The validity of serologic tests for Trypanosoma cruzi and the effectiveness of transfusional screening strategies in a hyperendemic region

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Several serologic tests for the screening of Trypanosoma cruzi (T. cruzi) infection in blood donors were examined. More specifically, an indirect haemagglutination test (IHA), an indirect immunofluorescence assay (IFA) and four enzyme-linked immunosorbent assays (ELISAs). The ELISAs were crude ELISA 1, crude ELISA 2, recombinant ELISA 1 and recombinant ELISA 2. Some combination tests (i.e. IHA plus ELISA, IHA plus IFA, ELISA plus IFA) were also considered.

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis.

Study population
The study population included samples of blood donors.

Setting
The setting was a blood bank. The economic study was carried out in Bolivia.

Dates to which data relate
The effectiveness and resource use data were gathered from August 1998 to January 1999. The price year was not reported.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was not performed on the same samples as those used in the effectiveness analysis.

Study sample
Power calculations, if performed, were not reported. A sample of 400 blood samples was randomly selected from a consecutive series of 1,200 banked serum samples of blood donors. The mean age of the donors (134 women and 266 men) was 31.1 (+/- 9.2) years.
Study design
This was a within-group comparison study (diagnostic study) that was performed at the regional blood bank (RBB) of Santa Cruz in Bolivia. Serum samples, which had been evaluated routinely using IHA and then stored, were unfrozen, divided into several aliquots, and blindly retested with the panel of serologic tests under evaluation. Four samples were excluded since there was insufficient serum to process the complete series of serologic tests.

Analysis of effectiveness
The analysis of the clinical study was restricted to the 396 samples with enough serum. The primary outcome measures used were the sensitivity and specificity of each screening test. These were estimated using latent class analysis (LCA), a modelling technique based on the assumption that a non-observed (latent) variable is determining the association between observed categorical variables. The effectiveness of isolated or parallel use of different assays was then calculated, using a statistical approach to derive the number of undetected infected blood units and the number of units falsely labelled positive per 1,000 screened donations for various T. cruzi infection rates (40, 20 and 5%).

Effectiveness results
A total of 173 of the 400 donations were positive for the presence of T. cruzi when screened in the RBB with IHA. This corresponded to a T. cruzi prevalence rate in donors of 43.3% (95% confidence interval, CI: 38.4 - 48.1). The infection rate varied significantly with gender, residence and age. In particular, the prevalence rate was significantly higher in women, rural residents and individuals aged more than 30 years.

The analysis showed that 207 samples (52.3%, 95% CI: 47.4 - 57.2) were positive for at least one test.

The observed sensitivity and specificity values for the sample of 396 blood donors were as follows:

- for IHA - routine testing at donation, 0.965 (95% CI: 0.935 - 0.995) and 0.870 (95% CI: 0.828 - 0.912);
- for IHA - retested by reference laboratory, 0.975 (95% CI: 0.948 - 1.000) and 0.939 (95% CI: 0.910 - 0.969);
- for IFA, 1 and 0.963 (95% CI: 0.940 - 0.987);
- for crude ELISA 1, 1 and 0.970 (95% CI: 0.948 - 0.992);
- for crude ELISA 2, 0.986 (95% CI: 0.967 - 1.000) and 0.966 (95% CI: 0.943 - 0.989);
- for recombinant ELISA 1, 0.989 (95% CI: 0.969 - 1.000) and 0.989 (95% CI: 0.976 - 1.000);
- for recombinant ELISA 2, 0.993 (95% CI: 0.980 - 1.000) and 0.953 (95% CI: 0.926 - 0.979).

When the statistic calculation was performed, the sensitivity, specificity, and numbers of false-negative units and false-positive units at prevalence rates of 40% (20%; 5%) were as follows:

- for IHA alone, sensitivity 0.970, specificity 0.910, false-negative 12 (6; 1.5) and false-positive 54 (72; 85.5);
- for ELISA alone, sensitivity 0.990, specificity 0.960, false-negative 4 (2; 0.5) and false-positive 24 (32; 38);
- for IFA alone, sensitivity 0.990, specificity 0.960, false-negative 4 (2; 0.5) and false-positive 24 (32; 38);
- for IHA plus ELISA, sensitivity 0.9997, specificity 0.874, false-negative 0.12 (0.06; 0.015) and false-positive 75.8 (101.1; 120.1);
- for IHA plus IFA, sensitivity 0.9997, specificity 0.874, false-negative 0.12 (0.06; 0.015) and false-positive 75.8 (101.1; 120.1);
- for ELISA plus IFA, sensitivity 0.999, specificity 0.922, false-negative 0.04 (0.02; 0.005) and false-positive 47.0
Clinical conclusions
The effectiveness analysis showed that the combinations of two tests were more effective than a single test in terms of sensitivity (less false-negative units), but it led to more false-positive units (lower specificity).

Measure of benefits used in the economic analysis
The summary benefit measure was the number of infected units detected. This was derived directly from the effectiveness analysis.

Direct costs
The perspective adopted in the study was unclear. The analysis of the costs included only the costs of the reagents used for each serologic test. The unit costs were presented separately from the quantities of resources used. The authors presumably set the costs using the RBB costs as reference prices. Resource use referred to a hypothetical sample of 1,000 donations. Discounting was not relevant since the costs were incurred during a short timeframe. The price year was not reported.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not considered in the cost analysis.

Currency
US dollars ($).

Sensitivity analysis
No sensitivity analyses were performed.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The total cost per 1,000 units screened was $200 with IHA alone, $1,000 with ELISA alone or IFA alone, $1,200 with IHA plus ELISA or with IHA plus IFA, and $2,000 with ELISA plus IFA.

Synthesis of costs and benefits
Average and incremental cost-effectiveness ratios (ACER and ICER, respectively), namely the cost per infected unit detected, were calculated to combine the costs and benefits of the alternative screening strategies.

The ACERs at prevalence rates of 40% (20%; 5%) were:

for IHA alone, $0.5 ($1.0; $4.1);

for ELISA alone or IFA alone, $2.5 ($5.1; $20.2);
for IHA plus ELISA or IHA plus IFA, $3.0 ($6.0; $24.0);
for ELISA plus IFA, $5.0 ($10.0; $40.0).

The ICERs in comparison with a strategy of a single hypothetical IHA (reference strategy) at prevalence rates of 40%
(20%; 5%) were:
for ELISA alone or IFA alone, $100 ($200; $800);
for IHA plus ELISA or IHA plus IFA, $84 ($168; $673);
for ELISA plus IFA, $151 ($301; $1,204).

Authors’ conclusions
Routine blood donor screening for Trypanosoma cruzi (T. cruzi) with a single test resulted in unacceptable numbers of
false-negative samples in highly endemic areas, or in at-risk population groups, such as Bolivia. Screening using a
combination of an indirect haemagglutination assay (IHA) and enzyme-linked immunosorbent assay (ELISA) was a cost-
effective serologic test for the screening of T. cruzi infection in blood donors.

CRD COMMENTARY - Selection of comparators
The selection of the comparators was valid since several screening tests, used either individually or in parallel, were
considered. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The clinical data came from a within-group comparison study. This was appropriate for the study question since the
same specimens were used for all serologic tests. Thus, there was no need for an external control group. The specimens
included in the study were obtained from a random sample of consecutive specimens, thus they are likely to have been
representative of the samples included in the blood bank. The sequence of tests was not reported, but the evaluation of
the clinical outcome was blinded, which represents a further strength of the analysis. Details of the statistical approach
used to derive the clinical outcomes were extensive. Only 4 specimens were excluded because of there being limited
serum available.

Validity of estimate of measure of benefit
The summary benefit measure was specific to the disease considered in the study. It would not be comparable with the
benefits of other health care interventions, although it appears to have been appropriate for the objective of the study.

Validity of estimate of costs
The perspective of the study was not explicitly stated, but the economic analysis was restricted to reagent costs. The
economic impact of serologic tests on other health care services, such as management of infected blood samples, was
not investigated. The authors stated that the analysis should have taken the full cost elements (e.g. investment,
equipment, personnel, chemoprophylaxis) associated with serologic screening into consideration. The source of the data
was not reported, but the unit cost of each reagent was provided. The cost calculation was carried out hypothetically in a
sample of 1,000 specimens and no statistical analyses were performed. Further, the potential use of alternative costs
was not considered. The price year was not reported, which may limit the possibility of replicating the analysis in other
time periods.

Other issues
The authors stated that their findings were quite consistent with those from other studies, although comparisons were
difficult on account of the lack of a reference ‘gold’ standard. The issue of the generalisability of the study results to
other settings was not addressed, and all estimates were specific to the study setting. Sensitivity analyses were not performed, which further limits the external validity of the study. The authors discussed the social and economic costs associated with a low specificity value.

**Implications of the study**
The study results support blood screening with two tests in settings with a high to moderate prevalence of *T. cruzi* infection in donors. The authors concluded that the best strategy would ultimately depend on local feasibility.

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**Other publications of related interest**


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