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Protocols

Evaluation of 30 commercial assays for the detection of antibodies to HIV in China using classical and Bayesian statistics

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A B S T R A C T

The purpose of this study was to evaluate the 30 commercial HIV-antibody (HIV-Ab) assays in the nationwide assessment program of China using classical and Bayesian statistical methods. The classical estimates of sensitivity and specificity varied from 95.9% to 100% and from 94.6% to 100%, respectively. The proportions of assays with 100% sensitivity and with 100% specificity reached 63.3% (19/30) and 3.3% (1/30), respectively. Using the Bayesian logit hierarchical model, the overall estimates of sensitivity and specificity were 99.8% (95% Bayesian credible interval [BCI]: 99.4–100%) and 98.1% (95% BCI: 97.4–98.7%), respectively, for the 17 ELISAs under evaluation. For the 13 rapid assays, the corresponding overall estimates were reported to be 99.2% (95% BCI: 98.5–99.8%) and 98.4% (95% BCI: 97.8–98.9%), respectively. In addition, given the prevalences of HIV infection among the general population of China and the intravenous drug user group in China, the positive predictive values were estimated for each individual assay in the framework of the two schools of statistical thought. Furthermore, by comparing the two types of estimates, it is concluded that the two types of statistical methods were complementary for the evaluation of very accurate HIV-Ab assays.

1. Introduction

There is evidence that the human immunodeficiency virus (HIV) is spreading from high-risk groups to the general population, creating the potential risk that the epidemic would spread further in China (State Council AIDS Working Committee Office & UN Theme Group on AIDS in China, 2007). Therefore, accurate and cost-effective detection of antibodies to HIV is essential for the control of HIV infection. Due to their accuracy, ease of performance and low cost, enzyme-linked immunosorbent assays (ELISAs) and rapid assays for the detection of HIV antibodies are used widely.

In general, a screening assay is evaluated in two respects (Zhou et al., 2002). The first is accuracy, which is generally measured by sensitivity (Se) and specificity (Sp), where Se (Sp) refers to the probability of identifying correctly an infected (non-infected) individual as infected (non-infected). The second is the predicative power, which is usually characterised by the positive predicative value (PPV), where the PPV measures the probability of classifying correctly an individual if the individual has a positive test result. For the evaluation of HIV-antibody (HIV-Ab) screening assays, the sensitivity and/or specificity are usually estimated to be 100% by classical statistical methods, resulting in some problems that have not been well solved, such as the estimation of the confidence interval for the Se, Sp and PPV (Liu and Chen, 2006). Fortunately, Bayesian statistics provide potential solutions to these problems by incorporating prior information with new data (Congdon, 2006). To date, many researchers (Berkvens et al., 2006; Dendukuri and Joseph, 2001; Enøe et al., 2000; Geurden et al., 2004, 2006; Joseph et al., 1995) have introduced either classical or Bayesian statistics into the evaluation of diagnostic tests in the absence of a "gold standard", and their results demonstrated that the sensitivity and specificity were often far from 100%. Nevertheless, studies that evaluate simultaneously the same set of highly accurate assays for the detection of HIV antibodies using classical and Bayesian statistical approaches are reported scarcely when the true infection status is known.

The objective of this study was to assess the 30 commercial HIV-Ab assays used in China with classical and Bayesian statistical methods and to compare the estimates from the two schools of statistical thought. First, the organisation, assays and panels of serum specimens in the 2006 nationwide assessment program of

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30 commercial HIV-Ab assays are presented. Secondly, the sensitivity, specificity and PPV, which are determined for the general population of China and the intravenous drug user group in China, are estimated by classical and Bayesian statistics, independently. Finally, it is determined that classical and Bayesian statistical methods are complementary for the evaluation of HIV-Ab assays by comparison of the two types of estimates.

2. Materials and methods

2.1. Organisation

The Ministry of Health of China issued the document "National regulations on enhancing the detection of HIV antibodies". Under the guideline of the document, the National AIDS Reference Laboratory organised the nationwide evaluation of 30 commercial HIV-Ab assays used widely in China in July 2006. Six provincial HIV reference laboratories participated in the evaluation. All works were accomplished in the National AIDS Reference Laboratory with the same set of equipment by the same technicians.

2.2. Assays

All the HIV-Ab assays under evaluation were approved by the State Food and Drug Administration of China, and they were selected randomly from the market of China by the laboratories involved in the nationwide evaluation. Among the 30 commercial HIV-Ab assays, 17 were sandwich type ELISAs, and the rest were rapid assays.

2.3. Panels of serum specimens

A panel of 355 serum specimens was tested by the 17 ELISAs under evaluation, and the panel tested by the 13 rapid assays under evaluation consisted of 358 serum specimens. The specific composition of the panels of serum specimens is summarised in Tables 1 and 2.

2.4. Statistical analyses

2.4.1. Classical statistical analyses

The sensitivity (Se) and specificity (Sp) of assay i in this study (denoted as Se_i and Sp_i, respectively) were calculated by the following equations (Zhou et al., 2002):

$$Se_i = \frac{Y_{1i}}{N_{1i}} \quad (1)$$

$$Sp_i = \frac{Y_{2i}}{N_{2i}} \quad (2)$$

The positive predicative value (PPV) of assay i for population j in this study (denoted as PPV_{ij}) was estimated as follows:

$$PPV_{ij} = \frac{Se_i \times P_j}{Se_i \times P_j + (1 - Sp_i) \times (1 - P_j)} \quad (3)$$

where N_{1i} (N_{2i}) refers to the number of serum specimens that have been confirmed positive (or negative) for HIV antibodies by confirmatory test in the panel tested by assay i, for the same panel, Y_{1i} (Y_{2i}) refers to the number of positive (or negative) serum specimens for HIV antibodies that were identified correctly as positive (or negative) by assay i. P_j denotes the HIV prevalence in population j.

In addition, the Clopper–Pearson exact interval (typically treated as the "gold standard") was utilised to estimate the 95% confidence intervals (95% CI) of the Se_i and Sp_i, though this procedure is conservative (Agresti and Coull, 1998). The 95% CI of the PPV_{ij} was calculated using the log-odds method (Heckerling, 1988; Monsour et al., 1991; Mossman and Berger, 2001; Zou, 2004a). All the results within classical statistics were obtained by running the SAS 9.1 (SAS Institute Inc., Cary, NC, USA) scripts (these scripts are available on request).

2.4.2. Bayesian statistical analyses

A logit hierarchical model in the framework of Bayesian statistics was built to assess the HIV-Ab assays in this study in terms of sensitivity (Se), specificity (Sp) and positive predicative value (PPV). All Bayesian results were obtained by the Markov chain Monte Carlo simulations in the statistical package WinBUGS (Spiegelhalter et al., 2003). The posterior distributions were simulated in two parallel chains of length $n = 100{,}000$ after a burn-in period of 5000. The convergence and simulation stability were checked with the variance ratio method (Brooks and Gelman, 1998). Because of the asymmetry of some of the resulting posterior densities, the median and 95% Bayesian credible interval (BCI) are described. The specific details of the model and the corresponding WinBUGs code appear in the statistical appendix.

It should be pointed out that the confidence interval and credible interval have different conceptual foundations, and the differences

Table 1
Composition of the panel of serum specimens tested on each of the 17 commercial ELISAs[a] under evaluation.

Specimen origin	Anti-HIV positive[b] (n[c])	Anti-HIV negative (n)	Total
National AIDS reference laboratory of China	30	25	55
Institute of Chinese Drug and Biological Product	26	20	46
Provincial HIV conformation laboratories	46	208	254
Total	102	253	355

[a] Enzyme-linked immunosorbent assays.
[b] Including HIV-1 and HIV-2 types.
[c] Number.

Table 2
Composition of the panel of serum specimens tested on each of the 13 commercial rapid assays under evaluation.

Specimen origin	Anti-HIV positive[a] (n[b])	Anti-HIV negative (n)	Total
National AIDS reference laboratory of China	26	35	61
Institute of Chinese Drug and Biological Product	23	20	43
Provincial HIV conformation laboratories	48	206	254
Total	97	261	358

[a] Including HIV-1 and HIV-2 types.
[b] Number.