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Review

The role of uncertainty regarding the results of screening immunoassays in blood establishments

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ABSTRACT

The risk of uncertain results in infectious agents' tests is recognized in blood establishments, being particularly evident during the blood donor selection. The current risk-based approaches require risk assessment and "risk-based thinking". Accordingly, the blood establishment should consider the effect of uncertainty in all the technical decisions taken in a screening laboratory. Since the post-transfusion safety is one of the blood establishments' goals, the risk of post-transfusion infection should be evaluated and actions taken to decrease the chance of blood donations validation use false negative results. This article reviews and discusses the sources of uncertainty of infectious agents' reported results in blood establishments. It describes a set of sources of uncertainty that should be considered in screening immunoassay's decisions. The infectious agents' uncertainty concern is critical for reporting reliable results.

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1. Introduction

The role of uncertain results is already stated in blood processing literature [1]. Uncertain results are those with a statistical significant probability to be false. Decisions taken on these results have a high chance of being incorrect. During the production process there is always a chance of uncertain results. They must be identified and actions must be taken. In blood establishments the chance of uncertain results due to the seroconversion window period was recognized principally since the first events of post-transfusion HIV infection [2]. To decrease the probability of seronegative donations, a set of questions are used to survey and select blood donors. However, there are other causes of uncertain screening tests' results.

The European Union directives [3] and the US standards [4] do not require the determination of uncertainty in screening tests' results. They are mainly focused in blood collection and processing. The laboratory technical requirements should include complementary approaches to evaluate uncertainty [note: in the US the blood establishments' laboratories' test must fulfill the Clinical Laboratory Improvement Amendments (CLIA)] [5]. EuBIS "Standards and criteria" [6] recommend risk assessment, i.e., the evaluation of the effect of uncertainty. Whether or not required, the blood establishments must be focused on the post-transfusion safety, and must evaluate the uncertainty in the screening tests' decision (e.g., test selection, verification, validation, internal quality control, external quality assessment) to report reliable results. This article reviews and discusses the sources of uncertainty in screening immunoassays' results, where the risk of false negatives must be considered.

2. Material and methods

2.1. Biological biased results: seroconversion window period

The seroconversion window period or seronegative period is one of the primary sources of infectious agents' false results. Bhushan and Vasan (2009) defined the window period as "(...) the time between first infection and when the test can reliably detect that infection", being "dependent on the time taken for seroconversion" [7]. Fauci and Lane (2008) presented a simpler definition, "the interval between infection and detection" [8]. Pereira et al. (2014) proposed an alternative definition "the window period for a test designed to detect a specific disease (particularly an infectious disease) is the time between first infection and when the test result cannot reliably rule out the possibility of infection (due to indeterminate results)" [9]. Theoretically, according to this definition, the window period could be shorter without increasing the risk of post-transfusion infection. It considers the use of a gray zone where gray zone results, i.e., indeterminate results, are treated as positive results, i.e., blood donations are rejected and the samples must be tested in a confirmatory scheme. Since blood donations from donors in the window period represent a high risk of false negative results, the window period should be determined as a component of the residual risk (entry 2.29 of Ref. 10). The determination requires a seroconversion panel(s). Since the panel is specific for an infected individual, the observed seronegative period cannot be inferred to the population of blood donors. Indeed, the true window period is unknown. Further information about window period can be found elsewhere [9].

2.2. Biased results caused by interferences

Biased results could arise also from interfering factors. The effect of these factors is a specimen-dependent bias. Potentially interfering substances must be assessed during the selection and evaluation of a method. Young (2000–2007) published a set of databases of reported effects of pre-analytical variables, disease, drugs and herbs and natural products in the medical laboratory results [11–14]. The pre-analytical effects must be addressed by good laboratory practices. If the sampling, centrifugation and storage conditions meet the requirements stated in the manufacturer's directions for use, the chance of interferences should be low. If the laboratory practices do not fulfill this requirements, the chance of false results increase. For example, a hemolyzed sample may affect the chemical or physical properties of sample matrix. The reagent kit insert should also disclose any interferences and the laboratory should verify also this information. Despite the fact that blood donors are carefully selected, there are still a set of conditions that do not cause rejection of the donation, but that could still cause to interferences, for example, rheumatoid arthritis. Some drugs that are present or allowed, but not reported in blood donor selection, could also cause interferences, for example, anticoagulants and drugs of abuse.

2.3. Lack in the equilibrium of immunoassay reaction

Poor quality laboratory practices, such as incorrect preparation, handling and storage of reagents, and inadequate reaction conditions may not guarantee the equilibrium of test reaction. The result will have a high probability to be false. The lack of equilibrium, when statistically significant, could be shown as measurement uncertainty (entry 2.26 of Ref. 15) component [16]. The effect of nonconforming reaction conditions may be detected by the analyzers calibration verification process and should also be detected in an internal quality control scheme.

2.4. Uncertainty around cutoff: gray zone

The cutoff is the clinical decision value in screening immunoassays. The numerical results for samples are classified on an ordinal scale (entry 1.26 of Ref. 15) according to cutoff. The results could be binary, positive or negative, and ternary, positive, indeterminate or negative. Considering the ratio of sample result divided by the cutoff result, the cutoff is as constant equal to 1.00. Numerical values equal or close to the cutoff have a significant chance to be false. Therefore, the measurement uncertainty at the cutoff value should be determined. The interval of uncertain results (expanded uncertainty) (entry 2.35 of Ref. 15) is designated "gray zone". Consequently, the laboratory should apply a ternary classification to the numerical results. Blood donations of donors