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Author manuscript

Clin Lab Med. Author manuscript; available in PMC 2020 September 01.

Published in final edited form as:

Clin Lab Med. 2019 September ; 39(3): 499–508. doi:10.1016/j.cll.2019.05.008.

We Can't Do It Alone: The Intersection of Public Health, Public Policy, and Clinical Microbiology

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Keywords

public health microbiology; epidemiology; Foodnet; Antimicrobial Resistant Laboratory Network; FDA-CDC Biobank; laboratory developed test; new antibiotics; multidrug resistance; verification; validation; antibiograms

Introduction

The intersection of public health with clinical microbiology has been apparent since John Snow established the connection of cholera with the Broad Street pump. As we have been challenged by communicable disease crises from the HIV epidemic to the rise of carbapenem-resistant Enterobacteriaceae, our society has amassed new tools to diagnose and treat these infections. Nevertheless, with evolving resistance and emerging infections, the urgent need to fight such threats in a coordinated fashion at a local and societal level continues. We therefore review microbiological public health resources and strategies, and reflect on policies needed to combat microbial threats of the future.

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JEK is a member of the Clinical Advisory Board of First Light Biosciences, Chelmsford, MA. TECAN (Morrisville, NC) provided an HP D300 digital dispenser and associated consumables used by JEK's research group during development of rapid and at-will antimicrobial susceptibility testing diagnostics. Neither First Light nor TECAN had a role in manuscript preparation or decision to publish.

National Resources Available at Local Level

Bringing new drugs on board.

New antibiotics offer potentially life-saving options for multidrug-resistant infections. However, they are only useful clinically if the microbiology laboratory can provide timely antimicrobial susceptibility testing (AST) results. Historically there has been a time lag in the availability of susceptibility testing methods for new antibiotics. As a result, isolates must be sent to a reference laboratory delaying AST results for up to a week or more. However, for an AST result to be meaningful for patient management, it usually must be available in a few days at most.

In the recent past, the time delay between Food and Drug Administration (FDA) approval of new antimicrobials and the availability of corresponding AST methods has been a significant hindrance to the utilization of new drugs for clinical care. Ceftaroline, for example, did not have an FDA cleared AST method until seven months after the initial approval in 2010 and automated systems took another 2.5–3.5 years to gain clearance. The FDA recognized this problematic discordance and hence made efforts to coordinate release of antimicrobials and commercial AST methods¹. However, it can still take years before novel antimicrobials become incorporated into commercial panels. Fortunately, diffusion-based methods may offer an interim solution.

Nevertheless, before implementation of any AST method for a new drug, clinical laboratories must still verify its performance per Clinical Laboratory Improvement Amendments (CLIA) '88 requirement. CLIA stipulations are non-specific, and for FDA approved assays only indicate the need to verify accuracy and precision to an unstated degree. In the absence of explicit guidance, use of accepted standards in the field are a reasonable and commonly used substitute, codified in documents such as Cumitech 31A².

Verification could entail comparing the new AST method to a reference standard such as broth microdilution (BMD), but this gold standard method requires significant assay expertise, technologist effort, and ready availability of antimicrobial powder. Most hospital laboratories consequently opt to verify new AST methods using a set of strains already characterized by a reference method such as BMD (or a non-reference, FDA-cleared method that has been previously verified in a CLIA-accredited laboratory) and which has an appropriate representation of susceptible and resistant isolates.

Practically, for new antibiotics, where to find such characterized strain sets is unclear. Availability of appropriate strains sets is also needed for “off-label” verification of existing methods when breakpoints are adjusted to reflect evolving best practice consensus (e.g., annual Clinical and Laboratory Standards Institute updates). The often-recommended fall back for the latter is to compare with the disk diffusion method using correspondingly updated zone sizes³. The rationale is that the disk diffusion method for common drugs was instituted prior to CLIA '88 and therefore is exempt from its own verification requirements⁴, a somewhat problematic strategy as the disks were originally cleared based on categorical performance around former, but not updated breakpoints, and accordingly important essential agreement metrics cannot be assessed.

Obviously for new drugs, appropriate, well-characterized strain sets must be possessed by pharmaceutical manufacturers or affiliates as data from these strains are required to establish the susceptibility breakpoints for the drug. Under current regulations, however, pharmaceutical companies are prohibited from proactively either providing or sourcing characterized strains sets for clinical laboratories. Oddly, clinical labs can independently inquire on a need-to-know basis, freeing pharmaceutical companies to reveal some potential options. Such obstructive policies should be remedied by governing bodies, as the ability for clinical labs to verify, and thereby enable clinicians to use novel antimicrobials is just as important as their commercial availability.

The FDA-CDC Antimicrobial Resistance Isolate Bank.

Fortunately, the FDA-Centers for Disease Control and Prevention (CDC) Antimicrobial Resistance (AR) Isolate Bank now provides a way to circumvent this conundrum. Launched in July 2015 as a tool to combat antimicrobial resistance, this highly valuable public health resource provides a curated repository of genotypically and phenotypically characterized bacterial isolates with clinically important resistance mechanisms and reference minimum inhibitory concentrations (MICs) to novel and standard antimicrobials^{5,6}.

The FDA-CDC AR Isolate Bank is a paradigm of a public health resource that supports clinical labs at a local level to provide potentially life-saving, rapid, and up-to-date AST reporting. For example, the AR Isolate Bank includes an *Enterobacteriaceae* carbapenem breakpoint panel designed to assist with verification and implementation of new CLSI carbapenem breakpoints given emergence of novel resistance mechanisms. The Gram-negative carbapenemase detection panel supports verification of tests for carbapenemase production such as the modified carbapenem inactivation method (mCIM) and EDTA-mCIM (eCIM), which can distinguish serine β -lactamases from metallo- β -lactamases⁷. Importantly, these strain sets include an assortment of well-characterized multidrug-resistance mechanisms, such as a range of serine and metallo-carbapenemases, which would be difficult for clinical laboratories to collect comprehensively from their own patients or purchase, and thereby allow clinical laboratories to gain experience with detection of critical resistance elements in their own laboratories.

Extending this idea further, imagine strain sets distributed widely to clinical laboratories for which curated modal MIC data for each new antibiotic would be released coincident with FDA approval. Analogously, as CLSI updates breakpoints, including changes such as new susceptible dose-dependent (SDD) categories to address emerging resistance patterns, there would ideally be concomitant AR Isolate Bank deployment of strain sets with modal MICs within and bordering the relevant MIC ranges to aid laboratories in verifying and promptly adopting these revisions. Particularly in the superbug era, accurate AST reporting of SDD categories formerly classified as “intermediate” can be crucial in providing appropriate salvage therapeutic options for multidrug resistant infections⁸.

In summary, the recently created FDA-CDC AR Isolate Bank provides welcome support for clinical microbiology laboratories as well as a resource for researchers, diagnostics, and pharmaceutical companies. This resource should be supported and strengthened, and ongoing “free availability” maintained with release/updating of panels to coincide with new

drug approvals to counterbalance disincentives for clinical laboratories and companies to invest in capacity for rarely used antimicrobials and testing.

Dare we ask?

We also might consider, if new AST methods were appropriately vetted by the FDA, the encore verification performance by clinical laboratories, whether limited or extensive, seems superfluous. We estimate that it takes approximately 2 days of technologist and director time to validate a new E-test or disk method with 30–40 strains—that is a discouraging barrier for bringing new AST tests on board. Importantly, labs also perform a mini-verification every time they perform a test by running quality control (QC) testing with confirmation that results are within specified limits (individualized quality control plan, IQCP, exceptions aside). Presumably QC requirements are deemed appropriately discriminatory for evaluation of ongoing assay performance, so why the initial extra verification step? Verification should be an issue for initial vetting by the manufacturer with appropriately large, representative strain sets, and test product deficits should not fall under the purview of post marketing discovery by laboratories with greatly differing capabilities. If this seemingly redundant and purposefully vague verification requirement were lifted, the broad array of AST testing for new drugs could be implemented within days! Another option, although potentially burdensome and perhaps unnecessary, would be to task a set of high complexity clinical laboratories on a volunteer basis or possibly with some financial recompense to perform an independent assessment to verify manufacturer’s claims that could be relied upon by the field.

Antimicrobial Resistance Laboratory Network (ARLN).

With emerging multidrug-resistance, clinical laboratories are more frequently encountering pathogens for which there are no active agents based on routine or even reference laboratory-based AST. While novel antimicrobials in clinical trials may be available on a compassionate-use basis, existing agents used in combination regimens are worthy of consideration as well. For example, aztreonam, a monobactam, remains active against metallo-carbapenemases such as the New Delhi metallo- β -lactamase 1 (NDM-1), and ceftazidime-avibactam provides activity against AmpC and extended-spectrum- β -lactamases (ESBLs), which are enzymes that inactivate aztreonam. Accordingly, a regimen that inhibits AmpC and ESBL degradation of aztreonam, which then can function in the presence of potent metallo-carbapenemases should be active against “superbugs” carrying these dangerous resistance elements⁹. However, the question remains how a clinical laboratory would determine whether combinatorial salvage regimens are active against a given isolate.

The CDC has recently set up the Antimicrobial Resistance Laboratory Network (ARLN) to offer such testing. Established in 2016, the ARLN is comprised of seven regional labs and the National Tuberculosis Molecular Surveillance Center where clinical laboratories around the United States can send resistant isolates for additional testing. Their lab network has adopted inkjet printing technology for this AST testing, originally described by Smith and Kirby, and Brennan-Krohn and Kirby, that allows highly accurate and precise at-will set-up and testing of any desired antimicrobial alone or in combination with reference broth microdilution equivalent AST results^{10–14}. The ALRN currently offers, for example, the

combination AST of aztreonam + ceftazidime-avibactam. Furthermore, it has the capacity to characterize isolates via whole genome sequencing and other molecular testing. Most importantly, ARLN provides a distributed lab network that brings new AST and surveillance capabilities closer to the point of patient care. Alternatively, in the future, equivalent technology and antimicrobial reagents could and should be deployed at referral hospitals where superbugs are more prevalent.

Central data and analyte repositories to support laboratory-developed test (LDT) design and validation.

There has been little industry interest in commercializing and seeking FDA approval for molecular diagnostics for clinically important yet less common infectious diseases. Laboratory developed tests (LDTs) fill this unmet need. LDTs are *in vitro* diagnostic tests developed and verified for local use. FDA-cleared methods that have been modified in any way by a clinical microbiology laboratory are also considered LDTs.²

Prominent examples of LDTs would include viral load testing for BK, Epstein-Barr and cytomegalovirus (CMV) viruses in the transplant setting. While there are FDA-cleared assays for CMV viral load testing in blood, testing in other specimen types such as bronchoalveolar lavage, urine, and saliva provide added value for certain populations. Application of revised breakpoints to existing commercial AST methods are also considered a modification and therefore an LDT. Commercial manufacturers often take years to seek clearance for such updates, as the FDA does not have the authority to require companies to submit data within a certain timeframe. Accordingly, during this interval, clinical laboratories must verify accuracy and precision across revised breakpoints. Without the capacity or expertise to implement LDTs, laboratories presumably must continue to use outdated breakpoints, which could miss resistant strains and undermine patient care. As one example of the magnitude of this issue, twenty-eight percent of labs in California had not yet lowered carbapenem breakpoints within five years of CLSI introducing revised, evidenced-based cutoffs in 2010¹⁵. Alternatively, LDT testing, whether for molecular diagnosis of target pathogens, or AST determinations with revised breakpoints, may be performed at reference laboratories, which have extensive menus of LDTs but with suboptimal turn around time delays.

There is ongoing debate about the appropriate level of regulation required for LDTs and whether routine laboratory quality assurance activities under CLIA '88 are sufficient. Given the rapid growth of LDTs in personalized medicine, the American Society for Clinical Pathology (ASCP) recommended that “the regulatory infrastructure adopted must be sufficiently meticulous to safeguard the public without being so burdensome that it impedes emerging technology”¹⁶. As a comparator, in Europe most diagnostic tests are considered low-risk and exempt from pre-market evaluation. Therefore, clinical quality of LDTs is managed through professionally driven quality assessment infrastructure¹⁶. We agree with this latter approach.

By analogy to the FDA-CDC AR Isolate Bank, we envision a public health resource to assist in LDT development that would have the added benefit of greater standardization of assays between institutions. Currently, microbiology laboratories independently construct and

validate LDTs for similar sets of pathogens given comparable clinical needs and the lack of commercial testing options. A free centralized publicly available database of pooled procedural and validation information would provide a much more comprehensive understanding of assay design and performance, and allow laboratories to benefit from collective experience instead of each reinventing the wheel on its own. Best practice procedures including reagent and assay performance characteristics could then be described in consensus guidelines, which would ultimately raise the quality of overall diagnostic testing.

An expansion of inter-institutional comparable LDTs would also significantly bolster surveillance programs as smaller facilities that otherwise may not have had the technical expertise to adopt LDTs may now be able to contribute to the nationwide diagnostic capacity to understand important microbiological concerns such as spread of viral subtypes, sexually transmitted infections, or antimicrobial resistance. To expand this idea further, we also propose a repository of free publicly available critical analytes that would allow standardization of LDT assays across facilities (for example, viral load standards) and ensure robust detection, for example, of critical viral subtypes in the face of genetic drift and emerging variants.

It is time to adopt a different model for diagnostic test approval in areas of unmet medical need.

An alternative and bolder strategy would be to lower the regulatory burden for approval of infectious disease diagnostics in areas of unmet need. Our proposal would be to lower the approval threshold for areas of focused need that would not normally be appealing for commercial development under current regulations. Specifically, companies would still have to establish robust analytical performance for their methodology, however without the need for extensive and costly clinical trials to establish clinical performance/utility. This would spur innovation, development, and implementation of laboratory tests in areas such as detection of rare emerging diseases (MERS, Ebola, carbapenemase detection and discrimination, blood parasites, seasonal influenza subtyping for therapeutic discrimination, tick-borne bloodstream infection, and *Candida auris* to forestall hospital outbreaks). Transplant and immunocompromised host infectious disease testing could also be extended to the range of sample types of importance (e.g., BAL fluid and other respiratory specimens for molecular detection of PJP and toxoplasma among others). The European diagnostics market, for example, offers excellent diagnostic support for clinical care without the extra layer of regulatory burden.

Freed of the need to determine clinical validity, companies could confirm analytical performance in multiple sample types, thereby in turn freeing clinical laboratories from replicative efforts to develop LDT's when existing testing platforms would suffice. Those companies that could offer testing on the multitude of sample types of interest would have a competitive advantage, and competition would then spur a comprehensive testing menu to the benefit of our patients.

Furthermore, the demand for expensive reference laboratory testing would be decreased and more timely local diagnosis would reduce inefficiencies in the health care system, avoid unnecessary expense associated delayed diagnosis, and contribute positively to patient well-being. We therefore encourage a rethinking of current regulatory framework in the United States. For areas of unmet need, we should put decision-making capability about clinical utility into the hands of medical specialists (laboratory medicine/clinical microbiology/infectious diseases) who can evaluate the most up-to-date medical and scientific literature in concert with evaluation of analytical performance capabilities, published in product inserts and vetted by the FDA, and make appropriate decisions about assays and platforms.

Setting the standard.

Strong national and international standards for quality assurance, method performance, and interpretative criteria should be strengthened and maintained. We acknowledge the contribution of both national and international organizations such as CLSI, EUCAST (European Committee on Antimicrobial Susceptibility Testing), USCAST (United States Committee on Antimicrobial Susceptibility Testing), SIS (Swedish Standards Institute), CEN (European Committee for Standardization), and ISO (International Organization of Standardization) that establish such standards. Many are volunteer-driven, membership-and/or government-supported not-for-profit entities. We also applaud coordination between organizations such as the FDA and CLSI. We encourage their continued, proactive review of breakpoints based on the most current understanding of pharmacokinetics and pharmacodynamics, which may suggest revisiting of values established during original drug approval.

Strengthening Public Health Laboratory Surveillance.

National surveillance programs represent a key intersection between public health and microbiology laboratories. One of the oldest examples is the Foodborne Diseases Active Surveillance Network (FoodNet), established in 1995 as a collaboration between ten state health departments, that monitors for significant infectious enteric pathogens¹⁷. FoodNet determines the burden and trends in foodborne illness in order to appropriately design prevention and intervention programs.

Several other CDC surveillance systems for tracking food and waterborne diseases including Foodborne Disease Outbreak Surveillance System (FDOSS), National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS), and Waterborne Disease and Outbreak Surveillance (WBDOSS) among others¹⁸. While certain programs function more closely with Infection Control and Epidemiology departments to gather relevant patient clinical data, all of these systems require interaction with the microbiology laboratory for appropriate identification and isolate collection.

Some of the programs, such as PulseNet provide bacterial DNA fingerprinting (previously pulsed-field gel electrophoresis now transitioning to whole genome sequencing) of foodborne illnesses. This data revolutionized epidemic investigations as outbreaks could be identified and intervened upon in hours to days instead of weeks in the previous era when

epidemiologists had to wait for new patients to meet appropriate case criteria in order to identify clinical patterns suggestive of a novel outbreak¹⁹.

The need for shared surveillance and diagnostic data repositories has been recognized among international collaborations as well. TBnet is one illustration of a partnership of European pulmonologists, epidemiologists, and infectious disease specialists organized on the premise of shared research goals, with a particular interest in immunodiagnostic tools. They accordingly have developed their own TB Biobank in addition to a data repository using common collection methods to simplify cross-study comparison²⁰.

Similarly, the Program for Monitoring Emerging Diseases (ProMED-mail) is an entity founded in 1994 and maintained by the International Society of Infectious Diseases. Conceived as a free internet listserv tool for rapid detection and report of emerging infectious or toxin-mediated diseases, ProMED-mail expanded from only 40 subscribers at its inception to >83,000 in over 150 countries. Subscribers receive e-mail reports filtered and moderated by a specialist panel on outbreaks and disease emergence. ProMED-mail voiced the earliest public account of severe acute respiratory syndrome (SARS) and warned the medical community throughout the world of this outbreak^{21,22}.

In this era of globalization with common threats and pathogens facing individual hospitals, states, and nations, it makes intuitive sense that these efforts to collect and share data should be fostered and strengthened.

Information Exchange.

Real-time publicly available data to track infectious diseases is essential to control and prevention efforts and ever more relevant as demonstrated by ProMED-mail's internet-based success. FluNet is a model prototype that should be extrapolated to other emerging infectious threats. Established in 1997, FluNet is a global web-based data collection and reporting tool for influenza and logs viruses by subtype with records updated weekly²³. SENTRY and ATLAS provide world-wide tracking of AST data for currently available antimicrobials.^{24,25}

Expanded surveillance programs that, for example, track carbapenem-resistant Enterobacteriaceae by genotype should be public health goals achievable with current bioinformatic platforms. As one example of potential impact, the Israel National Center for Infection Control (NCIC) initiated an effort in 2008 within long-term care facilities (LTCFs) where they collected a real-time database of all CRE carriers and events leading to acquisition. The program facilitated supervised information exchange and encompassed approximately 25,000 beds over 300 institutions enabling early detection of carriers and implementation of population-specific contact precautions²⁶. These efforts achieved over a ten-fold reduction of CRE point prevalence in their acute hospital network and 50% reduction in all facilities. We have no doubt that such efforts will become increasingly important as new resistance emerges.

Annually updated hospital-based antibiograms are insufficient to guide empiric therapy with emerging antimicrobial resistance. Automated, de-identified input from hospital and

laboratory information systems (HIS/LIS) that provide regional to national metadata to track and forecast patterns of antibiotic resistance is a reasonable goal for our public health infrastructure. Daily updated facility, regional, national, and international (for travelers) species and clone specific antibiograms should be available to guide empiric therapeutic choice. Integration with whole-genome sequencing will facilitate clone tracking, illuminate resistance evolution, and inform local and public health countermeasures. As sources of new epidemics, infections, and/or resistance may be identified, there may be local opposition to participation. However, with balanced levels of access by healthcare providers and the public, the overarching public good of this early detection and control infrastructure should outweigh economic disincentives.

Conclusion

Microbiological data is necessary to inform public health goals and strategies, and conversely public health goals help guide the diagnostic strategies pursued in laboratories. In an era of rising global infectious disease threats, the public health laboratory infrastructure requires maintenance and strengthening to forestall harm to individual patients and populations. A pressing public health and societal need is the framework and infrastructure to streamline adoption of new antimicrobials and diagnostics. We analogously need streamlined, real-time output from the microbiology laboratories with centralized data aggregation to detect spread of resistant organisms and direct appropriate local and public health countermeasures. Here, we review some of the major existing resources that have supported our public health efforts and also identify programs and policies that could be of significant benefit. Governments, standards organizations, researchers, industry and clinical microbiology laboratories should continue to collaborate to better address unmet public health goals and individual needs of infected patients.

Acknowledgements

Based on space limitations, it was not possible for us to reference and cite all of the relevant literature in the public health field related to clinical microbiology and necessarily were selective. We thank Kenneth P. Smith for helpful comments on the manuscript.

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Key Points

1. National resources like the FDA-CDC AR Isolate Bank can support clinical labs at a local level as they confront multidrug-resistant pathogens and should be supported, strengthened, and expanded.
2. Distributed networks like the Antimicrobial Resistance Laboratory Network offer specialized diagnostics to address specific needs such as unconventional antimicrobial susceptibility testing not yet available at a local level.
3. Public resources should be made available to help laboratories develop and standardize tests to address pressing infectious disease diagnostic needs that are not commercially compelling for assay development.
4. Continuously updated local, regional and national antibiograms should be available to guide therapeutic decisions with granularity and guide public health interventions.
5. Policies and regulations should balance reliability of laboratory testing with fostering rapid entrance of infectious diagnostics into the market.

Synopsis

Infectious diseases by definition spread, and therefore have impact beyond local hospitals and institutions where they occur. With increasingly complex and worrisome infectious disease evolution including emergence of multidrug resistance, regional, national, and international agencies and resources must work hand in hand with local clinical microbiology laboratories to address these global threats. Described are examples of such resources, both existing and aspirational, that will be needed to address the infectious disease challenges ahead. We comment on several instances of entrenched policy that are non-productive and may be worthy of revision to address unmet needs in infectious disease diagnostics.