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DOI: https://doi.org/10.1016/j.cll.2019.05.008

Article Title

We can't do it alone: the intersection of public health, public policy, and clinical microbiology

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disclosure statement

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.

Keywords

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

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.

70 # Introduction

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

79

80 **National Resources Available at Local Level**

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

87 In the recent past, the time delay between Food and Drug Administration (FDA) approval of new
88 antimicrobials and the availability of corresponding AST methods has been a significant hindrance to the
89 utilization of new drugs for clinical care. Ceftaroline, for example, did not have an FDA cleared AST
90 method until seven months after the initial approval in 2010 and automated systems took another 2.5-
91 3.5 years to gain clearance. The FDA recognized this problematic discordance and hence made efforts to
92 coordinate release of antimicrobials and commercial AST methods[1]. However, it can still take years

93 before novel antimicrobials become incorporated into commercial panels. Fortunately, diffusion-based
94 methods may offer an interim solution.

95 Nevertheless, before implementation of any AST method for a new drug, clinical laboratories
96 must still verify its performance per Clinical Laboratory Improvement Amendments (CLIA) '88
97 requirement. CLIA stipulations are non-specific, and for FDA approved assays only indicate the need to
98 verify accuracy and precision to an unstated degree. In the absence of explicit guidance, use of accepted
99 standards in the field are a reasonable and commonly used substitute, codified in documents such as
100 Cumitech 31A[2].

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

107 Practically, for new antibiotics, where to find such characterized strain sets is unclear.
108 Availability of appropriate strains sets is also needed for "off-label" verification of existing methods
109 when breakpoints are adjusted to reflect evolving best practice consensus (e.g., annual Clinical and
110 Laboratory Standards Institute updates). The often-recommended fall back for the latter is to compare
111 with the disk diffusion method using correspondingly updated zone sizes[3]. The rationale is that the disk
112 diffusion method for common drugs was instituted prior to CLIA '88 and therefore is exempt from its
113 own verification requirements[4], a somewhat problematic strategy as the disks were originally cleared
114 based on categorical performance around former, but not updated breakpoints, and accordingly
115 important essential agreement metrics cannot be assessed.

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

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

130 The FDA-CDC AR Isolate Bank is a paradigm of a public health resource that supports clinical labs
131 at a local level to provide potentially life-saving, rapid, and up-to-date AST reporting. For example, the
132 AR Isolate Bank includes an *Enterobacteriaceae* carbapenem breakpoint panel designed to assist with
133 verification and implementation of new CLSI carbapenem breakpoints given emergence of novel
134 resistance mechanisms. The Gram-negative carbapenemase detection panel supports verification of
135 tests for carbapenemase production such as the modified carbapenem inactivation method (mCIM) and
136 EDTA-mCIM (eCIM), which can distinguish serine β-lactamases from metallo-β-lactamases[7]. Importantly,
137 these strain sets include an assortment of well-characterized multidrug-resistance mechanisms, such as
138 a range of serine and metallo-carbapenemases, which would be difficult for clinical laboratories to

139 collect comprehensively from their own patients or purchase, and thereby allow clinical laboratories to
140 gain experience with detection of critical resistance elements in their own laboratories.
141 Extending this idea further, imagine strain sets distributed widely to clinical laboratories for
142 which curated modal MIC data for each new antibiotic would be released coincident with FDA approval.
143 Analogously, as CLSI updates breakpoints, including changes such as new susceptible dose-dependent
144 (SDD) categories to address emerging resistance patterns, there would ideally be concomitant AR Isolate
145 Bank deployment of strain sets with modal MICs within and bordering the relevant MIC ranges to aid
146 laboratories in verifying and promptly adopting these revisions. Particularly in the superbug era,
147 accurate AST reporting of SDD categories formerly classified as "intermediate" can be crucial in
148 providing appropriate salvage therapeutic options for multidrug resistant infections[8].
149 In summary, the recently created FDA-CDC AR Isolate Bank provides welcome support for
150 clinical microbiology laboratories as well as a resource for researchers, diagnostics, and pharmaceutical
151 companies. This resource should be supported and strengthened, and ongoing "free availability"
152 maintained with release/updating of panels to coincide with new drug approvals to counterbalance
153 disincentives for clinical laboratories and companies to invest in capacity for rarely used antimicrobials
154 and testing.
155 **Dare we ask?** We also might consider, if new AST methods were appropriately vetted by the
156 FDA, the encore verification performance by clinical laboratories, whether limited or extensive, seems
157 superfluous. We estimate that it takes approximately 2 days of technologist and director time to
158 validate a new E-test or disk method with 30-40 strains - that is a discouraging barrier for bringing new
159 AST tests on board. Importantly, labs also perform a mini-verification every time they perform a test by
160 running quality control (QC) testing with confirmation that results are within specified limits
161 (individualized quality control plan, IQCP, exceptions aside). Presumably QC requirements are deemed
162 appropriately discriminatory for evaluation of ongoing assay performance, so why the initial extra

163 verification step? Verification should be an issue for initial vetting by the manufacturer with
164 appropriately large, representative strain sets, and test product deficits should not fall under the
165 purview of post marketing discovery by laboratories with greatly differing capabilities. If this seemingly
166 redundant and purposefully vague verification requirement were lifted, the broad array of AST testing
167 for new drugs could be implemented within days! Another option, although potentially burdensome and
168 perhaps unnecessary, would be to task a set of high complexity clinical laboratories on a volunteer basis
169 or possibly with some financial recompense to perform an independent assessment to verify
170 manufacturer's claims that could be relied upon by the field.

171 **Antimicrobial Resistance Laboratory Network (ARLN).** With emerging multidrug-resistance,
172 clinical laboratories are more frequently encountering pathogens for which there are no active agents
173 based on routine or even reference laboratory-based AST. While novel antimicrobials in clinical trials
174 may be available on a compassionate-use basis, existing agents used in combination regimens are
175 worthy of consideration as well. For example, aztreonam, a monobactam, remains active against
176 metallo-carbapenemases such as the New Delhi metallo-β-lactamase 1 (NDM-1), and ceftazidime-
177 avibactam provides activity against AmpC and extended-spectrum- β-lactamases (ESBLs), which are
178 enzymes that inactivate aztreonam. Accordingly, a regimen that inhibits AmpC and ESBL degradation of
179 aztreonam, which then can function in the presence of potent metallo-carbapenemases should be active
180 against "superbugs" carrying these dangerous resistance elements[9]. However, the question remains
181 how a clinical laboratory would determine whether combinatorial salvage regimens are active against a
182 given isolate.

183 The CDC has recently set up the Antimicrobial Resistance Laboratory Network (ARLN) to offer
184 such testing. Established in 2016, the ARLN is comprised of seven regional labs and the National
185 Tuberculosis Molecular Surveillance Center where clinical laboratories around the United States can
186 send resistant isolates for additional testing. Their lab network has adopted inkjet printing technology

187 for this AST testing, originally described by Smith and Kirby, and Brennan-Krohn and Kirby, that allows
188 highly accurate and precise at-will set-up and testing of any desired antimicrobial alone or in
189 combination with reference broth microdilution equivalent AST results[10-14]. The ALRN currently offers,
190 for example, the combination AST of aztreonam + ceftazidime-avibactam. Furthermore, it has the
191 capacity to characterize isolates via whole genome sequencing and other molecular testing. Most
192 importantly, ARLN provides a distributed lab network that brings new AST and surveillance capabilities
193 closer to the point of patient care. Alternatively, in the future, equivalent technology and antimicrobial
194 reagents could and should be deployed at referral hospitals where superbugs are more prevalent.

195 **Central data and analyte repositories to support laboratory-developed test (LDT) design and**
196 **validation.** There has been little industry interest in commercializing and seeking FDA approval for
197 molecular diagnostics for clinically important yet less common infectious diseases. Laboratory
198 developed tests (LDTs) fill this unmet need. LDTs are *in vitro* diagnostic tests developed and verified for
199 local use. FDA-cleared methods that have been modified in any way by a clinical microbiology laboratory
200 are also considered LDTs.[2]

201 Prominent examples of LDTs would include viral load testing for BK, Epstein-Barr and
202 cytomegalovirus (CMV) viruses in the transplant setting. While there are FDA-cleared assays for CMV
203 viral load testing in blood, testing in other specimen types such as bronchoalveolar lavage, urine, and
204 saliva provide added value for certain populations. Application of revised breakpoints to existing
205 commercial AST methods are also considered a modification and therefore an LDT. Commercial
206 manufacturers often take years to seek clearance for such updates, as the FDA does not have the
207 authority to require companies to submit data within a certain timeframe. Accordingly, during this
208 interval, clinical laboratories must verify accuracy and precision across revised breakpoints. Without the
209 capacity or expertise to implement LDTs, laboratories presumably must continue to use outdated
210 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 2010[15]. 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 infrastructure[16]. 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

235 may now be able to contribute to the nationwide diagnostic capacity to understand important
236 microbiological concerns such as spread of viral subtypes, sexually transmitted infections, or
237 antimicrobial resistance. To expand this idea further, we also propose a repository of free publicly
238 available critical analytes that would allow standardization of LDT assays across facilities (for example,
239 viral load standards) and ensure robust detection, for example, of critical viral subtypes in the face of
240 genetic drift and emerging variants.
241

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

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

257 Freed of the need to determine clinical validity, companies could confirm analytical performance
258 in multiple sample types, thereby in turn freeing clinical laboratories from replicative efforts to develop

259 LDT's when existing testing platforms would suffice. Those companies that could offer testing on the
260 multitude of sample types of interest would have a competitive advantage, and competition would then
261 spur a comprehensive testing menu to the benefit of our patients.

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

271 **Setting the standard.** Strong national and international standards for quality assurance, method
272 performance, and interpretative criteria should be strengthened and maintained. We acknowledge the
273 contribution of both national and international organizations such as CLSI, EUCAST (European
274 Committee on Antimicrobial Susceptibility Testing), USCAST (United States Committee on Antimicrobial
275 Susceptibility Testing), SIS (Swedish Standards Institute), CEN (European Committee for
276 Standardization), and ISO (International Organization of Standardization) that establish such standards.
277 Many are volunteer-driven, membership- and/or government-supported not-for-profit entities. We also
278 applaud coordination between organizations such as the FDA and CLSI. We encourage their continued,
279 proactive review of breakpoints based on the most current understanding of pharmacokinetics and
280 pharmacodynamics, which may suggest revisiting of values established during original drug approval.
281

282 **Strengthening Public Health Laboratory Surveillance.**

283 National surveillance programs represent a key intersection between public health and
284 microbiology laboratories. One of the oldest examples is the Foodborne Diseases Active Surveillance
285 Network (FoodNet), established in 1995 as a collaboration between ten state health departments, that
286 monitors for significant infectious enteric pathogens[17]. FoodNet determines the burden and trends in
287 foodborne illness in order to appropriately design prevention and intervention programs.

288 Several other CDC surveillance systems for tracking food and waterborne diseases including
289 Foodborne Disease Outbreak Surveillance System (FDOSS), National Antimicrobial Resistance
290 Monitoring System for Enteric Bacteria (NARMS), and Waterborne Disease and Outbreak Surveillance
291 (WBDOSS) among others[18]. While certain programs function more closely with Infection Control and
292 Epidemiology departments to gather relevant patient clinical data, all of these systems require
293 interaction with the microbiology laboratory for appropriate identification and isolate collection.

294 Some of the programs, such as PulseNet provide bacterial DNA fingerprinting (previously pulsed-
295 field gel electrophoresis now transitioning to whole genome sequencing) of foodborne illnesses. This
296 data revolutionized epidemic investigations as outbreaks could be identified and intervened upon in
297 hours to days instead of weeks in the previous era when epidemiologists had to wait for new patients to
298 meet appropriate case criteria in order to identify clinical patterns suggestive of a novel outbreak[19].

299 The need for shared surveillance and diagnostic data repositories has been recognized among
300 international collaborations as well. TBnet is one illustration of a partnership of European
301 pulmonologists, epidemiologists, and infectious disease specialists organized on the premise of shared
302 research goals, with a particular interest in immunodiagnostic tools. They accordingly have developed
303 their own TB Biobank in addition to a data repository using common collection methods to simplify
304 cross-study comparison[20].

305 Similarly, the Program for Monitoring Emerging Diseases (ProMED-mail) is an entity founded in
306 1994 and maintained by the International Society of Infectious Diseases. Conceived as a free internet

307 listserv tool for rapid detection and report of emerging infectious or toxin-mediated diseases, ProMED-
308 mail expanded from only 40 subscribers at its inception to >83,000 in over 150 countries. Subscribers
309 receive e-mail reports filtered and moderated by a specialist panel on outbreaks and disease
310 emergence. ProMED-mail voiced the earliest public account of severe acute respiratory syndrome
311 (SARS) and warned the medical community throughout the world of this outbreak[21,22].

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

315

316 **Information Exchange.** Real-time publicly available data to track infectious diseases is essential to
317 control and prevention efforts and ever more relevant as demonstrated by ProMED-mail's internet-
318 based success. FluNet is a model prototype that should be extrapolated to other emerging infectious
319 threats. Established in 1997, FluNet is a global web-based data collection and reporting tool for influenza
320 and logs viruses by subtype with records updated weekly[23]. SENTRY and ATLAS provide world-wide
321 tracking of AST data for currently available antimicrobials.[24,25]

322 Expanded surveillance programs that, for example, track carbapenem-resistant
323 Enterobacteriaceae by genotype should be public health goals achievable with current bioinformatic
324 platforms. As one example of potential impact, the Israel National Center for Infection Control (NCIC)
325 initiated an effort in 2008 within long-term care facilities (LTCFs) where they collected a real-time
326 database of all CRE carriers and events leading to acquisition. The program facilitated supervised
327 information exchange and encompassed approximately 25,000 beds over 300 institutions enabling early
328 detection of carriers and implementation of population-specific contact precautions[26]. These efforts
329 achieved over a ten-fold reduction of CRE point prevalence in their acute hospital network and 50%

330 reduction in all facilities. We have no doubt that such efforts will become increasingly important as new
331 resistance emerges.
332 Annually updated hospital-based antibiograms are insufficient to guide empiric therapy with
333 emerging antimicrobial resistance. Automated, de-identified input from hospital and laboratory
334 information systems (HIS/LIS) that provide regional to national metadata to track and forecast patterns
335 of antibiotic resistance is a reasonable goal for our public health infrastructure. Daily updated facility,
336 regional, national, and international (for travelers) species and clone specific antibiograms should be
337 available to guide empiric therapeutic choice. Integration with whole-genome sequencing will facilitate
338 clone tracking, illuminate resistance evolution, and inform local and public health countermeasures. As
339 sources of new epidemics, infections, and/or resistance may be identified, there may be local opposition
340 to participation. However, with balanced levels of access by healthcare providers and the public, the
341 overarching public good of this early detection and control infrastructure should outweigh economic
342 disincentives.
343
344 **Conclusion**
345 Microbiological data is necessary to inform public health goals and strategies, and conversely
346 public health goals help guide the diagnostic strategies pursued in laboratories. In an era of rising global
347 infectious disease threats, the public health laboratory infrastructure requires maintainance and
348 strengthening to forestall harm to individual patients and populations. A pressing public health and
349 societal need is the framework and infrastructure to streamline adoption of new antimicrobials and
350 diagnostics.. We analogously need streamlined, real-time output from the microbiology laboratories
351 with centralized data aggregation to detect spread of resistant organisms and direct appropriate local
352 and public health countermeasures. Here, we review some of the major existing resources that have
353 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.

363

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