Methodologies and Strategies in Laboratory Practice Research

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The 1986 and 1989 Institutes on Critical Issues in Health Laboratory Practice focused on (a) changes in the health environment and factors that influence changes in laboratory testing practices, and (b) interactions among the components of the total testing process, particularly the importance of improved communications between clinicians and laboratorians. Apparent in these and subsequent discussions has been the paucity of data for assisting laboratorians and other health care providers in understanding the state of laboratory practice and for identifying the issues of testing quality. The purpose of the 1995 Laboratory Institute is to provide a forum for reviewing research activities and developing new strategies for future laboratory practice research.

The laboratory practice research agenda is generally determined by several factors:

- Institutional priorities
- Skills and experience of the research team (statisticians, epidemiologists, laboratorians and clinicians)
- Availability of research funds
- Opportunities to collaborate with others

Laboratory practice research conducted in the Division of Laboratory Systems (DLS), Public Health Practice Program Office (PHPPO), Centers for Disease Control and Prevention (CDC) incorporates a systems approach to evaluate the parameters of quality in the testing process. Using this approach, the following questions have been asked:

- Does the testing process work?
- What makes it work?
- What are the benefits?
- What guides laboratorians in critical decision-making?

DLS is attempting to address these questions primarily by developing surveillance and evaluation methodologies. Surveillance techniques can be used to determine the current state of laboratory practice while identifying important signal events. Evaluation methodologies are used to ascertain accuracy and reliability within the testing process, with the overall goal of improving the quality of laboratory practice and patient outcomes.

The research projects at CDC can be categorized into three general areas: research performed with surveillance networks, assessments of the determinants of quality, and evaluation studies. DLS collaborates with laboratory and physician networks to identify current practices and sentinel events in laboratory medicine. Research questions studied typically focus on the reliability of proficiency testing; the relationship between

quality control and quality assurance practices and test reliability and accuracy; and the impact of personnel requirements on the quality of laboratory testing. Finally, evaluation studies measure changes in laboratory practice and their relationship to health outcomes.

Over 20 different studies in the area of laboratory practice research are currently being conducted by DLS. This paper describes the strategies that went into designing two of these studies. The approaches used built on the experience of the division as well as of collaborators both past and present. They illustrate research protocols that work well and demonstrate the advantages and limitations of each study design. The two studies discussed are considered high priority at CDC in the area of human immunodeficiency virus/ acquired immunodeficiency syndrome (HIV/AIDS) laboratory testing practices. The first investigates the extent to which open proficiency testing (PT) performance reflects actual patient testing performance. The other examines the influences that motivate laboratorians to change or implement certain testing practices and whether changes lead to improvements in quality. For purposes of simplification, the former study is referred to as the PT study and the latter the evaluation study.

The PT Study

Proficiency testing and performance evaluation data suggest that the error rate for the HIV antibody test is low.[1] Regardless of the test performed, the results show an overall error rate ranging from 0.5-3.0% (Figure 1). Is proficiency testing an accurate measure of day-to-day performance on patients' samples, and does it reflect the true error rate? Two different study designs were considered to answer these questions: a blind study and a split-sample study. A blind study uses survey reference material or specially prepared samples that are aliquoted and submitted for testing. This design was rejected for several reasons. Using specially prepared samples would not provide data necessary to evaluate pre- and post-analytical sources of error. Actual patient specimens are more useful for evaluating errors in the total testing process. Finally, the blind sample approach had the potential for disturbing ongoing HIV surveillance reporting systems. For these reasons a split-specimen design was selected for the PT study.

As part of this design, it was critical to decide the number of samples needed to answer the study questions. Assuming an error rate of 0.5%, we calculated that 8000 samples would be needed to detect a 0.5% difference in error rate with 90% power. This took into account an estimate that the rate of HIV-positive samples received from the participating sites would be 15%. (The actual rate was 14% using patient specimens collected at testing sites geographically distributed throughout 44 states.)

In the study, two samples were collected from each patient, resulting in three different test reports: blind, open, and referral. One sample was processed normally and forwarded for routine (blind) testing. The second specimen was sent to a reference laboratory and split into aliquots. One was sent to the regular testing laboratory for open performance evaluation, and another was tested at the reference laboratory. A third aliquot was frozen and saved for later testing at CDC if there was disagreement among the other test results (Figure 2). Complete data for analysis were obtained for 93% of the collected samples. The loss of

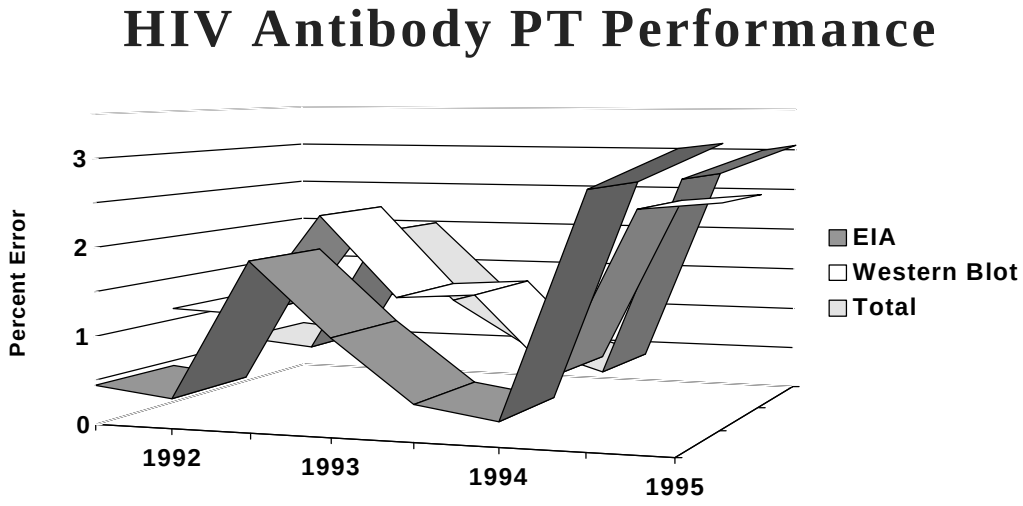

Figure 1

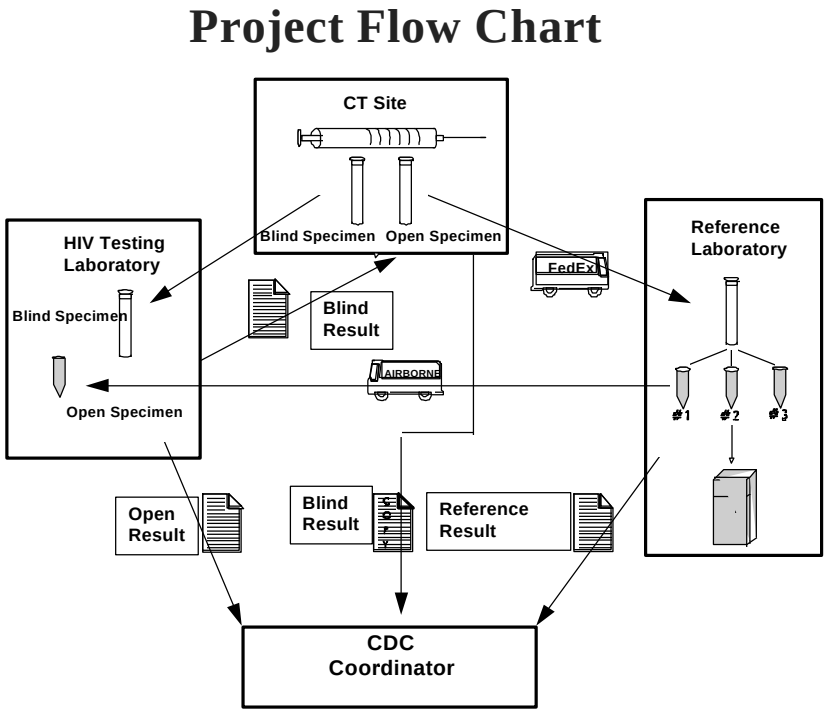

Figure 2

data was primarily due to pre- and post-analytical problems, such as tube breakage or reports not being received. Preliminary results demonstrated that pre- and post-analytical problems may occur more frequently than analytical problems. This finding is consistent with previously reported data.[2]

Using this study design it was possible to:

- Evaluate the difference between blind, open, and reference laboratory test results
- Determine the rates of pre-, post-, and analytical errors
- Measure turnaround times
- Evaluate the manner and format of HIV-antibody test results reporting
- Assess whether public health guidelines are followed for HIV-antibody sero-status and Western blot testing

Inherent limitations exist in this study design. Two disadvantages identified include the complex management process and the high cost. Another is that the distribution of the participants may not be representative of all laboratories that perform HIV antibody testing, and this could affect the generalizability of the study. When compared to all laboratories that perform HIV antibody testing, a larger percentage of health department laboratories participated in the study. Even though previous studies have suggested no difference in performance evaluations when the results are stratified by laboratory type,[2] we would be cautious in generalizing these results to all laboratories.

There are several notable advantages to this study design: First, it enabled us to answer the testing process questions that were posed, which is very important to any study. The design facilitated the use of a large number of samples, increasing the statistical power and confidence in the findings. Finally, the research methodology is transferrable to other research settings.

The Evaluation Study

This study evaluates factors that influenced change in T-lymphocyte immunophenotyping (TLI) laboratory practices between 1990 and 1994 (Figure 3). It attempts to identify past and current practices, barriers to change, and outcomes that occurred as a result of changes in practices.

The study examines these factors for their influence on changes in laboratory practice:

- External quality assurance programs, e.g., CDC's Model Performance Evaluation Program (MPEP) and the College of American Pathologists (CAP)
- Laboratory training, e.g., through CDC, the National Laboratory Training Network, and manufacturers
- Guidelines, e.g., the Morbidity and Mortality Weekly Report (MMWR), National Committee for Clinical Laboratory Standards (NCCLS), and National Institutes of Health (NIH)
- Regulations and accreditation requirements, e.g., Clinical Laboratory Improvement Amendments (CLIA) of 1988

Data were collected from four study groups:

- Laboratories in the United States

Factors Influencing Change

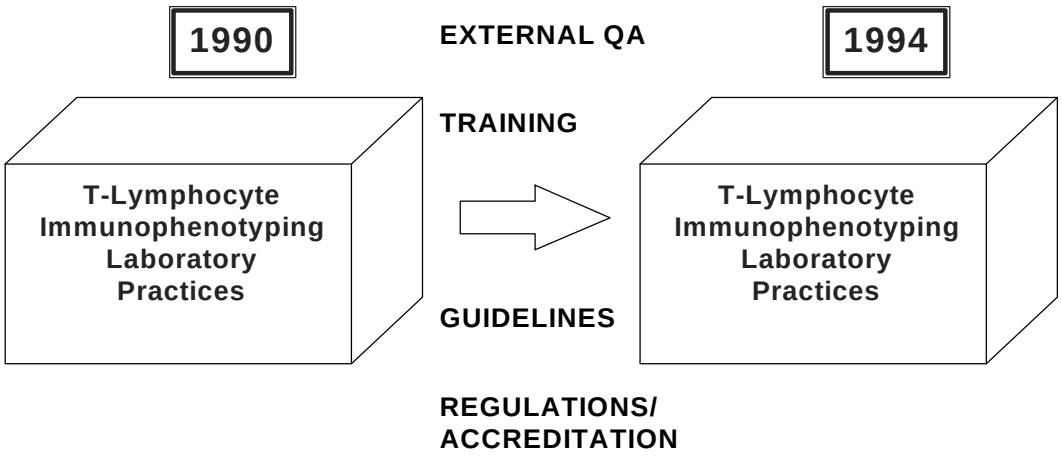

Figure 3

performing T-lymphocyte immunophenotyping (TLI) by flow cytometry (Laboratory Evaluation Survey)

- TLI laboratories participating in CDC's performance evaluation program (TLI MPEP)
- Physicians responding to a medical practice questionnaire (Clinician Survey)
- Laboratorians attending National Laboratory Training Network (NLTN)-sponsored TLI courses

The remaining discussion focuses on the methodology and results from the Laboratory Evaluation Survey. We sent this survey to the entire population of laboratories that perform clinical TLI and obtained a response rate of 76%, which is considered high for this type of survey. The following practices were evaluated:

- Safety
- Training
- Specimen collection and integrity
- Sample preparation
- Data acquisition, storage and reporting
- External quality assurance (proficiency testing and proficiency evaluations)

This study demonstrated that from 1990 to 1994, the percentage of laboratories following published guidelines has increased. The total number of laboratories (primarily hospital and independent labs) performing TLI has grown, with a concomitant increase in the number of patient samples received for testing.

Changes in Practice and Sources of Influence

Practice Changed	N	Factors
Initiated T-cell check	320	MMWR, NCCLS guidelines
Reagent panel	318	MMWR guidelines, CAP checklist
Safety practices	164	OSHA, CAP checklist
Enrolled in PE/PT program	160	CAP checklist, CLIA
Specimen rejection criteria	113	MMWR guidelines, CAP checklist
Sample preparation	64	MMWR guidelines, Manufacturer
Training requirements	45	MMWR guidelines, CAP checklist
Data storage	34	CAP checklist, State regulations, MMWR guidelines
Instrument standardization	27	Manufacturer, CAP checklist

Figure 4

Laboratories indicating that they had initiated a change in laboratory practice since 1990 were asked to specify the reason from a list of choices (Figure 4). They were also asked if the changes had made a difference in testing quality. The study design facilitated the stratification of laboratories in several different ways: by laboratory type, by the year in which TLI testing was begun, and by participation in training and external PT. We could then calculated the overall measure of factors that influence change in different types of laboratories. For all laboratories, CAP checklists and MMWR guidelines were most influential, followed by NCCLS guidelines, manufacturers' instructions, and CLIA regulations. This type of information may be useful for deciding where to apply additional efforts to facilitate further improvement.

Other preliminary observations indicated that:

- Many laboratories (66%) reported an increased ability to identify discrepancies in immunophenotyping results because of changes in monoclonal antibody panels
- Implementing T-cell checks resulted in laboratories reporting an increased ability to check instrumentation
- Laboratories participating in external QA reported increased test reproducibility
- Changes in blood collection instructions resulted in 53% of laboratories reporting decreased collection of unacceptable specimens
- Implementing written specimen

rejection criteria resulted in an increased number of rejected specimens and a decreased number of unsatisfactory samples

- Of the laboratories that changed training requirements, 71% reported increased troubleshooting ability

As in the PT study, one disadvantage of this study design was its complexity; another was that results were self-reported, which could introduce bias.

The advantages of this design were that the study supplied a significant amount of useful information about laboratory testing and changes that occurred from 1990 to 1994. It illustrated methods for successful collaboration among laboratorians, manufacturers and clinicians. Finally, numerous checks to validate the data were built into the study design because the data were collected in several different ways.

In summary, two studies have been presented where the common goal was to expand the knowledge and experience base from previous methodologies to develop new study designs. Successful implementation required forging new partnerships, working collaboratively and assimilating data from different sources. The ongoing development of these and other strategies will continue to be a major focus of DLS research.

The manner in which laboratory practice will be conducted in the future will not be determined by laboratorians alone. Clinicians, manufacturers, and third party payers have significant interests and important roles. To make good decisions that lead to high quality laboratory testing, research data and information are necessary components. Because those with interests in laboratory testing may have different quality expectations, it is vital that laboratory practice research be based on sound scientific methods and principles, involving collaboration between laboratory professional and nonprofessional parties who have vested interests in the outcomes and can make critical contributions. Then it will be possible to learn from both successes and mistakes and share this knowledge with the laboratory practice research community.

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