

Editorial

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Quality controls for serology: an unfinished agenda

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The quality control process (QC), both as internal quality control (IQC) and external quality assessment programs, is a must for clinical laboratories to guarantee consistency and accuracy of results. While QC procedures are well established for clinical chemistry and most immunochemistry analyses that provide a quantitative measurement, assays employed for the serological testing of infectious diseases pose several challenges. First, in this field, a true quantitation is hard to achieve. Most assays are qualitative and results are expressed as positive or negative by comparing the signal generated to a threshold value, alternatively called “cutoff”. Secondly, whenever a quantitative result is provided – usually for antibodies – a true quantitation is disputable. Even in case a reference standard and International Units (IU) are available for reporting results, assays may differ in composition – use of different antigens or of similar antigens with different expression – in assay kinetics and in signal generation. A classic example comes from IgG antibodies to Rubella virus: most assays are calibrated by (or against?) the WHO reference standard and the “protective” threshold is set at 10 IU/mL [1], but the absolute values may differ by 10-fold or more among different assays [2].

Finally, antibody assays are detecting the relative affinity to specific antigenic epitopes and thus the signal generated is deeply influenced by the stage of infection: a lower signal may be generated in the late stages or in chronic infections that are under control by the immune system, with only a few active clones releasing antibodies with high affinity, as well as in acute/recent infections when circulating antibodies have a low affinity, though the absolute number of activated clones may be higher.

Despite these limitations, QC schemes for serology are in place and the results are evaluated according to the same rules that apply to other immunometric assays [3], with a few differences [4]. In the current issue of the Journal, Dimech et al. [5] bring up a substantial contribution to this field by highlighting the relevance of an eventual shift in EQC values linked to reagent lot changes, reporting how such a change did affect a widespread assay

for the detection of antibodies directed to the hepatitis C virus (HCV). The evidences brought up by those authors are of actual relevance in two different levels, one pertaining to the analytical environment and the other on the clinical side. The analytical issues are described keenly: a change in the reagent lot of the Abbott ARCHITECT assay for anti-HCV resulted in a downward shift of the low-level QC sample employed. The basic questions they tried to answer concern the amount of QC reactivity change and on this purpose, they have compared affected and unaffected reagent lots’ reactivity of EQA scheme samples. A lower reactivity by the affected lots was found on almost all samples, and by one affected lot the result was below the reactivity threshold on four specimens.

The second question, and possibly the most relevant one, is how much change is allowed before there is an increased probability of reporting an incorrect clinical result. This has been addressed by analyzing the effect of this change of reactivity on early seroconversion samples on two different sets. Results not lower than the cutoff value have been recorded on four samples in the first set, and in none on the second set, though several specimens gave results lower than 2.0 times the cutoff on both affected and unaffected lots. According to the CLSI EP23A guideline, risk assessment depends on a two-factor model that includes the probability of occurrence of harm and the severity of harm [6].

In this perspective, Dimech et al. correctly indicate that the occurrence of a false-negative result for anti-HCV in a diagnostic setting is unlikely, as there is a very low chance of obtaining a sample during the time span when the sample to cutoff value is between 1.0 and 2.0. It shall also be mentioned that the current standard for the laboratory diagnosis of acute HCV is an HCV antibody seroconversion (negative HCV antibody test before a suspected exposure and a positive antibody test following potential exposure), combined with a positive HCV RNA test and elevated alanine aminotransferase (ALT). In blood donation screening setting the false negativity may bear a higher risk, which is mitigated by the additional pre-donation procedures and the addition of nucleic acid testing. This paper emphasizes the need to move toward a better harmonization

of procedures and processes adopted by clinical laboratories working in different fields of laboratory medicine [7, 8]. It is time to review procedures and processes adopted for QC not only in clinical chemistry but in all other fields of laboratory medicine, including microbiology and point-of-care testing (POCT). The consolidation of different specialties and analytical techniques in clinical laboratories answers physicians' and patients' need to receive a unique and harmonized laboratory report with results from clinical chemistry, hematology, coagulation, molecular diagnostics and microbiological-virological tests [9]. Technological improvements based on common analytical platforms and advanced informatics tools facilitate this process, but more efforts are requested to laboratory professionals as appropriate and accurate rules for QC are needed to ensure reliability and accuracy to laboratory information.

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