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Scheme for the selection of measurement uncertainty models in blood establishments' screening immunoassays

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ABSTRACT

Blood establishments routinely perform screening immunoassays to assess safety of the blood components. As with any other screening test, results have an inherent uncertainty. In blood establishments the major concern is the chance of false negatives, due to its possible impact on patients' health. This article briefly reviews GUM and diagnostic accuracy models for screening immunoassays, recommending a scheme to support the screening laboratories' staffs on the selection of a model considering the intended use of the screening results (i.e., post-transfusion safety). The discussion is grounded on a "risk-based thinking", risk being considered from the blood donor selection to the screening immunoassays. A combination of GUM and diagnostic accuracy models to evaluate measurement uncertainty in blood establishments is recommended.

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1. Introduction

Risk assessment in blood establishments has been gaining importance on the fulfillment of ISO quality management systems [1], and on the satisfaction of the European Blood Inspection System and the European Directorate for the Quality of Medicines & HealthCare claims [2,3]. Currently, risk evaluation is not required by the European Union regulatory directives [4–7] or by the American Association of Blood Banks Standards for Blood Banks [8]. However, on ISO/DIS 9001:2015 "risk-based thinking" must be considered [1]. Considering risk defined as "the effect of uncertainty on an expected result" [entry 3.9 of (1)], evaluating measurement uncertainty through an appropriate model is a step toward risk evaluation. ISO 15189 requires "measurement uncertainty" determination in all the laboratory tests [9]. Measurement uncertainty data are also important to support the analysis and control stages of a total quality management cycle [10], and can be associated with blood establishments' budget waste [11].

The effect of the risk caused by the prevalence of transmissible diseases on post-transfusion infection is already considered in blood establishments on the screening's interview of blood donor candidates. The risk of uncertain/false results on screening tests is also of major importance for blood establishments, as evidenced, for example, by cases where nucleic acid testing gives a false negative output due to virus mutations [12]. The Guide to the Expression of Uncertainty in Measurement (GUM) [13] is considered by the metrology global organizations as the seminal guide to evaluate measurement uncertainty. However the application of its models to the screening tests is not a current practice in blood establishments since it is usually seen in this community as a method that only applies to numerical results, when the output of a screening immunoassay is an ordinal quantity that yields a binary decision. Alternatives to GUM models for uncertainty determination, focusing on diagnostic accuracy, are usually preferred [14,15].

2. Methods and materials

2.1. GUM models

The International Vocabulary of Metrology (VIM) defines "measurement uncertainty" as a "non-negative parameter characterizing the dispersion of the quantity values being attributed to a measurand, based on the information used" (entry 2.26 of [16]). It considers the uncertainty arising from the variance of a measure. GUM proposed a methodology that is widely used in chemistry and physics, but that is rarely used in blood establishments' screening laboratories, as well as in other medical laboratories. GUM is focused uniquely in numerical quantities, thus its applicability to ordinal screening tests producing a binary result (positive/negative) is questionable. However, GUM models provide a useful way to evaluate the measurement uncertainty interval at the clinical decision point or cutoff, where there is a statistical significant chance of false results due to analytical variance.

GUM models could be divided into modeling and empirical models. The modeling models require a specific mathematical model for each screening test respecting the stoichiometry of the test's reaction. This model combines the major measurement uncertainty components into a combined uncertainty using the law of the propagation of uncertainty (partial derivative method [13]) or the propagation of distributions (Monte Carlo simulation method [17]). Measurement uncertainty evaluation should be focused on the clinical decision point, where the ratio between the sample's test value and the cutoff value is equal to 1.00, or close to this level. The modeling estimations require mathematical and statistical skills which are usually unavailable in blood establishments. The propagation of variance rules used in the model assume that all the sources of uncertainty are uncorrelated, which may not be true, thus leading to an over-estimation of the MU.

The empirical models use data already available in screening laboratories, namely coming from single laboratory validation (including quality control), laboratory intercomparisons and external quality assessment/proficiency testing (EQA/PT). One of three methods can be used. In the single laboratory model (intralaboratory) model, within-laboratory reproducibility standard deviation (SD) and bias uncertainty (from laboratory intercomparisons) are used to compute the measurement uncertainty. The reproducibility SD could be determined from method validation or from internal quality control data. In the laboratory intercomparisons (interlaboratory) model, within-laboratory reproducibility SD and bias uncertainty are combined. In the EQA/PT model the standard uncertainty is equal to group's SD [18]. In either method, data should be collected through measures of samples with concentrations as close as possible to the cutoff concentration. A non-homogeneous EQA/PT group of laboratories (e.g., laboratories using different tests) may lead to an unrealistic estimation of MU.

The output of the GUM models is an uncertainty interval, usually referred to as the "expanded uncertainty", generally representing a 95% confidence interval (CI) for the average of the test results for a cutoff sample. The blood establishments must then define the rejection zone [19] which must be equal or larger than the expanded uncertainty. The use of a rejection zone (gray-zone) implies the use of ternary results, i.e., positive/indeterminate/negative. In blood establishments, the rejection zone has the practical effect of reducing the chance of binary results to be classified as false. The blood components with indeterminate results shall be eliminated. For an in depth discussion of GUM models in blood establishments' screening tests please refer to ref. 20.

2.2. Seroconversion window period

The window period of an infectious disease test is the time between the first day of infection and the day when the test can reliably detect the infection [21]. The seroconversion window period (WP) expresses the major diagnostic bias component and is part of the residual risk (entry 2.29 of ref. 22) of post-transfusion infection. Samples from patients on WP are seronegative, i.e., false negative