

Cost-effectiveness of competing diagnostic-therapeutic strategies for visceral leishmaniasis

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Reported are the results of a formal decision analysis which facilitated the choice of the most appropriate test-treatment strategy for visceral leishmaniasis in areas where the disease is endemic. The following strategies were compared: treatment of all suspects (strategy A); testing by means of parasitological investigation followed by treatment of positives (strategy B); two-step testing by means of the direct agglutination test (DAT) followed by treatment of patients with high titres as well as those with parasitologically confirmed borderline titres (strategy C); and DAT followed by treatment of positives (strategy D).

The results for each strategy were expressed as costs in US\$ per death averted. The effectiveness of strategies C and D was close to that of strategy A and far better than that of strategy B. The cost-effectiveness ratio for strategies C and D (US\$ 465 per death averted) was not substantially higher than that of testing by means of parasitological investigation followed by treatment of positives (strategy B), which was the most cost-effective strategy at US\$448 per death averted. At current prices of antimonial drugs, the cost of test-treatment strategies depends more on the cost of treatment than on that of testing. The use of a sensitive serological test such as the DAT is recommended as the basis of test-treatment strategies for visceral leishmaniasis in areas where the disease is endemic.

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Introduction

Visceral leishmaniasis, a protozoal disease estimated to cause 414 000 new cases annually (1) occurs mainly in India and Sudan. The case fatality rate is close to 100% in untreated cases but the therapeutic arsenal is limited and not innocuous. A one-month course of parenteral pentavalent antimonials is given as first-line therapy if parasitological confirmation has been obtained (2). Cure rates do not exceed 90% in field settings (3, 4).

Diagnosis requires a balance to be struck between the sensitivity, specificity, cost and side-effects of the various techniques. The sensitivity of parasitological evidence on splenic aspirate smears is estimated to be in the range 90–95% (5, 6). A relatively safe splenic aspiration technique has been developed in Kenya (7); nevertheless, it is an invasive procedure requiring a prior platelet count and coagulation tests, the availability of blood for transfusion, and observation for 24 h in a surgically equipped facility. Kager et al. reported one death

associated with a series of 671 splenic aspirations among 113 clinical suspects (7). Thakur reported that three deaths were associated with 3000 splenic aspirations and that blood transfusion was required in 1 of 90 aspirations by the abdominal route (8). The precautions required make the procedure unsuitable for routine use in district hospitals in areas of endemicity, and it therefore cannot be considered for the comparison of test-treatment strategies in such facilities. The sensitivity of parasitological studies on aspirates of bone marrow (8) and lymph node (5) is much lower, and up to 50% of cases of visceral leishmaniasis can be expected to remain untreated if treatment is conditional on confirmation by such investigations.

The validity of serological diagnostic tests for visceral leishmaniasis depends on the technique and on the source and purity of the antigen employed. Sensitivity is generally high for cases of active visceral leishmaniasis but the specificity is not unequivocal (9). The cost and feasibility of serological tests are variable, and only the direct agglutination test (DAT) (9–13) has proved convenient for use in field conditions. High estimates for the specificity of DAT have been reported in laboratory studies (10, 14, 15) and a community study (11). Doubts have been expressed, however, as to whether these estimates applied among groups of clinical suspects (16) but it was found that the alleged poorer specificity of DAT in the clinical setting was mainly attributable to the weak sensitivity of the reference test, as indicated by mathematical modelling of the gold standard (17).

The discomfort caused to patients by the use of bone marrow aspirates is greater than that associated

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with lymph node aspirates. A venous or capillary blood sample is even more readily acceptable from this standpoint.

In order to assess whether DAT could effectively and cost-effectively replace parasitological investigation in district health services, we used formal decision analysis to compare two diagnostic-therapeutic strategies incorporating the test; one strategy was based on parasitological confirmation and the other relied on clinical diagnosis.

Methods

Clinical decision analysis is a quantitative method for evaluating the consequences of alternative strategies and permitting the choice of the most effective or most cost-effective course of action in complex situations. The method requires the following:

- a decision tree describing possible alternative strategies;
- information on the probabilities attached to the events in each strategy;
- a judgement about the clinical and economic consequences of each intervention (18).

We have considered which diagnostic-therapeutic strategy to apply in the event of clinical suspicion of active visceral leishmaniasis. For this purpose we define a clinical suspect as a person living in an area where visceral leishmaniasis is endemic who presents with fever of more than two weeks' duration and with either splenomegaly or enlarged lymph nodes, and in whom malaria has been excluded.

Diagnostic-therapeutic strategies

In an area where visceral leishmaniasis is endemic a clinician may forgo diagnostic testing and treat every clinical suspect (strategy A). This happens in remote district hospitals in East Africa, where there is a high fatality rate among untreated cases and a lack of diagnostic facilities. Alternatively, the following diagnostic strategies based on laboratory tests may be considered:

- parasitological examination of lymph node or bone marrow smears and treatment of patients with positive smears (strategy B);
- perform a DAT, treat all suspects with high titres, and, in suspects with borderline results, carry out a parasitological investigation followed by treatment if the result is positive (strategy C);
- perform a DAT and treat cases with high titres (strategy D).

Decision-tree structure

A decision-tree was constructed in order to compare the above-mentioned strategies (Fig. 1). The branches of the decision-tree lead to the outcomes below.

- “Visceral leishmaniasis — treated”, i.e. a real case of visceral leishmaniasis is correctly diagnosed and treated accordingly.

- “Erroneously treated”, i.e. a person without visceral leishmaniasis is incorrectly diagnosed and wrongly receives treatment for the disease.
- Visceral leishmaniasis — untreated”, i.e. a real case of visceral leishmaniasis is missed because of a false-negative test result and consequently is not appropriately treated.
- “Correctly ruled out”, i.e., a person without visceral leishmaniasis in whom the disease is correctly ruled out and who does not receive specific treatment for the disease.

Probabilities, effectiveness and cost assumptions

Probability estimates

Table 1 shows the baseline probability estimates used in the decision analysis. They are based on a cross-sectional population survey in a village in Gedaref State, Sudan (11). An exhaustive literature review provided a range of plausible values for those parameters about which uncertainty exists. The high cut-off titre of the DAT corresponds to the serum cut-off of 1:6400 recommended by El Harith et al. (15); the low cut-off corresponds, on the same scale, to a titre of 1:400. The specificity of the DAT in clinical suspects was set at 0.98 in the baseline analysis and was allowed to vary between 0.6 and 1 in subsequent sensitivity analyses.

Effectiveness

The marginal health benefits or losses of a strategy and its utility, i.e. the patient's perceptions of the quality of life associated with a health state, were disregarded, and overall effectiveness was expressed as deaths averted relative to mortality in the absence of intervention. However, it should be noted that sequelae occur; for example, within 6 months after discharge up to 50% of initially cured kala-azar patients develop post-kala-azar dermal leishmaniasis, a cutaneous complication that is not life-threatening and is treated by repeating the 30-day course of antimonials. Table 2 gives the values for the four possible outcomes. Based on data from a programme in eastern Sudan, we assumed that 0.88 deaths would be averted for each true case of visceral leishmaniasis that was diagnosed and treated. Between 1996 and 1998 this programme enrolled 7500 patients and resulted in the initial cure of 90% of them (case fatality and defaulter rates were 8% and 2%, respectively). However, relapses occurred in 13% of the initially cured subjects, and the same cure rate was assumed in this group (19). The correct ruling out of visceral leishmaniasis may give psychological benefit but does not avert deaths, and effectiveness was therefore valued at 0 in such instances. A false-positive diagnosis exposes a person to a relatively toxic treatment lasting a month and, moreover, delays correct diagnosis and any other potentially life-saving treatment. Sudden death during antimonial

treatment has been attributed to the cardiotoxic effects of the drug in high-dosage regimens (20–25). Although iatrogenic risk is low at correct drug dosage, it is difficult to quantify. It is estimated to be approximately 1 in 10 000 treatment courses in hospitals in developed countries, where careful cardiac monitoring is possible. After a panel of specialists in infectious diseases had been consulted, we assigned an effectiveness value of 0.001 to the unnecessary treatment of a person without visceral leishmaniasis in an area of endemicity; this value reflects 1 iatrogenic death per 1000 treatment courses, a high estimate. An effectiveness value of 0 was assigned to a missed diagnosis of a real case of visceral leishmaniasis.

Costs

In the baseline analysis the costs incurred under the four strategies were compared from the perspective of the health service. Labour costs were calculated on the basis of an annual salary of US\$ 2000 applicable in the Sudan, i.e. US\$ 1 per working hour.

Each parasitological test, including sampling and slide preparation, takes 1 hour. The cost of such a test was fixed at US\$ 1, given that consumables (slides, dyes) cost only US\$ 0.03 and that microscope depreciation and other capital costs are negligible.

The labour cost for a DAT was estimated at US\$ 0.04. The cost of consumables comprises that of the antigen, which is not commercially available at present, and that of laboratory supplies. In an evaluation of a prototype kit (26) the price of the 600 µl of antigen used per test was estimated to be US\$ 1.1, and there was an additional cost of US\$ 1.2 for pipettes, microtitration plates and other supplies. Including transport and negligible capital costs, the total cost of a test was thus approximately US\$ 2.5.

The cost of treating one person for visceral leishmaniasis depends on whether the patient is treated on an ambulatory basis, and is determined

Fig. 1. Decision tree for four competing test treatment strategies for visceral leishmaniasis (VL) (DAT = direct agglutination test)

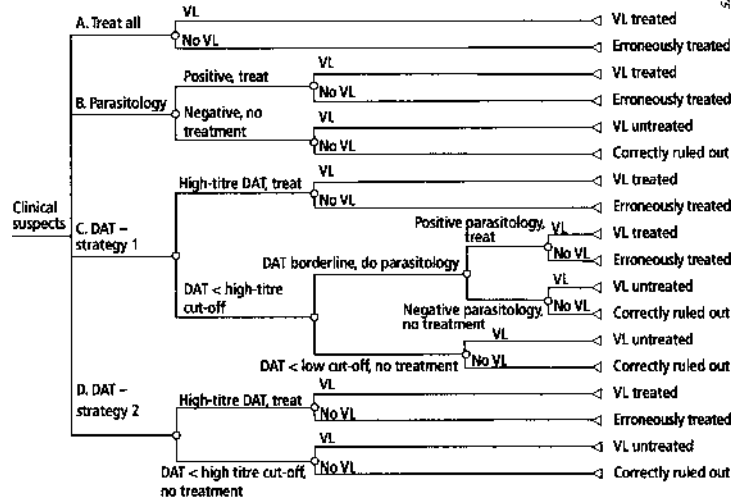


Table 1. Probability values used in the decision analysis

	Baseline estimates ^a	Plausible ranges	Reference
Prior probability in clinical suspects	0.4	0.1–0.5	
Sensitivity of parasitology	0.6	0.5–0.9	(5, 10, 12, 16, 28, 29)
Specificity of parasitology	1		
Sensitivity of DAT ^b at high cut-off	0.96	0.8–1	(10, 13–16, 28, 30–34)
Specificity of DAT at high cut-off	0.98	0.6–1	(10, 13–17, 28, 30–34)
Sensitivity of DAT at low cut-off	1	0.9–1	(14)
Specificity of DAT at low cut-off	0.85	0.70–0.95	

^a Based on Boelaert et al. (11).

^b Direct agglutination test.

Table 2. Effectiveness of outcomes relative to deaths averted

Disease status	VL ^a -specific therapeutic action		Effectiveness (deaths averted)	Plausible range	Source
VL +ve	Treated	True positive	0.88	0.80–0.95	(3, 4, 19)
VL –ve	Correctly ruled out	True negative	0		By assumption
VL –ve	Erroneously treated	False positive	–0.001	(–0.001)–(–0.0001)	Expert poll
VL +ve	Untreated	False negative	0		By assumption

^a Visceral leishmaniasis.

also to a great extent by drug cost. The price of a 30-day course of treatment is US\$ 150 with sodium stibogluconate (Pentostam, Wellcome, Manchester, England) (4) and, on average, US\$ 120 with meglumine antimoniate. On average, generic antimonials, which are still undergoing quality evaluation, would cost US \$16 per course (4). Information on other treatment costs is scarce and highly variable depend-

ing on the context (level of care, percentage of patients hospitalized, relapses, post-kala-azar dermal leishmaniasis cases, etc.). Médecins sans Frontières-Netherlands reported the total cost of visceral leishmaniasis care to be US\$ 394 per patient treated in a programme in southern Sudan (3), and this led us to assume that the average cost of care, excluding

drug and test costs, would be US\$ 240 [US\$ 394–(US\$ 150 + US\$ 4)] per month.

Analysis

The expected effectiveness of each strategy was estimated by calculating the sum of the effectiveness values of each possible outcome of the strategy weighted by their probability of occurring; the strategy averting most deaths was considered to be the most effective. A cost-effectiveness analysis was then performed and the strategy minimizing the cost per death averted was designated the most cost-effective.

Subsequently, a one-way sensitivity analysis was performed on those parameters of probability and cost that were subject to appreciable uncertainty.

The analysis was performed using DATA™ V.3.0 software (TreeAge, Williamstown, Massachusetts, USA).

Results

Strategy A was the most effective approach in the baseline analysis, averting 0.35 deaths per clinical suspect enrolled, or 88% of all possible deaths attributable to visceral leishmaniasis in a group of clinical suspects with a prior probability of 0.40 of having the disease.

Strategy C and strategy D each prevented 0.34 deaths per clinical suspect (85%). Parasitological examination (strategy B) prevented 0.21 deaths per clinical suspect (53%).

These proportional effectiveness estimates were not affected by variations in the prior probability of disease between 0.1 and 1 (Fig. 2). At prior probabilities below 10%, the iatrogenic effects of strategy A became apparent. Strategies C and D performed better than strategy A at prior probabilities below 0.03 because they had fewer iatrogenic effects; below a prior probability of 0.001, strategy A became counterproductive, causing more deaths,

attributable to drug toxicity, than it prevented. However, the proportional effectiveness estimates of strategies B, C and D were unaffected at this low level of prior probability: they still prevented 53%, 83% and 82%, respectively, of all avoidable deaths. At very low prior probabilities (<0.00006), strategy B exceeded the effectiveness of strategies C and D. At extremely low prior probabilities (<0.00002), strategies C and D caused more deaths than lives saved, while strategy B remained valid, preventing 50% of avoidable deaths.

Subsequently, we compared the effectiveness of strategies using lower estimates of sensitivity and specificity for the DAT. At prior probabilities >0.10 the proportional effectiveness estimates were not altered if the specificity of a high-titre DAT cut-off was lowered to 0.60, well below a previous conservative estimate of 85% in clinical suspects without prior treatment (17). If the sensitivity of this cut-off was lowered to 0.80, strategies C and D prevented 72.5% and 70% of deaths, respectively (Fig. 3).

The effectiveness estimates of the two strategies that included parasitological examinations were examined over a range of parasitological sensitivities (Table 3). Strategy C was only barely sensitive over the range of sensitivities examined, whereas strategy B was clearly sensitive. By setting the sensitivity of parasitological examination at 0.9, which seems hardly achievable by combining multiple lymph node and bone marrow aspirates, the effectiveness of strategy B did not exceed 80%, and remained the least effective of the four strategies.

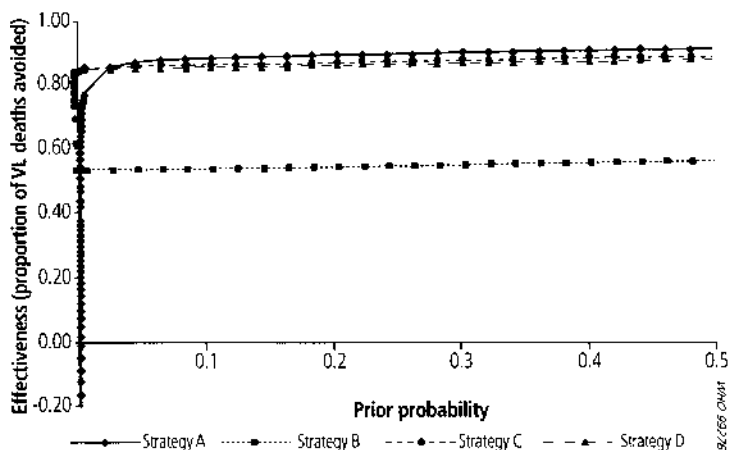
We conclude that strategies C and D are highly effective compared with strategy B, since they consistently prevented almost 85% of the deaths attributable to visceral leishmaniasis over the entire spectrum of prior probabilities and parasitology sensitivities examined. Also, the proportional effectiveness of strategies C and D was close to the theoretical maximum of 88%, the limitation imposed by current drug effectiveness. In the sensitivity range that applies to lymph node and bone marrow smears, i.e. 60–70%, the parasitology strategy averted only 53–62% of deaths attributable to visceral leishmaniasis in a wide range of prior probabilities.

The cost-effectiveness ratios of strategies A, B, C and D were US\$ 1110, US\$ 448, US\$ 465 and US\$ 464 per death averted, respectively. The last three estimates held for variations in prior probability over the range 0.1–0.9.

Table 4 shows the change in the cost-effectiveness ratios of the test-treatment strategies depending on variations in the cost of DAT at the three cost levels of currently available drugs.

At present the cost of DAT relative to the cost of drugs and clinical care is so low as to be negligible, and the most cost-effective diagnostic strategy is that yielding the smallest number of false positives for treatment. Even if the much less expensive generic version of the antimonial drug were in use, costing

Fig. 2. Effect of variation in the prior probability of visceral leishmaniasis (VL) on the effectiveness of the four treatment strategies



US\$ 16 per course, the ranking of the strategies by cost-effectiveness would not change.

Discussion

District doctors in areas where visceral leishmaniasis is endemic often treat suspects on the basis of clinical evidence only (27). This is clearly not cost-effective, nor would it be even if generic antimonials were employed. While splenic aspiration is routinely performed in tertiary care centres, this technique is not feasible in many rural hospitals and is certainly not available in primary care facilities. Some district doctors practise lymph node or bone marrow aspiration but the sensitivity of these techniques is too low; "trial of treatment" has been the clinician's option in parasitologically negative clinical suspects. In the present study it was found that a parasitological test-treatment strategy would save only 52% of avoidable deaths.

Can a serological test such as DAT validly replace parasitology in clinical algorithms? The effectiveness of serological strategies C and D was close to that of strategy A, in which all clinical suspects were treated. Strategies C and D were similar to one another in cost-effectiveness and over twice as cost-effective as strategy A.

Since the difference between strategies C and D is only marginal, it would be more logical in areas where the disease is endemic to introduce strategy D, which is exclusively based on serology, than strategy

Fig. 3. Effect of variation in the sensitivity of the direct agglutination test (DAT) on effectiveness of the four treatment strategies

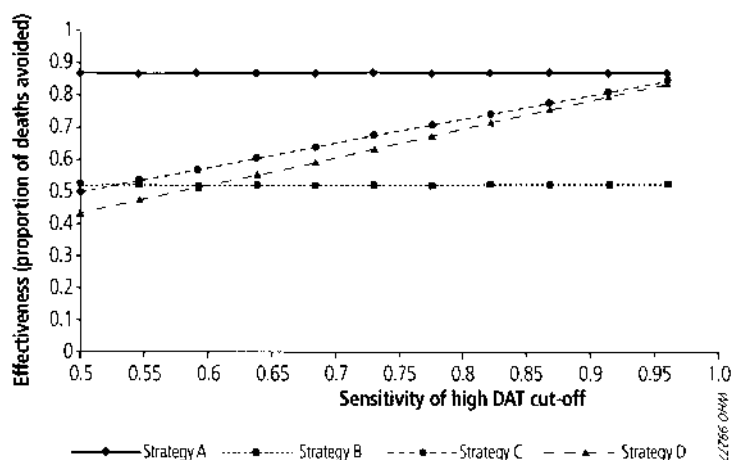


Table 3. Proportion of deaths attributable to visceral leishmaniasis averted by strategies B and C according to the sensitivity of the parasitological examination

	Proportion of deaths averted when the sensitivity of parasitological examination is				
	0.50	0.60	0.70	0.80	0.90
Strategy B	0.44	0.53	0.62	0.70	0.79
Strategy C	0.85	0.85	0.85	0.85	0.85

Table 4. Cost-effectiveness ratios (US\$ per death averted) in relation to cost of drugs and of the direct agglutination test (DAT)

Drug cost (US\$)	Strategy ^a	Cost-effectiveness of DAT at a cost (US\$) of							
		0	1	2	3	4	5	6	7
150	A	1109.8							
	B	447.9							
	C		460.8	463.7	466.6	469.6	472.5	475.5	478.4
	D		460.0	463.0	465.9	468.9	471.8	474.8	477.8
120	A	1024.5							
	B	413.8							
	C		425.6	428.5	431.5	434.4	437.4	440.3	443.2
	D		424.9	427.8	430.8	433.7	436.7	439.7	442.6
16	A	728.5							
	B	295.6							
	C		303.8	306.7	309.6	312.6	315.5	318.5	321.4
	D		303.0	305.9	308.9	311.8	314.8	317.8	320.7

^a A: treatment of all clinical suspects.

B: parasitological test and treatment of positives.

C: direct agglutination test, treatment of positives, and parasitological test if result of direct agglutination test borderline.

D: direct agglutination test and treatment of positives.

C, which requires skills in both serology and parasitology.

The limitations of serology should, however, be acknowledged. No serological test is completely specific for visceral leishmaniasis. A major objection to DAT is that it cannot distinguish acute disease from subclinical infection or past disease, because titres remain high for several months after treatment (16). As yet, the control of visceral leishmaniasis in humans does not aim at treating asymptotically infected persons. In the clinical setting, DAT can thus be used following the screening of patients on the basis of a clinical case definition, which excludes asymptotically infected persons and increases the prior probability of the disease in the group to be tested serologically.

Prior probability levels in the range 30–40% among clinical suspects are common in the area of eastern Sudan where the present study was based, and may be particularly characteristic of epidemic outbreaks. However, the findings were unaffected by prior probabilities as low as 10%, which are likely to be achieved through clinical screening even in areas of moderate endemicity. Some uncertainty surrounds the specificity of the DAT, which was estimated to be nearly 100% in the general population but 85% in groups of clinical suspects. The effectiveness estimates in our decision analysis were, however, unaffected if the specificity of the DAT was reduced to 60%, which is implausibly low given the evidence from the different settings. The decision to treat for visceral leishmaniasis can be based on the result of the DAT for clinical suspects, excluding persons already having received antimonial treatment.

As the effectiveness of a test-treatment strategy for visceral leishmaniasis is mainly determined by the sensitivity of the diagnostic test — sensitivity losses in the serological test clearly influence the results. If the sensitivity of the DAT decreases to 80%, the same test-treatment strategy will only prevent 70% of avoidable deaths instead of 85%. A multicentre study has shown that the test loses sensitivity in the field as a consequence of handling and storage problems (26). Technical solutions for the thermostability problem already exist: a freeze-dried antigen is available and should be urgently evaluated. In the meantime the performance of the aqueous antigen in the field depends on good handling and storage practice.

Although the DAT is not perfect, present knowledge allows for its rational use in the control of visceral leishmaniasis. The decision analysis showed that a diagnostic strategy based on this test is better than parasitology for control at the district level. In the light of the high case fatality rate of the disease, and given the relatively safe if expensive treatment, suspected cases should be treated more promptly on the basis of the best available evidence. The introduction of the DAT in diagnostic-therapeutic algorithms should raise the quality of evidence used in treatment decisions and contribute to the rationalization of control efforts. ■

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Résumé

Rapport coût/efficacité des stratégies concurrentes de traitement-diagnostic de la leishmaniose viscérale

Afin de faciliter le choix de la stratégie diagnostic-traitement la mieux appropriée pour lutter contre la leishmaniose viscérale dans les régions où la maladie est endémique, on a procédé à une analyse décisionnelle formelle. Quatre stratégies ont été comparées : A) le traitement de tous les cas cliniquement présumés de leishmaniose viscérale; B) le test par examen parasitologique suivi du traitement des cas positifs; C) une stratégie de test en deux étapes comprenant le test d'agglutination directe suivi du traitement des cas ayant un titre élevé et des cas ayant un titre limite mais confirmé parasitologiquement; D) le test d'agglutination directe suivi du traitement des cas positifs. Un examen de la littérature médicale a fourni des données sur l'efficacité et le coût des tests et des interventions. Les résultats en matière de coût/efficacité ont été exprimés

en coût (US \$) par décès évité pour chaque stratégie. L'efficacité des stratégies C et D était proche de celle qui consistait à traiter tous les cas cliniquement présumés, et elle s'avérait bien meilleure que celle qui consistait à traiter uniquement les cas parasitologiquement positifs. Le rapport de coût/efficacité des stratégies C et D, \$465 par décès évité, n'était guère plus élevé que celui de la stratégie B, qui présentait le rapport coût/efficacité le plus avantageux : \$448 par décès évité. Le coût des stratégies de diagnostic-traitement est actuellement en grande partie déterminé par le coût du traitement plutôt que par le coût des tests, vu le prix élevé des antimoniés. L'utilisation du test d'agglutination directe pour servir de base à une stratégie de diagnostic-traitement en zone d'endémie est recommandée.

Resumen

Relación costo-eficacia de estrategias alternativas de diagnóstico y tratamiento de la leishmaniasis visceral

A fin de facilitar la elección de la estrategia de diagnóstico y tratamiento más adecuada para controlar la leishmaniasis visceral en las regiones donde la enfermedad es endémica, se realizó un análisis formal de decisiones. Se compararon cuatro estrategias: A) el tratamiento de todos los casos clínicamente sospechosos de leishmaniasis visceral; B) el examen parasitológico seguido del tratamiento de los casos positivos; C) una estrategia en dos etapas consistente en una prueba de aglutinación directa seguida del tratamiento de los casos con títulos elevados y de los casos con títulos medios pero confirmados parasitológicamente; D) la prueba de aglutinación directa seguida del tratamiento de los casos positivos. Examinando la literatura médica se obtuvieron datos sobre la eficacia y el costo de las pruebas y las intervenciones. La relación costo-eficacia se expresó

como el costo (US\$) por defunción evitada con cada estrategia. La eficacia de las estrategias C y D fue muy similar a la de la consistente en tratar todos los casos clínicamente sospechosos, y mucho mejor que la correspondiente al tratamiento exclusivo de los casos parasitológicamente positivos. La relación costo-eficacia de las estrategias C y D, US\$ 465 por defunción evitada, no fue sustancialmente más alta que la de la estrategia B, que era la más ventajosa: US\$ 448 por defunción evitada. Actualmente, el costo de las estrategias de diagnóstico y tratamiento está determinado en gran parte por el costo del tratamiento más que por el de las pruebas, debido a la carestía de los derivados del antimonio. En zonas endémicas, se recomienda usar la prueba de aglutinación directa como base de una estrategia de diagnóstico y tratamiento.

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