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Time to address quality control processes appliedto antibody testing for infectious diseases

Mr. S.Gowtham, Mr. K. Rambabu, Mr. N.Johanraju, Ms. K. Sai Srisha

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Abstract: Controlling these assays has also evolved to mirror those used in clinical chemistry as testing for infectious illnesses progresses from manual, biological testing like complement filtration to high throughput automated autoanalyzers. But clinical chemistry testing and infectious disease serology vary greatly from one another, and when typical quality control techniques are applied to serology, these discrepancies are ignored. Highly controlled, infectious illness serology finds antibodies to many and diverse antigens and of distinct classes that fluctuate depending on the genotype/serotype and stage of disease of the organism. While the tests provide a number (often signal to cut-off), what they are really assessing is the degree of binding within the test system, not the quantity of antibodies. Lot-to-lot variance is a feature of all serology tests, hence clinical chemistry quality control techniques are unsuitable. Many jurisdictions require the test run to be validated by using the manufacturer-provided kit controls. Third-party controls must be produced in a way that minimises lot-to-lot variance and meets the highest standards set by ISO 15189 and the World Health Organisation. a level where they detect exceptional variation. This paper outlines the differences between clinical chemis- try and infectious disease serology and offers a range of recommendations when addressing the quality control of infectious disease serology.

Keywords: clinical chemistry; infectious disease serology; recommendations; third party controls; quality control.

Introduction

Auditor reviews of laboratory procedures against local and international guidance materials, legislation, and regulations are required of laboratory personnel [1–5]. Quality control (QC) guidelines were created and used for clinical chemistry starting in the 1950s. Since then, the detection of infectious disease antibodies and antigens has been moved from manual, labor-intensive test systems like hemagglutination inhibition and complement fixation to more automated testing platforms found in clinical chemistry. Many bigger clinical labs have introduced the idea of a "core laboratory," clinical chemistry testing and infectious disease serology, evaluates the paradigm already in use.

Assistant Professor, HOD1, Assistant Professor2,3,4,
KGRL COLLEGE (A) PG COURSES, BHIMAVARAM

Table 1: Differences between clinical chemistry and infectious disease serology testing.

Clinical chemistry	Infectious disease serology
"Type A" inert analyte - Known molecular structure - Known molecular weight - Invariable composition - No change over time	
Several medical decision points - e.g. hyper- and hypo-glycaemia	
Quantitative - Determining absolute amount of measurand (i.e., concentration)	
Single homogeneous molecule - No or minimal heterogeneity - Test systems developed for specific molecular composition	
Lower level of regulation - Generally low-risk analytes - Classified by regulators as Class B (2) or C (3) as low risk tocommunity	
Linear dose response curve - Usually highly sensitive tests detect low concentrations of analyte - Assay demonstrates a linear response of concentration to signal throughout the analytical measurement range	
Adjust for reagent lot variation (Bias) - Can re-calibrate test system to adjust for bias - Calibrators traceable to international standard available	
International standards available - Well-defined international standards available for many analytes - Secondary standards are traceable to international standard	
Certified reference methods (CRM) - Well established CRM - e.g. Atomic absorption, HPLC, mass spectrometry	

"Type B" functional biological analyte
- Variable structures
- Different classes and subclasses
- Antibody response varies over time
- Antibodies may be fragmented, polyclonal or monoclonal, freeor complexed
- Variable avidity and affinity

Single decision point
- Determining the absence of presence of antibodies and/orpositivity or negativity in comparison to a cut-off

Qualitative
- Determining binding efficiency
- Use chemical signal to detect measurand

Multiple and varying antigens
- Different genotypes/serotypes
- Antigenic mutations

Highly regulated
- Generally moderate to high risk
- Classified by regulators as Class C (3) or D (4) indicating high riskto the individual and the community

Non-linear dose response curve
- No response if analyte concentration is low
- No increase in response if test system is saturated
- Strength of signal is dependent on affinity of the antigen:antibody binding

Cannot adjust for reagent lot variation (Bias)
- Tests are highly regulated not allowing modification
- A limited number of international standards available
- Modest commutability to international standards

Poor or no international standards
- International standards unavailable for many tests
- Where international standard is available, standardisationefforts are mainly unsuccessful
- Many tests are not calibrated to international standard evenwhen they exist

No Certified reference methods
- No CRM available
- Variable quantitative results between test systems

Differences between clinical chemistry and infectious diseaseserology testing

Clinical chemistry measurements and infectious diseases serology are measured in rather different ways (Table 1) [6]. These differences originate from the fact that, while testing for an inert molecule like glucose in (human) fluids, the test equipment is figuring out the real amount (or concentration) of glucose. By comparison, with an antibody test, the test system is figuring out how well (or not) of Antibodies directed against a specific antigen. A patient sample having a high affinity and avidity to a particular antigen but low antibody levels may be more reactive than one with a high number of low-avidity antibodies. Differences across test techniques that identify antibodies against the same virus have been brought to light by the experience with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The many SARS-CoV-2 serology tests differ in the antigens (whole disrupted virus, recombinant spike protein and/or nucleocapsid protein); in the antibody detected (binding antibodies include IgG only, IgM only, IgG and IgM, total including IgA, dimeric IgA); and in the structure of the antigen derived from one or more SARS-CoV-2 variants

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Both in chemistries (quick tests, colorimetric microtiter enzyme immunoassays, chem-iluminescence, plaque neutralisation) and/or lineages (most tests still employ antigens derived from the ancestor virus found in Wuhan in 2019, which is no longer circulating). It is impossible to see any of the serological tests for SARS-CoV-2 as testing the same metric. For all serological tests in infectious illnesses, including HIV, hepatitis, and diseases preventable by vaccination, this is the case [6]. Infectious disease serology does not measure the quantity of antibodies in a patient sample as does testing for quantitative analytes. Generally expressing the findings as a signal to cut-off Regulation of infectious diseasetests

The International Medical Device Regulators Forum (IMDF), along with the Global Harmonization Task Force (GHTF) classifies *in-vitro* diagnostic devices (IVD) into four risk categories [10]. The assessment and regulation of IVDs in most countries now comply with these classifications. Thehighest risk IVDs (Class D in Europe; Class 4 in Australia) include testing for blood-borne infections such as hepatitisand HIV, irrespective whether pre-transfusion screening orclinical diagnosis [11]. In the USA, tests with an intended use for blood screening are regulated differently from those witha diagnostic intended use, however, are more highly regu- lated compared with clinical chemistry tests [12]. In Europe, anti-SARS-CoV-2 testing is classified as Class D, whereas in Australia it is classified as Class 3 (i.e. Class C in Europe). Allother infectious disease tests are regulated at Class C or 3; whereas most clinical chemistry tests are Class B or 2. The IVD regulations of most countries require manufacturers of these high risk IVDs to provide extensive pre-market perfor- mance evidence and, in some cases, undergo independent performance evaluations [5]. In Europe, this evidence is evaluated by a Notified Body operating under European Law; the Centre for Biologics Evaluation and Research (CBER) in the United States regulates blood screening tests. The IVD user is required, after it is issued to the market, to employ the manufacturer's instructions for use (IFU) exactly, including evaluating the manufacturer's kit controls and applying the manufacturer's kit control acceptance criteria. A user cannot modify the test system to correct for bias. Using the test kit "off-licence," or as a "in-house assay," would be against the manufacturer's IFU and is prohibited for high- risk IVDs in some countries. Every new batch of high risk IVDs has to be evaluated by the US and European regulatory bodies before being released for use, often via performance testing by a licenced .

(S/Co) value or equivalent, the test systems assess the chemical reaction intensity against a pre-defined cut-off. Note that although the dosage response curve is often linear, the signal only indicates the binding strength and not necessarily the "amount" of antibodies present. Usually, the antibody response to infection decreases with time. But when people are re- exposed to the same or similar antigens (like spike protein from several SARS-CoV-2 strains), their memory B cells produce robust and targeted antibody responses. The level of protective immunity does not thus always correlate with the finding of binding antibodies [9].

Guidance documents

For almost all medical laboratory testing, the 2014–2015 Milan hierarchy is the prevailing paradigm for setting performance criteria (goals) [13, 14]. This consensus paper offers analytical performance criteria based on one of three models: a) the impact of analytical performance on clinical outcomes using direct or indirect research; b) based on components of biological variation of the measurand; and c) based on state-of-the-art. Put another way, applying the best analytical performance that is practically possible. Only the first of these possibilities has

any bearing on infectious disease serology since there are no higher order test methods and the biological variability of serological measurands is significant and varies with time. Milan Acceptance criteria are derived from several factors contributing variation from many sources, such as different reagents and reagent lots, instruments, operators, and internal processes. These criteria are externally set by QC sample manufacturers, control material vendors, or EQA providers using peer data. Thus, only data from the same test equipment, evaluating the same material (peer group), may be utilised to define acceptance criteria in infectious disease serology [15]. Still, because the sources of variation are smaller within a laboratory environment than they are from several laboratories, the acceptance range computed from these data is by definition wider (sometimes much larger) than those computed from data obtained from an individual laboratory using that test system. Using acceptance criteria derived from the combined data of multi-laboratory peer groups carries some risk in that the acceptability range might become so large that significant unsatisfactory findings are missed.
Alternatively, calculating a "too narrow" acceptance range from data from a single laboratory using a small number of data points can result in "false rejections," wherein acceptable QC results are flagged as "errors," needless worry, and time and resource waste in troubleshooting. For example, labs are specifically advised to set control limits using the mean and standard deviation (SD) on as little as 20 data points data collected from their own laboratory by CLSI C24-A3 [1] and the UK Standards for Microbiology Investigations [16]. ISO 15189 further strongly advises labs to create their own quality control processes [17]. Nevertheless, all of these methods will provide excessively narrow acceptance ranges, which in infectious disease serology settings will result in erroneous rejections.
Concerning the use of quality control, the present performance specifications, usually stated as percentages, define acceptable bias, permitted imprecision, and/or allowable total analytical error.
edition of ISO 15189 is mute and unspecific. According to it, a medical laboratory must create quality control protocols with quality control materials that should be evaluated on a regular basis depending on the stability of the test system and the possibility of patient injury. It also says that manufacturer's control material should be taken into account either in addition to or instead of a third-party QC material. While QC guidelines should be followed, a laboratory should have a process for taking remedial action when they are broken.
Rather than defining analytical performance goals, the CLSI paper "Laboratory Quality Control Based on Risk management" (EP23-A) outlines a quality control procedure that takes the risk of a testing system failing into account [18]. Staff working in serology labs must overcome the difficulty of determining specific limitations from these guidelines, which seldom (if ever) take into consideration measurands being detected in infectious disease serology. Thus, current recommended best practices for QC in serology are vague and at odds with each other comparedwith other laboratory testing areas.

Kit control materials vs. third party control materials

The use of kit control materials supplied by the manufacturer and non-manufacturer, third-party control materials is not distinguished in guidance guidelines for quality control [1, 4, 16]. This is probably so because, in clinical chemistry, control materials supplied by a third party and the manufacturer may be used interchangeably as long as they are calibrated against a recognised reference material [19]. In infectious diseases serology, the functions of kit control materials and third-party control materials are distinct. The reagent manufacturer optimises the kit control

materials for their calibrator and reagent, sometimes for a specific batch of reagents. Before patient findings can be published, the manufacturer usually specifies acceptance requirements for their kit controls in their IFU that must be met. That is, a test run is controlled by the kit. Usually, these kit control acceptability limitations are somewhat broad. It should be mentioned that regulatory bodies evaluated IVDs according to the manufacturer's kit control acceptance criteria as stated in the IFU before they were made available for market clearance. Both the sensitivity and the specificity of the IVD are said to be stable if the kit control values are within that range. The laboratory is required by Australian registration procedures and the European Commission IVDR requirements to use the kit control materials as part of the IFU [3, 5]. Generally speaking, changing the kit controls with a third-party control material is forbidden when the IFU indicates to use them, especially in high risk IVDs like HIV or hepatitis. Kit controls are, however, often produced in lots with lot-to-lot fluctuation, sometimes especially to accommodate variations in reagent lot and provide a reactivity that meets the manufacturer's acceptance standards. When this happens, kit controls are inappropriate for long-term assay performance monitoring.

Choice of third-party quality control materials

Third-party control materials track test system variance over time, unlike manufacturer's kit controls, and should not be used to validate a test. Do a run. The test is therefore being utilised "off-licence" without the IVD's regulatory clearance. Unexpected variance is found via effective monitoring of third-party QC findings. Optimised for the monitored test system, a third- party control material should ideally respond on the linear portion of the dose response curve (often a low positive reactivity). Usually two or three control materials—a negative, a mild positive (around the clinical deci-sion limit), and a strong positive—are tested in clinical chemistry [20]. Although all three levels may be helpful in clinical chemistry, in infectious disease serology the low positive control closest to the critical decision level (the assay cut-off) is advised because it measures the variation at low levels of reactivity and is more sensitive to changes in the test system [15, 21]. Reagent lot to lot variance affects all infectious disease serology assays, independent of the analyte or manufacturer. This variance is not re-calibrated to remove, unlike other chemical exam systems. Identification and response to unacceptable variance is the task facing laboratory scientists. Where the third-party control remains stable during that time, the best way to compare reagent lot-to-lot variation is to monitor the reactivity of the same third-party control material over an extended period of time [15]. This may be accomplished by the laboratory buying a lot of third-party QC in bulk with a lengthy expiration date. The third-party QC should ideally be produced to have little lot-to-lot variance in QC. A long-term continuous monitoring of IVD performance will be possible for the user using control materials that have little lot-to-lot variance. The task facing labs is to develop meaningful, fact-based, and scientifically sound acceptance standards that take into consideration the possibility of inaccurate findings.

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Establishing control limits for infectious disease serology

Control limits are established traditionally using mean ±1, 2, 3 SD computed on a comparatively limited number of findings [1, 4, 16]. Normal reagent lot-to-lot variation is not taken into account by these techniques, even though lot-to-lot variation in clinical chemistry has been acknowledged more recently [22–24]. Once a fresh batch of reagent becomes available, previously set restrictions might become invalid and the acceptance criteria would need to be

reestablished [25, 26]. Sometimes labs may buy one batch of reagent and use it for a while without having to re-establish the acceptability limits. For tiny labs, however, who are unable to maintain substantial stock, or for

low volume testing. A laboratory setting control limits usingsolely its own quality control results can only assess the unprecision of the test system in their testing environment and is therefore vulnerable to the difficulties of regular reagent lot changes. Reagent lot-to-lot variation has to be resolved more universally [7]. One cannot evaluate the bias or determine if variations in the QC mean are caused by variance in the laboratory or reagent lot using QC findings from a single laboratory. Systematic mistakes, including a poor signal reading, an improper incubation temperature, or a failure to wash unconjugated antibodies, will thus be invisible to a laboratory. A laboratory can only really quantify its bias by taking part in an EQA or peer-review quality control programme. Performance criteria must be developed depending on the impact of analytical variance on clinical outcomes in order to better align serology with the Milan Consensus. This information should then be customised into acceptability ranges for control limits. Labs may benefit from parametric statistics as findings of third-party control materials have a somewhat normal distribution over time for IVDs reporting results as a S/Co or comparable. Third- party control providers can offer laboratories pre-determined control limits; but, before calculating and implementing the suggested range, the vendor must do the extra work of customising the performance specification to the particular context of the laboratory (method, instrument, reagent lot). This demand can only be met by a well-structured quality control programme that has access to a plethora of various performance data on operators, equipment, and reagent batches. Fortunately, a few control material suppliers that participate in peer group programmes gather these statistics and may utilise the past data to set appropriate quality control limitations. The power of a peer group control vendor is the larger view; tracking the universe of tools, techniques, antibody and reagent batches; gathering a plethora of information and knowledge that no one laboratory

Analytical performance and clinical outcomes

Many times, laboratory personnel believe that changes in the clinical sensitivity of the assay, which would lead to a false negative patient result, may be predicted by a decline in low positive QC reactivity. This method has certain problems and makes some assumptions. It is widely assumed that the seroconverting samples and the third-party control material may be mixed. Remarkably, a true clinical low-positive reaction only appears after seroconversion. The avidity is often modest and the antibody response is juvenile at this point, dominated largely by IgM (notice that serology tests quantify how strongly binding occurs). Some particular proteins have a rapid decline in the early antibody reaction. As a matter of fact, a person will only exhibit low-level reactivity during a sero- conversion event for a maximum of 72 hours. On the other hand, mature, highly avid antibodies are represented in a low-positive third-party control material that is usually made by diluting plasma from chronically ill people. The commutability of third-party control materials, actual negative [29–31] and low positive clinical samples has been mapped by the National Serology Reference Laboratory, Australia (NRL) [27]. Tested on a couple of the six reagent lots that were exhibiting unexpectedly low reactivity, only clinical samples with a S/Co less than 2.3 in the assay/control combi-nation evaluated (Abbott Architect anti-HCV) produced false negative findings. They came to the conclusion that although there is a small chance of a false negative clinical sample result linked to a

significant drop in controls reactivity, this risk may be reduced by molecular testing and/or clinical history.

Recommendations

Although clinical chemistry has established guidelines for control analysis, serologic testing has been utilised generally without fitness-for-purpose evaluation. Unlike homogeneous and clearly characterised clinical chemistry analytes, infectious illness testing offers a new paradigm. Basically qualitative, serology tests reveal whether or not antibodies are present. The S/Co value or equivalent units given is a measure of the capacity of the antibodies present to bind to specific proteins, not of the quantity of antibodies. Noteworthy, infectious illness serology assays exhibit typical lot-to-lot variance, in contrast to most clinical chemistry testing [24] [15]. A serology quality control guideline should contain a number of the recommendations in our paper. – For serological testing, every laboratory has to abide by the most recent national and international regulations.
—Tests for infectious illness serology do not quantify or concentrate any one analyte. You are qualitative test devices that provide a signal to identify whether or not the measurand is present.
—Every test for an organism (e.g., SARS-CoV-2) looks for various measurands, such antibodies to spike and/or nucleocapsid proteins; it uses various conjugates (e.g., mouse monoclonal, human polyclonal); it looks for various antibody classes or subclasses (IgG, IgM, IgA, total) and uses various chemistries to find the signal. Consequently, it is not possible to compare quantitative signal findings from one test with another that purports to find antibodies against thesameorganism.Normal and undesirable lot-to-lot reagent variation must be distinguished using criteria. Assuming little reagent lot-to-lot variation, current quality control standards provide labs little helpful guidance when lot-to-lot variation
–Always utilise the manufacturer kit control materials to confirm the assay performance as directed, if the manufacturer specifies in the IFU. Kit controls let reagent makers troubleshoot problems.
•The sensitivity or specificity of an assay is unlikely to be affected by variations in the mean of reactivity of a third-party control material, so third-party QCs should not be utilised for this purpose when kit controls are within the manufacturer's acceptability range specified in the IFU.
It is strongly advised that third-party control materials be tested and monitored as an industry standard for infectious disease testing.
–Though well-designed third-party control materials may track the test system performance over time, kit control materials approve a test run in order to deliver patient findings.
–Optimised for certain immunoassays, well-designed third-party control materials should exhibit little lot-to-lot variation and long-term stability.
–While control material levels may vary, at least one third-party QC should be reactive on the linear portion of the dose response curve—which isn't always at the test cut-off.
—Each morning before patient samples are tested on automated chemical analyzers, or with each test run during batch testing, a third-party control material should be examined at the very least. Assay calibration, after a significant maintenance event, or in any other circumstance that may possibly introduce a change to the test system, should all ideally include analysis of the third-partyQCmaterial.
-Periodically, new virus variations and the release of new immunoassays onto the market should cause QC materials to be updated and verified.
—Reagent lot-to-lot variations are typical, as third-party QC data show. Welcome doesoccur.
–Clinical chemistry recommendations call for setting quality control acceptance limits using the mean ± 2 SD of 20 results, but this method ignores "normal" reagent lot-to-lot variation and

will result in many false rejections for infectious disease serology tests, which waste resources and reduce confidence in the assay and/or the quality controls.
--Labs that only track quality control findings from internal testing will track test accuracy but not systemic error or bias.
--"Normal" variation, including fluctuation in reagent lot over time, should be part of the acceptance criteria for infectious disease test quality control findings. Peer comparison programme historical data is perfect for defining evidence-based acceptability boundaries and for understanding normal variance.
The laboratory user has more chance to look into unexpected findings when quality control programmes with peer comparison gather and analyse control data from other labs using the same control materials and test equipment.
- Even if the mean of control reactivity varies, the imprecision of infectious disease serology tests is usually constant lot to lot. Laboratory monitoring of test performance may find this performance measure o be a helpful tool. Since no clinical mistake is acceptable, it is difficult to determine the Total Allowable mistake of infectious disease serology tests. Nevertheless, historical data may be used to calculate the bias and intrinsic analytical error and ascertain if such variance, given the possibility of erroneous patient findings, resulted in acceptable therapeutic outcomes.Specialised guidelines for the quality control of infectious disease should be created and current medical test quality control standards should be revised to exclude infectious disease testing. Funding for study: None reported. Author contributions: Every author has given their approval for the submission of this paper and acknowledged responsibility for its whole content.
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