Control of *Schistosoma haematobium* morbidity on Pemba Island: validity and efficiency of indirect screening tests

N.J.S. Lwambo,[1] L. Savioli,[2] U.M. Kisumku,[3] K.S. Alawi,[3] & D.A.P. Bundy[4]

Four indirect screening methods for the detection of Schistosoma haematobium *morbidity are compared (history of haematuria, visual haematuria, and microhaematuria at the 1+ and 2+ positivity limit by reagent strips) in terms of their diagnostic performance under conditions of progressive decrease in prevalence of infection, intensity and risk of morbidity as a result of repeated schistosomiasis control programmes on Pemba Island, United Republic of Tanzania. The results show that the sensitivity of a history of haematuria was higher (71%) in children but lower in adults (40%), similar to the findings for visual haematuria in children (60%) and adults (40%) at baseline. However, visual haematuria had a higher specificity, positive predictive value, and efficiency than a history of haematuria in both children and adults. Microhaematuria at the 1+ positivity limit (by reagent strips) had the highest sensitivity of all the methods investigated, but the lowest specificity, positive predictive value, and efficiency. Quantitatively, the indirect methods tended to increase in specificity, negative predictive value, and efficiency during the course of the intervention programme. In contrast, positive predictive value tended to decrease, while the sensitivity remained fairly stable. Overall, these findings suggest that a history of haematuria and/or visual haematuria are appropriate methods for preliminary screening of communities to identify those at risk of morbidity. Thereafter, microhaematuria (1+ positivity limit) may be the more appropriate method for targeting intervention at the individual level.*

Introduction

The validity and efficiency of different measures of haematuria in detecting individuals with *Schistosoma haematobium* infection have been compared by Lwambo (*1*). Microhaematuria elicited by reagent strips at the 1+ positivity limit showed the best diagnostic performance in detecting *S. haematobium* infection in both children and adults throughout the intervention phase of the schistosomiasis control programme on Pemba Island, United Republic of Tanzania.

In this article, we report the validity and efficiency of such reagent strips to detect haematuria in individuals at risk of *S. haematobium* morbidity. Schistosomiasis haematobia morbidity has been reviewed by Chen & Mott (*2*), Hatz et al. (*3*) and Lwambo (*1*). Egg excretion intensity and haematuria correlate positively with morbidity due to *S. haematobium* infection at the individual level.

In 1985 WHO set a cut-off count of ≥50 eggs per 10ml of urine as the threshold for risk of *S. haematobium* morbidity (*4*). Lwambo showed that on Pemba Island the prevalence of ≥50 eggs per 10ml urine is linearly related to, and positively correlated with, the prevalence of visual haematuria and of microhaematuria at the 2+ positivity limit among school-age children (*1*). However, the prevalence of such heavy infection and of visual haematuria are nonlinearly related to the prevalence of infection. The prevalence of visual haematuria may therefore approximate to that of heavy morbidity in the community. Nevertheless, the diagnostic performance of these haematuria techniques in detecting individuals with ≥50 eggs per 10ml urine (at risk of morbidity) has not been adequately studied.

In this article we report the results of a study to determine the validity and efficiency of different measures of haematuria to detect individuals at risk of *S. haematobium* morbidity and the effect of repeated selective population chemotherapy on the validity and efficiency of these methods using data

[1] Wellcome Trust Research Centre for Parasitic Infections, Imperial College of Science, Technology and Medicine, Prince Consort Road, London, England. Present address: National Institute for Medical Research, Mwanza Research Centre, Mwanza, United Republic of Tanzania.

[2] Division of Control of Tropical Diseases, Schistosomiasis and Intestinal Parasites unit, World Health Organization, 1211 Geneva 27, Switzerland. Requests for reprints should be sent to Dr. Savioli at this address.

[3] Ministry of Health, Zanzibar, United Republic of Tanzania.

[4] WHO Collaborating Centre for the Epidemiology of Intestinal Parasites, Wellcome Trust Centre for the Epidemiology of Infectious Diseases, University of Oxford, Oxford, England.

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Table 1: **Collation of data used for each of the indirect screening methods**[a]

Test status	True disease status (filtration results) +ve[b]	−ve[b]	Total[b]
+ve	*a*	*b*	*a* + *b*
−ve	*c*	*d*	*c* + *d*
Total	*a* + *c*	*b* + *d*	

[a] History of haematuria, microhaematuria 1+ and 2+, and visual haematuria.
[b] *a* = No. of individuals whose screening test is positive and the individual is at risk of disease (i.e. those who excrete ≥50 eggs per 10 ml of urine) (true positives); *b* = No. of individuals whose screening tests is positive but are not at risk of disease (i.e. those who excrete <50 eggs per 10 ml urine) (false positives); *c* = No. of individuals whose screening test is negative but are at risk of disease (false negatives); and *d* = No. of individuals whose screening test is negative but are not at risk of disease (i.e. those who excrete <50 eggs per 10 ml urine) (true negatives).

from the first three evaluation surveys in the Pemba Island schistosomiasis control programme (*5*, *6*).

Methods

The study area and data collection techniques have been described by Savioli et al. (*5*, *6*), while the methods for determining the validity and efficiency of screening techniques have been described by Lwambo (*1*). A case at risk of *S. haematobium* morbidity is defined as any individual excreting ≥50 eggs per 10 ml of urine. The validity and efficiency of haematuria as an indirect screening method for *S. haematobium* morbidity were evaluated against a single urine filtration technique as the "gold standard".

Data for all schools and villages for each evaluation study were pooled in a single measure. For each of the indirect screening methods (history of haematuria, microhaematuria 1+ and 2+, visual haematuria) data were collated as shown in Table 1.

For each indirect screening method in all the evaluation studies, the validity and efficiency were determined as described by Lwambo (*1*).

Results

Validity and efficiency of indirect screening methods

The baseline (evaluation 1) validity and efficiency of the four different measures of haematuria as indirect screening methods for *S. haematobium* morbidity are shown in Table 2.

Microhaematuria at the 1+ positivity limit had the greatest sensitivity, while visual haematuria had the highest specificity and the highest overall diagnostic performance (i.e., efficiency). Visual haematuria also had the highest positive predictive value. These trends were also observed in the subsequent evaluations.

Effect of repeated selective population chemotherapy on the validity and efficiency of indirect screening methods

Visual haematuria. The effect of repeated selective population chemotherapy on the validity and efficiency of visual haematuria as an indirect screening test for *S. haematobium* morbidity in school-age children is shown in Table 3. The sensitivity of visual haematuria declined significantly (χ^2 test = 75.80, $P < 0.0001$) between the first (1986) and third (1987–88) evaluations, perhaps reflecting the decreasing prevalence of heavy infection arising from repeated treatment of all infected subjects.

The specificity (χ^2 test = 1002.54; $P < 0.0001$) and efficiency (χ^2 test = 1444.07; $P < 0.0001$) of this screening method increased significantly. However, the positive predictive value declined with decreasing prevalence of heavy infection.

Table 2: **Validity and efficiency of indirect screening methods for detecting *Schistosoma haematobium* morbidity in children aged 5–19 years on Pemba Island during the evaluation study**[a]

Indirect screening method	Sensitivity (%)	Specificity (%)	Predictive value (%): Positive	Predictive value (%): Negative	Efficiency (%)
History of haematuria	70.5	68.0	46.4	85.5	68.7
Visual haematuria	59.9	88.3	66.9	84.9	80.3
Microhaematuria, 1+	98.0	51.3	44.2	98.5	64.5
Microhaematuria, 2+	78.9	81.7	62.9	90.8	80.9

[a] The prevalence of heavy infection was 27.9%.

Table 3: **Effects of repeated population chemotherapy on the validity and efficiency of visual haematuria as a screening method for *Schistosoma haematobium* morbidity in school-age children on Pemba Island during the intervention phase of the schistosomiasis control programme**

Evaluation study, year	Sensitivity (%)	Specificity (%)	Predictive value (%): Positive	Predictive value (%): Negative	Efficiency (%)
1, 1986	40.0	91.7	28.0	95.0	87.8
2, 1986–87	21.7	99.4	45.5	98.2	97.6
3, 1987–88	35.9	99.6	66.7	98.5	98.1

Microhaematuria at the 1+ positivity limit. The effect of repeated selective population chemotherapy on the validity and efficiency of microhaematuria (1+) as an indirect screening test for *S. haematobium* morbidity in school-age children is shown in Table 4.

The sensitivity of microhaematuria (1+) in detecting individuals with heavy *S. haematobium* infections in school-age children remained above 90% throughout the intervention, despite repeated selective population chemotherapy. The difference in sensitivity between the first and third evaluation studies was not significant (χ^2 test = 0.585; $P = 0.4443$) but the specificity (χ^2 test = 1354.06; $P < 0.0001$) and the efficiency (χ^2 test = 638.26; $P < 0.0001$) of this screening method increased significantly.

Microhaematuria at the 2+ positivity limit. Table 4 also shows the effect of repeated selective population chemotherapy on the validity and efficiency of microhaematuria (2+) as an indirect screening test for *S. haematobium* morbidity in school-age children.

The sensitivity of microhaematuria (2+) remained between 68% and 85% throughout the intervention phase, which is less than the lowest sensitivity for microhaematuria (1+). The difference in the sensitivity of microhaematuria (2+) between the first and third evaluation studies was not significant (χ^2 test = 4.60; $P = 0.0320$). The specificity of microhaematuria (2+), however, increased significantly (χ^2 test = 346.41; $P < 0.0001$) as did the diagnostic efficiency of this screening method (χ^2 test = 434.36; $P < 0.0001$). The positive predictive value declined.

Discussion

The schistosomiasis control programme on Pemba Island is unique in the sense that it was the first to employ indirect morbidity on a large scale as a control programme indicator and to undertake annual validation of indirect screening methods throughout its execution.

The merits and disadvantages of using either a disease-specific (*6*) or a community diseases perception interview approach (*7*) have been evaluated in terms of their ability to identify infected individuals. We used the disease-specific interview/questionnaire method in the first evaluation study of the present investigation, which tested for a simple anamnestic recall, not as an indirect indicator of schistosome infection but as a screening method for

Table 4: **Effects of repeated population chemotherapy on the validity and efficiency of microhaematuria (1+) and microhaematuria (2+) as screening methods for *Schistosoma haematobium* morbidity in school-age children on Pemba Island during the intervention phase of the schistosomiasis control**

Evaluation study, year	Sensitivity (%)	Specificity (%)	Predictive value (%): Positive	Predictive value (%): Negative	Efficiency (%)
Microhaematuria (1+)					
1, 1986	98.0	51.3	44.2	98.5	64.5
2, 1986–87	92.3	71.3	24.1	98.9	73.2
3, 1987–88	97.3	82.0	12.0	99.9	82.4
Microhaematuria (2+)					
1, 1986	78.9	81.7	62.9	90.8	80.9
2, 1986–87	67.8	90.3	40.8	96.6	88.2
3, 1987–88	84.7	92.3	21.8	99.6	92.1

S. haematobium morbidity. The sensitivity of a history of haematuria was high in children (71%) but low in adults (40%). Furthermore, the sensitivity of this method was lower than that for microhaematuria at the 1+ and 2+ positivity limits for both children and adults, but was higher than, and similar to, visual haematuria. Specificity for a history of haematuria in both children and adults was higher than for microhaematuria at the 1+ limit, but lower than for the other methods. This screening method had a low positive predictive value for both children and adults and a low efficiency, although it was higher than for microhaematuria 1+.

The low sensitivity of a history of haematuria may make it inadequate as a practical screening method for detecting individuals at risk of *S. haematobium* morbidity (i.e. ≥50 eggs per 10 ml of urine) or for detecting infected individuals (*1*). These findings are in close agreement with those reported by Lengeler (*7*). However, the rapidity with which questionnaires can be administered over an entire endemic area (*7*), coupled with high specificity, makes our method suitable as a preliminary technique for identifying and subsequently excluding areas of low prevalence of *S. haematobium* morbidity during the planning phase of a schistosomiasis control programme. Lengeler et al. have used a history of haematuria/schistosomiasis in schoolchildren in a two-step survey of urinary schistosomiasis in the south of the United Republic of Tanzania to exclude areas that had a low risk of morbidity (*8*).

Visual haematuria, as an indirect screening method for *S. haematobium* morbidity, was the least sensitive of all the four methods tested in children during the first evaluation study (see Table 2). Its specificity, however, was the highest for both children and adults (*1*). Furthermore, visual haematuria had the highest positive predictive value in both children and adults, and its efficiency was also high. Nevertheless, its low sensitivity may make it inappropriate for identifying individuals for selective population chemotherapy. Its high specificity in both children and adults, however, qualifies it as being suitable for use in preliminary surveys to identify areas of low prevalence of *S. haematobium* morbidity. Thus, visual haematuria and a history of haematuria are both suitable for preliminary screening, but the latter method has been favoured because it is easier to use (*9*).

Reagent strips are capable of detecting minute amounts of blood in urine, as low as only 5 erythrocytes per μl (0.015 mg of soluble haemoglobin per 100 ml of urine (*10*)). The source of haematuria, especially in children, is mainly lesions in the urinary bladder caused by *S. haematobium* infection (*10*), with the level of haematuria possibly being proportionate to the severity of morbidity. On Pemba Island, reagent strips were used semiquantitatively to identify individuals for selective population chemotherapy. Microhaematuria at the 1+ positivity limit had the highest values of both sensitivity and negative predictive value in both children and adults, but the lowest efficiency. This method had the lowest specificity and one of the lowest positive predictive values of all the screening tests (Table 2 and Table 4). Restricting the microhaematuria positivity limit to 2+ reduced the sensitivity but improved the specificity, positive predictive value and efficiency in both children and adults (see Table 2 and Table 4). These techniques may therefore be the most effective for identifying individuals at risk of morbidity, but at the same time identify a large proportion of false positives.

The tests of the validity and efficiency of the indirect screening methods examined in this article are based on the efficiency of the single urine filtration test (which serves as the gold standard) to classify correctly individuals with heavy schistosome infections. Lengeler (*7*) and Savioli et al. (*11*) have shown that egg counts are highly variable on a day-to-day basis, such that a single urine filtration test may occasionally diagnose as negative a heavily infected individual (i.e. with ≥50 eggs per 10 ml urine). This high day-to-day variation in *S. haematobium* egg counts led Hatz et al. to question the appropriateness of using egg count limits based on single filtration results for indirect morbidity grading (*12*). However, the day-to-day variation in haematuria had the lowest coefficient of variation compared with other indirect morbidity indicators, including egg counts (*9*, *12*). King et al. showed that haematuria, with morbidity confirmed by ultrasound, can be detected even among individuals who are apparently parasitologically negative (*13*). This finding might account for the discrepancy between egg count categories determined by single urine filtration, on the one hand, and positive/negative tests for visual haematuria and/or history of haematuria, on the other, and hence, the apparently low sensitivities of the two methods for detecting morbidity. This conclusion is further strengthened by the findings of Savioli et al. (*11*), who showed that a higher proportion of individuals with ≥50 eggs per 10 ml of urine could be detected using a single reagent strip examination for microhaematuria than by a single urine filtration test. Future evaluations of the validity and efficiency of indirect morbidity indicators of *S. haematobium* infection should therefore be based on morbidity confirmed by ultrasonic imaging of uropathy or, at least, on the results of more than one urine sample filtration.

Microhaematuria at the 1+ positivity limit is the screening method with the highest sensitivity (79–91%) for detecting individuals with *S. haematobium* infection (*1*). This method is the most appropriate for identifying infected individuals for selective population chemotherapy. Similarly, the present study shows that microhaematuria at this limit has the highest sensitivity (91–100%) in both children and adults for identifying individuals with heavy infection (≥50 eggs per 10 ml urine), and who are at a presumed risk of morbidity from schistosome infection. Thus, reagent strip testing may be the haematuria-based method of choice for identifying individuals for treatment.

The present findings also provide insights into temporal changes in the validity and efficiency of haematuria during the course of a successful control programme. As shown by Lwambo (*1*), selective population chemotherapy on Pemba Island reduced the prevalence of heavy infection from 28% at baseline to 9% a year later (evaluation 2). However, the qualitative pattern of diagnostic performance for all the screening methods remained unchanged (Table 3 and Table 4), with microhaematuria at the 1+ limit having the highest sensitivity and visual haematuria having the highest specificity, positive predictive value, and efficiency.

A total of 2 years after the baseline study (evaluation 3), the prevalence of heavy infection had reduced further to 2.4%. However, the qualitative pattern of diagnostic performance of all the screening methods remained as in the two previous evaluation studies (Table 3 and Table 4). Microhaematuria at the 1+ limit again had the highest sensitivity.

The quantitative effect of the progressive decrease of prevalence of heavy infection, as a result of repeated selective population chemotherapy, was examined by assessing the diagnostic performance of each screening method for each evaluation study. Visual haematuria (Table 2), microhaematuria at the 1+ level (Table 4), and microhaematuria at the 2+ level (Table 4) all had a general tendency to increase in specificity, negative predictive value, and efficiency during the course of the intervention programme. In contrast, positive predictive value tended to decrease, while the sensitivity remained fairly stable and showed no significant change during the course of the control programme.

One potential consequence of these patterns is that the decrease in the positive predictive value could reduce the cost effectiveness of a programme, since the presence of an increasingly lower yield of true positives may result in the treatment of a progressively larger number of false positives. On the other hand, it is encouraging that the sensitivity of the microhaematuria (1+) test in detecting morbidity was unchanged or even marginally increased during the control programme. This implies that the screening method remains consistently appropriate at all stages of the control programme, particularly since the major objective of interventions is to reduce both morbidity and the risk of morbidity.

Overall, the findings we have reported here suggest that a history of haematuria or of visual haematuria is an appropriate method for preliminary screening of communities to identify those at low risk of morbidity. Thereafter, microhaematuria (1+) may be the more appropriate method for targeting intervention at the individual level. These conclusions are based on the diagnostic performance and practicality of the tests and may change when cost is taken into account.

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Résumé

Lutte contre la morbidité due à *Schistosoma haematobium* dans l'île de Pemba: validité et efficience des tests de dépistage indirects

La présente étude compare la validité et l'efficience diagnostiques de quatre méthodes indirectes de dépistage de la morbidité due à *Schistosoma haematobium* (antécédents d'hématurie, hématurie macroscopique, et microhématurie aux seuils de positivité 1+ et 2+, déterminée au moyen de bandelettes réactives) dans des conditions de diminution progressive de la prévalence, de l'intensité de l'infection et du risque de morbidité, à la suite de la réalisation de programmes répétés du lutte contre la schistosomiase dans l'île de Pemba. Les résultats montrent que la sensibilité des antécédents d'hématurie est plus élevée chez l'enfant (71%) et plus faible chez l'adulte (40%), et qu'elle est similaire à celle de l'hématurie macroscopique lors de l'examen initial (60% chez l'enfant et 40% chez l'adulte). Ce dernier indicateur est toutefois meilleur que les antécédents d'hématurie, chez l'enfant comme chez l'adulte, en ce qui concerne la

spécificité, la valeur prédictive positive et l'efficience. La microhématurie au seuil de positivité de 1+ (mesurée au moyen de bandelettes réactives) est, parmi les méthodes étudiées, celle qui possède la meilleure sensibilité, mais la plus faible spécificité, la plus faible valeur prédictive positive et la plus faible efficience. Sur le plan quantitatif, la spécificité, la valeur prédictive négative et l'efficience des méthodes indirectes tendent à s'améliorer au cours du programme d'intervention. En revanche, leur valeur prédictive positive tend à diminuer, tandis que leur sensibilité reste relativement stable. Dans l'ensemble, ces observations indiquent que les antécédents d'hématurie et/ou l'hématurie macroscopique sont des méthodes appropriées pour le dépistage préliminaire des sujets à faible risque de morbidité au sein d'une communauté. La microhématurie (seuil de positivité 1+) peut être plus adaptée pour le ciblage ultérieur des interventions au niveau individuel.

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