

CLINICAL REVIEW

Strongyloides serology – useful for diagnosis and management of strongyloidiasis in rural Indigenous populations, but important gaps in knowledge remain

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ABSTRACT

General practitioners who care for Aboriginal patients in rural and remote communities from tropical Australia must be aware of strongyloidiasis. The prevalence of this parasitic infection is high and occasional cases can have a fatal outcome. Other groups in Australia at high risk of strongyloidiasis are immigrants from endemic countries, particularly from Southeast Asia, and military personnel who have served overseas in endemic areas. Elimination programs for enteric parasites in rural Australian Indigenous communities are so important that a nationally coordinated approach has been advocated. Wisely used, cost-effective diagnostic tests are a critical component of an elimination program. Strongyloidiasis must be confirmed by laboratory diagnosis and the strongyloides ELISA, although not ideal, is a useful test that can be used to diagnose strongyloidiasis and to monitor cure. In this article the value of the current strongyloides ELISA is discussed and a cost-benefit analysis is conducted using direct costs only. In a typical rural Aboriginal community in tropical Australia with prevalence of strongyloidiasis at 20% each true positive case detected by the strongyloides ELISA is estimated to cost approximately AU\$590 to diagnose and manage until cure, proven by negative serology.

Key words: clinical epidemiology, cost benefit, diagnosis, Indigenous Australians, serology, *Strongyloides stercoralis*.



Introduction

Rural general practitioners who care for Aboriginal patients in Australia must be aware of strongyloidiasis because this chronic parasitic disease commonly affects these patients, particularly those in rural and remote tropical communities¹. Other groups in Australia at high risk of strongyloidiasis are immigrants from endemic countries and military personnel who have served in endemic areas. Elimination programs for enteric parasites in rural Australian Indigenous communities are so important that a nationally coordinated approach has been advocated². Wisely used cost-effective diagnostic tests are a critical component of an elimination program.

Strongyloidiasis diagnosis has relied on laboratory examination because the only pathognomic clinical sign of strongyloidiasis is larva currens, a rapidly moving erythematous, serpiginous skin lesion similar to cutaneous larval migrans, but moving much faster, often at rates of 10 cm per day. Diagnostic tests include: (i) serology to detect anti-strongyloides antibody; and (ii) faecal examination. In this article, comments are confined to strongyloides serology and its role in the diagnosis and management of strongyloidiasis.

Strongyloides ELISA

The ELISA test to detect serum antibodies against the pathogenic gut nematode, *Strongyloides stercoralis*, complements tests to detect larvae, mainly in the stools of infected individuals. Recent research has confirmed that the detection of positive cases is improved when both tests are used³. This is not surprising because complementary diagnostic tests used simultaneously (ie, in parallel) maximize diagnostic sensitivity⁴. Nevertheless, unlike many other serological diagnostic tests for microorganisms, application of strongyloides ELISA is frequently challenged on the grounds of uncertain usefulness⁵. Humans, including clinicians, crave certainty, but in biological systems certainty is an illusion and a relentless crusade for certainty may

retard the application of useful but imperfect measures to improve human health⁶. The degree of uncertainty inherently characterising a diagnostic or screening test is expressed as its sensitivity and specificity. These are conditional probabilities that are properties of the test per se. When the test is used in a particular patient population, its value also depends on the prevalence of the disease in that population. It is worth emphasising that all diagnostic and screening tests and subsequent interventions based on test results have benefits and costs, and the value of a particular test depends on how much the benefits exceed the costs in the specific population. This article examines the role of the strongyloides ELISA in diagnosing and managing human strongyloidiasis, and discusses what additional data is needed to better define this role. The Australian context is ideal for this exercise because it provides populations at both ends of the prevalence spectrum.

In Australia the strongyloides ELISA is standardised, and has a sensitivity and specificity of 93% and 95% respectively, originally determined in a group of former prisoners of war from Singapore⁷. This test performance is comparable to well-established serological tests for other diseases^{7,8}. Sackett and Haynes⁹ proposed that in evaluating the usefulness of diagnostic tests, four phases of questions should be answered. The strongyloides ELISA has progressed to Phase II only ('Are patients with positive strongyloides ELISA more likely to have the target disorder than patients with a negative or borderline result?'), providing the current values for sensitivity and specificity⁷. The Phase III question ('Does the test distinguish patients with and without strongyloidiasis among patients in whom it is clinically reasonable to suspect that the disease is present?') needs to be answered for the various target groups. Independent, blind comparison with a gold standard of diagnosis will be required for these studies⁹. A major constraint is that there is no available gold standard for diagnosis¹⁰⁻¹¹ because the strongyloides ELISA has a greater sensitivity than the examination of faeces for larvae of strongyloides^{3,8,12,13}.



Table 1: Components comprising costs of positive and false negative strongyloides ELISA

Positive strongyloides ELISA test	
Cost	
Treatment	Ivermectin 36 mg (3 treatments x 12 mg)
Consultations	Initial, months 1, 2, 6, 12, 24
Repeat serology to document cure	Months 6, 12, 24
Side effects	Minimal because treatment is safe
Re-treatment	Incidence not known, but low because treatment with x 3 ivermectin regimen seems highly effective
Lost productivity	Not quantified: (1) Time not working due to illness; (2) Time attending medical care.
False negative strongyloides ELISA test or undiagnosed case of strongyloidiasis	
Morbidity	70% of patients have symptoms and signs
Repeat visits to medical care	Not quantified; above population average
Multiple diagnostics tests	Not quantified; above population average
Therapies against diseases other than strongyloidiasis	Not quantified; therapy for complications of strongyloidiasis, and ineffective therapies used for misdiagnosed diseases
Hospitalisation for severe disease	Reported, but incidence unknown
Lost productivity	Not quantified: (1) Time not working due to illness; (2) Time attending medical care
Mortality	Incidence in strongyloidiasis cases is unknown

Table 2: Estimate of direct cost of diagnosing, treating and monitoring patients using the strongyloides ELISA. Consultation costs are the Australian Medicare benefit for standard consultation (Item 23) and Australian Medicare benefit for the strongyloides ELISA (Item 69384)

	Positive case AUS	Negative case AUS
Consultation 1	26	26
Serology 1	20.50	20.50
Ivermectin 36 mg (3 treatments x 12 mg)	87	–
Retreat consultation in 1 month	26	–
Retreat consultation in 2 months	26	–
Consultation 6 months post-treatment	26	–
Serology 6 months post-treatment	20.50	–
Consultation 12 months post-treatment	26	–
Serology 12 months post-treatment	20.50	–
Consultation 24 months post-treatment	26	–
Serology 24 months post-treatment	20.50	–
Total	325	46.50

Positive case = ELISA is positive; Negative case = ELISA is negative.
–, Not applicable.



Benefits of treating strongyloidiasis

Although there are clearly no perfect tests currently available for strongyloides diagnosis, there are definite psychological, economic, morbidity/mortality alleviation and epidemiological benefits to diagnosing and correctly treating strongyloidiasis. Available diagnostic tests, including the strongyloides ELISA should be optimally utilised until better alternatives are available. Most people with strongyloidiasis have symptoms, and infected individuals occasionally progress to severe disease and death. The knowledge that the parasite has been eradicated from a patient's gut is reassuring both for the treating clinician and the worried symptomatic patient. Economic benefits include those that directly accrue to the health service through preventing severe disease and recurrent health service presentations, and the costs to the individual patient and their family, in terms of healthcare costs and lost productivity due to chronic ill health. If a patient is liable to contaminate the soil with faeces, then effective treatment will also reduce transmission in the patient's community, with attendant epidemiological benefits.

Costs

What are the costs associated with strongyloides serology? The direct costs of diagnosis include a consultation involving a venepuncture and the costs of the ELISA test (Table 1), approximately \$46.50 using the Australian Medicare benefits for a standard consultation and laboratory test (Table 2). Of course, these costs can be higher or lower depending on whether cases are managed through private GPs, Aboriginal health services or through health departments. The costs used provide a starting point allowing comparison between groups. Further costs are negligible if the test is negative, while if the test is positive, direct costs include those for therapy and subsequent monitoring. The ideal monitoring regimen post-treatment has not been determined. We would recommend six-monthly monitoring for 1 year and if the 12 month test is negative, a

final serological test at 2 years; that is, three repeat serological tests¹⁴. Because the most effective drug, ivermectin, has a very low incidence of side effects¹⁵⁻¹⁷, the indirect costs associated with adverse events are probably negligible.

Role of strongyloides ELISA in Management of strongyloidiasis

Although it has been postulated that the ELISA might demonstrate greater sensitivity in people chronically exposed to *S. stercoralis*¹⁸, this was not proven until recently when infected adults in the UK were shown to be more likely to have a negative ELISA than those with more long-standing strongyloidiasis³. Young age per se does not guarantee seronegativity¹⁹. In Australia, positive serology was demonstrated in immigrant children as young as one year of age from Indochina²⁰. Five per cent of children who were aged between one and two years gave positive reactions, and the positive reaction rate in this population increased by approximately 7% per year until the age of seven to eight years at which point it leveled off²⁰. The time necessary for seroconversion is unknown for human strongyloidiasis. Dogs experimentally infected with *S. stercoralis* had a rise in anti-strongyloides IgM at one week and in IgG soon after²¹. Although acute infections may be seronegative in humans, the window period in humans is unknown. This needs to be determined by studying short-term travelers of all ages exposed to high risk situations.

The role of the strongyloides ELISA in the management of strongyloidiasis is equally important. Although the ELISA detects anti-strongyloides IgG, the titre falls after effective treatment^{7-8,22}. This makes the test potentially valuable as a monitoring tool. A failure of the titre to fall can thus be used by clinicians to determine whether retreatment is required. This remains controversial, with those arguing against the usefulness of serology for monitoring patient response often basing their arguments on trials using inadequate treatment regimens, in most cases a single treatment with albendazole



or ivermectin³. Single treatment failure is not uncommon owing to two unique aspects of the biology of *S. stercoralis*. First, *S. stercoralis* has autoinfective larvae, which are more difficult to kill with either albendazole or ivermectin^{7,23}. Second, the parasitic female, the only adult parasitic stage, reproduces by parthenogenesis, and one worm is a patent infection. Parthenogenesis is a feature of the genus while production of autoinfective larvae has been identified in only two species of strongyloides, *S. stercoralis* and *S. felis*; the latter being a parasite of cats in India and Australia^{24,25}. Even if all adult *S. stercoralis* in the small intestine mucosa/wall are killed by a single dose of anthelmintic medication, autoinfective larvae may not be killed, and can return to the gut to mature to adulthood and produce larvae, including autoinfective larvae. This maintains infection or even steadily increases the intensity of infection. Hence, before a study can be accepted as providing evidence of the inadequacy of the strongyloides ELISA as a monitoring tool, it must make use of highly effective treatment. Currently this should entail repeated doses of ivermectin²⁶. The optimal retreatment period is unknown but, on biological grounds, monthly retreatment may be preferable because the only experimental study to date showed that the prepatent period after infective larvae penetrated the skin was 28 days²⁷. Retreatment on at least two occasions with one month intervals after the initial dose (ie, three monthly doses) will theoretically kill adults derived from autoinfective larvae, hopefully before they produce autoinfective larvae themselves. A limited number of studies that have adopted this approach to treatment have shown that strongyloides ELISA will revert to negative in the majority of patients¹³. However, additional studies are required to confirm the utility of strongyloides ELISA as a monitoring tool after effective treatment.

Cost-benefit of strongyloides ELISA

The cost-benefit of a diagnostic test is related to its positive predictive value (ie, yield) and thus the particular disease prevalence in specific populations. This is well illustrated using the Australian situation. In Australia, strongyloidiasis is a problem restricted to rural and remote Aboriginal

communities in the tropics^{1,28,29}, immigrants from high endemicity countries particularly Southeast Asia^{19,30}, returned prisoners of war from Southeast Asia^{31,32}, and military personnel that have served in Southeast Asia³³. Strongyloidiasis is uncommon in Australian urban communities because faeces are safely deposited in toilets and the life cycle cannot continue³⁴. In some Australian Aboriginal communities the prevalence of strongyloidiasis in cross-sectional faecal surveys is 15% or greater, implying a higher true infection rate because faecal examination is a less sensitive diagnostic technique^{28,35-37}. For illustrative purposes, the present study will use a prevalence of 20%.

In the urban Australian community, strongyloidiasis is a very rare disease; the present study will use an arbitrary prevalence of 1/10 000, which is probably an overestimate. What is the cost-benefit of screening with the strongyloides ELISA in each community? Since humans, including clinicians feel more comfortable interpreting natural frequencies rather than probabilities, the present study will use the former³⁸. Of 10 000 members of the rural Aboriginal community with a prevalence of 20%, 2000 can be expected to have strongyloidiasis. If these individuals are tested with the Australian strongyloides ELISA with a sensitivity and specificity of 93% and 95% respectively⁷, 1860 true positives will be detected and 400 false positives. Of the urban group of 10 000, approximately one true positive (actual value = 0.93) and 500 false positives will be detected. Thus, the number needed to test to detect one true positive will be 5.4 and 10 753 for the rural Aboriginal and urban groups, respectively.

Another useful perspective is to consider the number of people who test positive who are true positives. This is a particularly useful perspective for individual patients from these communities, because there are considerable costs, both psychological and in terms of exposure to further investigation or treatment, if a person is falsely 'diagnosed' as infected⁶. For every 1000 rural Aboriginal Australians who have a positive strongyloides ELISA, 823 will be true positives; while for every 1000 urban people with a positive test, only 2 (actual value = 1.99) will have strongyloidiasis.



Clearly, for the urban group with its low prevalence, the costs of testing exceed the benefits, while for high prevalence rural Aboriginal communities, the benefits are much greater. Using figures for direct costs of detection and treatment only (Table 2), every true positive case detected in the remote Aboriginal community costs AU\$588 to manage, while every true positive case detected in the urban community costs AU\$649 995 (Table 3). If the focus was further refined to individuals within Aboriginal communities who were symptomatic, with respiratory, gastrointestinal or cutaneous symptoms/signs, the cost per positive case detected would decrease further^{3,9,39}.

This is a simplistic analysis that assumes 100% success in treatment and does not allow for indirect costs. It is only a beginning. From a public health perspective other costs must be known before decisions on screening can be undertaken, in particular the medical impact of untreated chronic strongyloidiasis. Chronic strongyloidiasis is symptomatic in approximately 70% of cases^{3,39}, but the cost of ongoing illness has not been calculated. Avoidance of episodes of severe disease by prompt treatment of chronic strongyloidiasis and prevention of progression to hyperinfection must be factored in, as any intensive hospital treatment immensely increases cost. One episode of hyperinfection treated in an intensive care unit may cost US\$80 000 in the USA⁴⁰. This would appear to be an overestimate of costs in the Australian system, but no figures are available for Australia. Severely ill patients in isolated, remote northern Australian Aboriginal communities are evacuated to major hospitals by air at a cost of \$6 per km (B. McGuire, Royal Flying Doctor Service, pers. comm., 2004). Thus, an emergency evacuation may cost from \$3000 to \$10 000 depending on the distance flown. Severe strongyloidiasis occurs in remote Aboriginal communities^{36,41-44}, but the incidence of severe strongyloidiasis, including death, is not known. To obtain a comprehensive cost-benefit analysis prior to screening communities with strongyloides ELISA, data is needed on the cost of untreated strongyloidiasis and severe strongyloidiasis, as well as reasonably accurate estimates of the prevalence of strongyloidiasis in the communities of

interest. Additional cost data is needed for communities with different prevalences in order to construct a cost-benefit algorithm. Health departments also need to decide how much they are willing to spend on detecting and treating a positive case. Consultation costs for detecting strongyloidiasis could be decreased in rural and remote tropical Indigenous communities by including serological screening for strongyloidiasis in well-person health checks with the other chronic diseases currently included.

Conclusion

In summary, although a new strongyloides ELISA or a new test with higher sensitivity and specificity would be ideal, the current ELISA is a useful tool for diagnosing strongyloidiasis and for monitoring response to adequate treatment. It is of particular value in communities and subgroups hyperendemic for strongyloidiasis where the cost, per positive case detected, is considerably lower. Phase III trials⁹ should be carried out for subgroups selected on the probability of having strongyloidiasis. To better define the role of the strongyloides ELISA, we require a more complete understanding of the length of the window period to seroconversion after infection, and whether failure of the titre to fall to negative values always indicates treatment failure. To make fully informed decisions about screening endemic communities, data on the prevalence and costs of chronic and severe strongyloidiasis are needed. Although community-wide interventions for strongyloidiasis has been advocated^{17,45} and implemented on a limited number of occasions⁴⁶, comprehensive data are not available on the most effective approach in the Australian situation. Any intervention program should be evaluated in terms of epidemiological parameters (prevalence, intensity and transmission dynamics of infection), impact on general health (clinic attendances, hospitalisations, time off work, quality of life), and direct and indirect economic costs and benefits to allow development of appropriate cost-benefit algorithms.



Table 3: Estimate of direct cost of detecting a true positive using the strongyloides ELISA (sensitivity 93%, specificity 95%) in remote northern Aboriginal community and urban community in Australia. Natural frequencies are used³⁶ with a base population of 10 000 chosen to give whole integers in urban population.

	Remote Aboriginal community	Urban community
Prevalence	20%	0.0001%
Total population	10 000	10 000
True cases of strongyloidiasis	2000	1
True positives detected by ELISA	1860	1 (0.93)
False positives detected by ELISA	400	500
Direct cost of managing positive ELISA cases (from Table 2)	\$734 500	\$162 786
Direct cost of managing negative ELISA cases (from Table 2)	\$359 910	\$441 709
Total cost per 10 000 people	\$1 094 410	\$604 495
Cost per true positive case detected	\$588	\$649 995

Costs in AU\$.

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