60% of the specimens from which a bacterial pathogen was detected by a CIDT.

As clinical microbiologists in front-line diagnostic laboratories and in regional public health laboratories, we should take the initiative to make sure that isolates needed for epidemiologic investigations are available for that purpose. It is possible that regulations will be put into place to specifically require that clinical laboratories perform reflex cultures for specimens positive for CIDTs, and that would make the task clear (8). Regardless of the regulatory requirements, I think that those of us in front-line diagnostic laboratories should work with our colleagues in public health to figure out how to perform reflex testing to isolate bacteria detected by CIDTs when the isolates are needed for public health investigations. More-rapid detection of outbreaks of infectious diseases and of emerging antimicrobial resistance will clearly provide significant benefits to many, and we should not let unanticipated consequences of changes to clinical testing deny us these benefits.

ACKNOWLEDGMENTS

I thank Dr. Karen C. Carroll, Dr. Carey-Ann D. Burnham, and Dr. Andrew B. Onderdonk for thoughtful comments on this Editorial.

REFERENCES

1. M'Ikanatha NM, Dettinger LA, Perry A, Rogers P, Reynolds SM, Nachamkin I. 2012. Culturing stool specimens for *Campylobacter* spp., Pennsylvania, USA. Emerg Infect Dis 18:484–487. https://doi.org/10.3201/eid1803.111266.
2. Bryan A, Youngster I, McAdam AJ. 2015. Shiga toxin producing *Escherichia coli*. Clin Lab Med 35:247–272. https://doi.org/10.1016/j.cll.2015.02.004.
3. Binnicker MJ. 2015. Multiplex molecular panels for diagnosis of gastrointestinal infection: performance, result interpretation, and cost-effectiveness. J Clin Microbiol 53:3723–3728. https://doi.org/10.1128/JCM.02103-15.
4. Hanson KE, Couturier MR. 2016. Multiplexed molecular diagnostics for respiratory, gastrointestinal, and central nervous system infections. Clin Infect Dis 63:1361–1367. https://doi.org/10.1093/cid/ciw494.
5. Marder EP, Cieslak PR, Cronquist AB, Dunn J, Lathrop S, Rabatsky-Ehr T, Ryan P, Smith K, Tobin-D'Angelo M, Vugia DJ, Zansky S, Holt KG, Wolpert BJ, Lynch M, Tauxe R, Geissler AL. 2017. Incidence and trends of infections with pathogens transmitted commonly through food and the effect of increasing use of culture-independent diagnostic tests on surveillance—Foodborne Diseases Active Surveillance Network, 10 U.S. sites, 2013–2016. MMWR Morb Mortal Wkly Rep 66:397–403. https://doi.org/10.15585/mmwr.mm6615a1.
6. Fitzgerald C, Patrick M, Gonzalez A, Akin J, Polage CR, Wymore K, Gillim-Ross L, Xavier K, Sadlowski J, Monahan J, Hurd S, Dahlberg S, Jerris R, Watson R, Santovenia M, Mitchell D, Harrison C, Tobin-D'Angelo M, DeMartino M, Pentella M, Razeq J, Leonard C, Jung C, Achong-Bowe R, Evans Y, Jain D, Juni B, Leano F, Robinson T, Smith K, Gittelman RM, Garrigan C, Nachamkin I. 2016. Multicenter evaluation of clinical diagnostic methods for detection and isolation of *Campylobacter* spp. from stool. J Clin Microbiol 54:1209–1215. https://doi.org/10.1128/JCM.01925-15.
7. Allard MW, Strain E, Melka D, Bunning K, Musser SM, Brown EW, Timme R. 2016. Practical value of food pathogen traceability through building a whole-genome sequencing network and database. J Clin Microbiol 54:1975–1983. https://doi.org/10.1128/JCM.00081-16.
8. Shea S, Kubota KA, Maguire H, Gladbach S, Woron A, Atkinson-Dunn R, Couturier MR, Miller MB. 2017. Clinical microbiology laboratories' adoption of culture-independent diagnostic tests Is a threat to foodborne-disease surveillance in the United States. J Clin Microbiol 55:10–19. https://doi.org/10.1128/JCM.01624-16.