Transactions of the Royal Society of Tropical Medicine and Hygiene (2009) xxx, xxx–xxx

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevierhealth.com/journals/trst

SOCIETY MEETING PAPER

Improving control of African schistosomiasis: towards effective use of rapid diagnostic tests within an appropriate disease surveillance model☆

J. Russell Stothard*

Wolfson Wellcome Biomedical Laboratories, Department of Zoology, Natural History Museum, Cromwell Road, London SW7 5BD, UK

Received 25 September 2008; received in revised form 15 December 2008; accepted 16 December 2008

KEYWORDS
Schistosoma;
Circulating cathodic antigen;
Diagnostic tests;
Lateral flow dipsticks;
Oligochromatography;
LAMP

Summary Contemporary control of schistosomiasis is typically reliant upon large-scale administration of praziquantel (PZQ) to school age children. Whilst PZQ treatment of each child is inexpensive, the direct and indirect costs of preventive chemotherapy for the whole school population are more substantive and, at the national level where many schools are targeted, maximising cost effectiveness and the health impact are essential requirements for ensuring longer-term sustainability (i.e. >5 years). To this end, the WHO has issued a set of treatment guidelines, inclusive of re-treatment schedules, such that, where possible, treatment decisions by school are based upon local disease prevalence as determined by parasitological and/or questionnaire methods. As each diagnostic method has known shortcomings, presumptive treatment of at-risk schools may initially be preferred, especially if the existing infrastructure for disease surveillance is poor. It is against this background of school-based preventive chemotherapy that a rapid diagnostic test (RDT) for schistosomiasis is most urgently needed, not only to improve initial disease surveillance but also to focus drug delivery better through time. In this paper, the development, evaluation and application of selected diagnostic tests are reviewed to identify barriers that impede progress, foremost of which is that a new disease surveillance and evaluation model is required where the in-country price of each RDT ideally needs to be less than US$1 to be cost effective both in the short- and long-term perspective.

1. Introduction

Throughout much of sub-Saharan Africa there is a plethora of freshwater habitats, of man-made or natural origin, that actually or potentially harbour aquatic snails of the genera *Bulinus* and/or *Biomphalaria*. The genera are each of medical importance as intermediate hosts of parasitic blood flukes of the *Schistosoma haematobium* and *S. mansoni*

☆ Based on a presentation to a Joint Meeting of the Royal Society of Tropical Medicine & Hygiene and Royal Geographical Society Expedition Advisory Centre (Medical Cell) on 22 May 2008, entitled 'Field epidemiology in sub-Saharan Africa: will rapid diagnosis tests (RDTs) ever replace microscopy?'.

* Tel.: +44 207 942 5490; fax: +44 207 942 5518.
E-mail address: r.stothard@nhm.ac.uk

0035-9203/$ – see front matter © 2009 Published by Elsevier Ltd on behalf of Royal Society of Tropical Medicine and Hygiene.
doi:10.1016/j.trstmh.2008.12.012

Please cite this article in press as: Stothard JR. Improving control of African schistosomiasis: towards effective use of rapid diagnostic tests within an appropriate disease surveillance model. *Trans R Soc Trop Med Hyg* (2009), doi:10.1016/j.trstmh.2008.12.012

groups, respectively, although not all snail species play a role in disease transmission.[1] Schistosome infections in man give rise to schistosomiasis, which is conveniently divided into two forms, urinary or intestinal, that typically represent monospecific infection with *S. haematobium* in the former and *S. mansoni* in the latter.[2] Dual infections (so-called co-infections, where both schistosome species parasitise the same individual) occur but, surprisingly perhaps, this aspect of the present global disease burden is still only poorly known, in contrast to monospecific disease burdens.[3,4] Two other *S. haematobium* group species, *S. intercalatum* and *S. guineensis*, are able to infect man but are very geographically restricted and, when taken together with infections occasioned by other schistosomes of veterinary significance, are of medial interest alone.[5,6]

Like other helminths, schistosomes themselves do not directly reproduce within the human host but rather the female worm produces copious amounts of eggs, which are either voided in the host's excreta or become trapped within tissues. For *S. haematobium* infections, the passage of eggs perforating the bladder wall gives rise to the classic sign of infection, macrohaematuria (visible blood in the urine). Whilst eggs of *S. mansoni* perforate the bowel wall, the associated release of blood is visible only in exceptional cases, as faecal material usually occludes. Detection of microhaematuria (cryptic blood in the urine) with reagent strips is a well known proxy marker of urinary schistosomiasis,[7] whilst faecal occult blood tests generally lack the sensitivity required for proxy diagnosis of intestinal schistosomiasis.[8] More usually it is the detection of schistosome eggs, which are of characteristic size and shape for each species, either in stool or urine that provides unequivocal evidence of infection. A precise diagnosis, however, may be hampered as individuals may, or may not, continuously shed eggs throughout the period of their infection. Indeed, sporadic egg excretion, especially when numbers of infecting worms are low, typically confounds the sensitivity of parasitological methods of diagnosis, but it is the gradual accumulation of trapped eggs over a period of several months or years that induces host morbidity.[4]

2. Geography of schistosomiasis

In sub-Saharan Africa, schistosomiasis has a complicated distribution owing to the complex interplay of biotic and abiotic factors, but it is a significant blight upon the populace especially in places where people, snails and parasites are brought together on a regular basis.[4] In such locations, schistosomiasis can be almost universal and contributes to the daily entrapment of those often already in poverty and marginalisation. Disentangling macroepidemiological and microepidemiological determinants of the disease is particularly challenging, as an intriguing feature of schistosomiasis is its geographical overdispersion or tight focality.[9] Thus far, predictive epidemiological models have struggled to encapsulate this feature precisely but can, at least, identify environments unfavourable for transmission and therefore exclude areas quite confidently, e.g. landscapes that are too cold or dry.[10] School-based questionnaire methods reporting the occurrence of red urine can also be useful for targeting, or eliminating, areas for treatment where urinary schistosomiasis is likely endemic.[11]

At the local level, however, disease endemicity is often the product of 'place-specific' factors both in time and space, e.g. the seemingly chaotic occurrence and fluctuations of infected freshwater snails through seasons.[12] It has previously been stated that no two disease transmission foci are the same,[2] and the applied significance of this heterogeneity, unfortunately, is that precise mapping of the endemicity of schistosomiasis at the local level can be difficult, short of exhaustive investigative sampling within the human populace (see Figure 1). Moreover, even with such precise geographical information at hand it is still necessary to understand both physical and molluscan aspects of transmission for, as people travel, the place at which infections were encountered does not always correlate, or best predict, the actual place where infections were initially or subsequently acquired. It is this peculiarity where the distribution of the snail, and not man, actually restricts, in time and space, the active disease transmission zone to people.[12] Whilst not all populations of *Bulinus* or *Biomphalaria* have the capacity to transmit schistosomes, resulting from a complex evolutionary interplay between snail and parasite,[1] within a context of disease control, efforts for more precise mapping of permissive intermediate hosts is not always given sufficient support.

Whilst a detailed knowledge of this aspect of snail-related transmission is very much needed, this information is notoriously difficult to acquire at each of the key local environments short of performing extensive malacological surveys and schistosome–snail infection experiments.[1] Doing the above is all the more difficult given that precise identification and classification of natural populations of *Bulinus* and *Biomphalaria* can be problematic, even with molecular methods. So like the progress needed to abate disease transmission with improvements in sanitation and water hygiene (which are still vitally needed), substantial progress towards an enduring snail transmission map useful for control of schistosomiasis is both arduous and slow.[12] However, this progress sharply contrasts with the rapid impact that chemotherapy with the orally administered anthelminthic praziquantel (PZQ) can provide for morbidity reduction in the human populace. Indeed, this is especially pervasive as the tools and drug delivery systems are essentially to-hand and infected communities, e.g. school age children, can be reached relatively easily with school-based infrastructures utilising universal primary education (UPE) initiatives, e.g. trained school teachers distribute medications. Moreover, after treatment, children usually feel an immediate improvement in their health.

3. A changing face of schistosomiasis control

Use of chemotherapy in the control of schistosomiasis was advocated long ago,[2] but a driving force in its present widespread application has been the significant reduction in price of PZQ tablets following from off-patent production of the drug by generic manufacturers. In addition, as part of the World Health Assembly 54.19 resolution, deworming is firmly on the international health agenda and increasing

Please cite this article in press as: Stothard JR. Improving control of African schistosomiasis: towards effective use of rapid diagnostic tests within an appropriate disease surveillance model. *Trans R Soc Trop Med Hyg* (2009), doi:10.1016/j.trstmh.2008.12.012

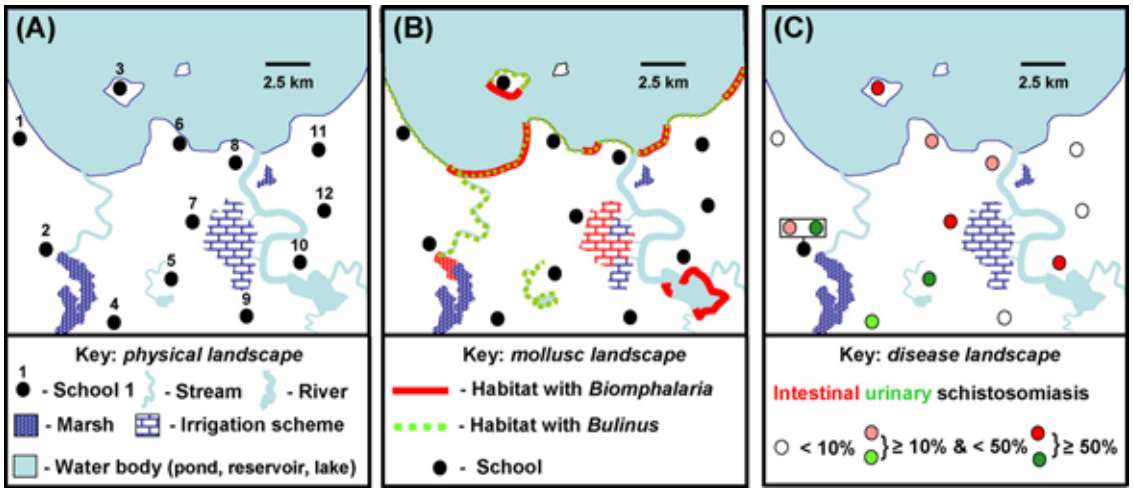

Figure 1 Schematic maps representing the complex distribution of schistosomiasis by depiction of three primary landscape features (physical, molluscan and disease), which collectively combine to produce the focal, or patchy, occurrence of schistosomiasis. The area depicted is adjacent to a major lake and typical of a subcountry level; in Lake Victoria, for example, where the shoreline is some 3400 km long there would be up to 200 similar epidemiological patchworks likely inclusive of some 2400 schools. Whilst the disease landscape (C) can be thought of as an end product of both the physical (A) and mollusc (B) factors, it directly interacts with the physical and molluscan in determining ways, for example, the activities of infected humans influence the spread of infection back to aquatic snails and/or the behaviour of the human population itself sometimes creates new physical landscape features, e.g. irrigation schemes, or coalesces around existing features to intensify transmission, e.g. harvesting fish. (A) A total of 12 schools is shown with associated aquatic features set within a 10 km swath from the shoreline of a large lake. (B) The depicted colonisation patterns of intermediate snail hosts in the aquatic habitats is based upon the known malacology of Lake Victoria.[1] Note that the lacustrine *Bulinus* (e.g. *Bu. transversalis* and *Bu. trigonis*) do not transmit urinary schistosomiasis whereas *Bulinus* found in riverine and pond environments do (e.g. *B. globosus*). The colonisation patterns of *Biomphalaria* differ, with *Bi. choanomphala* being found in the lake whilst *Bi. pfeifferi* and/or *Bi. sudanica* is restricted to marshes and irrigation schemes. (C) Prevalence map of urinary and intestinal schistosomiasis at each of the 12 schools. Note that School 2 is exceptional in that dual infections of *Schistosoma haematobium* and *S. mansoni* co-exist. These maps are based upon typical data from Uganda.[13,14]

access to anthelminthics, particularly in school age children, is a key target promoted by the WHO, e.g. by 2010 at least 75% of school age children at risk of morbidity should have regular access to chemotherapy. More recently, the delivery of PZQ is now set within a new integrated strategy for preventive chemotherapy for the control of human helminthiasis that aims, as a rapid impact package, to bring future returns in averting host morbidity that would otherwise develop in the absence of treatment. The rationale and ethical arguments for adopting this strategy are particularly convincing given all alternatives.[15]

Whilst many of the anthelminthic drugs used in integrated preventive chemotherapy are donated, or are very low cost, generic production of PZQ still has an associated cost that typically results in in-country prices of PZQ tablets between US$0.04 and US$0.08 per 600 mg tablet, or higher, subject to local taxes/delivery.[16] As part of the Schistosomiasis Control Initiative (SCI), further negotiations to procure PZQ from a variety of competitor generic manufacturers are set hopefully to decline this price further still. As the correct dose (40 mg/kg) of PZQ is calculated by patient weight, fractions or multiples of PZQ tablets are therefore needed.[16] In the context of national control programmes and to speed administration of treatment, weighing scales have been replaced by a PZQ treatment or dosing pole that, for school age children, spans the corresponding doses of one to three tablets (in half-tablet divisions) across a child's height range from 94 cm to 160 cm. In Uganda, for example, field use has estimated that for a typical primary school an allocation of 2.7 tablets per child gives sufficient surplus to ensure that no drug shortages are encountered, especially as non-enrolled children of school age are also eligible for treatment on the day of treatment, and that the actual average treatment per child dosing is slightly lower, approximately 2.2 tablets per child.[17,18]

Thus, at a cost of less than US$0.20 (for the absolute price of tablets) for each PZQ-treated child,[16] the basic economics of chemotherapy for school children are particularly attractive and have become a fundamental cornerstone of international health advocacy that few could begrudge. Nevertheless, given the geographical distribution of schistosomiasis, the large school aged populace and extensive country-wide landscape to be covered, this simple health advocacy ascertain is not particularly convincing, especially when the following two questions are considered: where are the schools with schistosomiasis, and which schools need regular re-treatment?

Answers to these questions can be found, in part, by the WHO treatment guidelines issued in 2002; for example, in schools where the parasitological prevalence of schistosomiasis is in excess of 50% (high prevalence schools) annual mass treatment of school age children is recommended, whilst in schools where the prevalence is $\geq$10% but <50% (medium prevalence schools) mass treatment once every 2 years is advised, and in schools where the prevalence is <10% (low prevalence) mass treatment of children twice

Please cite this article in press as: Stothard JR. Improving control of African schistosomiasis: towards effective use of rapid diagnostic tests within an appropriate disease surveillance model. *Trans R Soc Trop Med Hyg* (2009), doi:10.1016/j.trstmh.2008.12.012

during their primary schooling (at entry and on leaving) is directed.[19,20] Following these guidelines ensures that a considered balance between cost effectiveness and health impact is struck; in high prevalence schools the majority of treatments are administered to children who are likely infected, whilst in low prevalence schools treatments are more sparsely allocated through time to ensure that wastage of drugs is minimised yet those infected children, a minority, receive some form of medication. A prerequisite of implementation of these guidelines is, of course, knowledge of the prevalence of disease by school, but in the majority of cases this is not known or the information is decades out of date.[3]

Unfortunately, as parasitological surveys are not cheap,[13,19] collecting this epidemiological information at such a fine scale school by school is expensive, thus blanket mass treatment of putative at-risk schools can be a preferred option. From an ethical perspective, promotion of treatment is more justifiable than withholding treatment unless there is substantial evidence to the contrary. Evidence to the contrary usually takes the form of cost effectiveness; it makes no economic sense to mass treat schools on a regular basis where schistosomiasis is actually absent or scaling-up factors become unmanageable.[21] An example of this trade-off is illustrated in Table 1, which considers four treatment options within a 5-year intervention programme given a typical epidemiological landscape in sub-Saharan Africa, as previously depicted in Figure 1. These data are developed in simplified format from Brooker et al.[13] and Stothard et al.[14]

4. School-based control: is there any room for rapid diagnostic tests?

Whilst there are a variety of arguments in favour of the use of rapid diagnostic tests (RDT), e.g. it allows evidence-based decision-making, their absolute necessity could be immediately justified if their application in improving the efficiency of correctly allocating PZQ treatments could be off-set neutral, or even better off-set positive, in favour of the costs to be saved through drug wastage, as illustrated in Figure 2. To explore this scenario further, the costs associated within Table 1 are taken further in Table 2 where three in-country RDT pricing scenarios, of US$1, 3 and 5 per test, are explored. In this model of field surveillance, a vehicle with driver carrying two health technicians is envisaged with site visits to each of the 12 schools as depicted in Figure 1, taking a total of 5 days. To obtain a reasonable estimate of the prevalence of disease by school, it has been previously shown by computer simulations and field-based evaluations that testing a sample of 15 children per school could confidently gather evidence sufficient for the WHO prevalence-based treatment thresholds.[13] Thus, testing in this manner, the total expenditure ranges from an estimated US$1034.0 to US$1850.0 such that the percentage cost allocated for the RDTs themselves within the field surveillance team increases from 19.7% to 55.1% (Table 2).

Using these values, it is immediately apparent that a RDT priced in-country at US$5 per test, at best, can only

Table 1 Prevalence of schistosomiasis by school at the onset of a 5-year intervention, and direct costs of praziquantel (PZQ) tablets (an assumed average of US$0.075 per treated child) for each of four simple models of drug delivery

School[a]	Schistosomiasis (%)			Cost of PZQ per school (US$)			
	Intestinal	Urinary	Both[b]	BMDA, 1 round[c]	BMDA, 5 rounds[d]	SMDA, 5 rounds[e]	PMDA, 5 rounds[f]
1	6.0	0.0	6.0	75.0	375.0	22.5	75.0
2	37.5	60.0	78.0	’’	’’	292.5	375.0
3	100.0	0.0	100.0	’’	’’	375.0	375.0
4	1.0	15.0	15.5	’’	’’	58.1	150.0
5	0.0	65.0	65.0	’’	’’	243.8	375.0
6	40.0	0.0	40.0	’’	’’	150.0	150.0
7	95.0	2.0	96.0	’’	’’	360.0	375.0
8	45.0	0.0	45.0	’’	’’	168.8	150.0
9	0.0	0.0	0.0	’’	’’	0.0	75.0
10	75.0	0.0	75.0	’’	’’	281.2	375.0
11	7.0	0.0	7.0	’’	’’	26.3	75.0
12	0.0	0.0	0.0	’’	’’	0.0	75.0
Total	33.9	11.8	44.0	900.0	4500.0	1955.6	2625.0

[a] There were approximately 1000 children in each school.
[b] Total prevalence is not cumulative owing to co-infection.
[c] Blanket (not targeted) treatment with delivery of drugs to all schools only once.
[d] Blanket (not targeted) treatment with delivery of drugs to all schools every year for 5 years.
[e] Selective treatment of positive individuals each year as originally identified at intervention baseline (NOTE: a hypothetical scenario only, as children neither leave nor exit the school during the 5-year cycle).
[f] After an initial blanket mass drug administration in the first year, selective treatment following WHO guidelines according to prevalence by school based upon initial baseline assessment (NOTE: prevalence is determined by a rapid diagnostic test, the costs of which are as estimated in Table 2).

Please cite this article in press as: Stothard JR. Improving control of African schistosomiasis: towards effective use of rapid diagnostic tests within an appropriate disease surveillance model. *Trans R Soc Trop Med Hyg* (2009), doi:10.1016/j.trstmh.2008.12.012

Table 2 Estimated budgets for at-school-site testing for each of the 12 schools. Three rapid diagnostic test (RDT) pricing schemes, with ancillary costs (i.e. the field surveillance team with vehicle), are indicated. Whilst other transport and staffing models are possible (e.g. use of motorbikes), the field team consists of a driver with car accompanied by two health technicians. By inspecting at least four schools each day, a budget of 5 field-days is required allowing for travel to and from the working area

Price per test (US$)	Total cost of RDTs[a]	Ancillary costs for at-school-site testing					Total (% for RDTs)
		Staff[b]	Vehicle[c]	Teachers[d]	Disposables[e]	Contingency[f]	
1	204.0	475.0	250.0	60.0	20.0	25.0	1034.0 (19.7)
3	612.0	,,	,,	,,	,,	,,	1442.0 (42.4)
5	1020.0	,,	,,	,,	,,	,,	1850.0 (55.1)

[a] A total of 17 tests per school is needed assuming an invalid test rate of approximately 10%, the cost per test is the final 'in-country' price.
[b] Staff field per day rates: one driver at US$25 and two technicians at US$35.
[c] Car costs at US$50 per day allowing for field and general vehicle up-keep.
[d] Assisting teacher(s) at each school are given a lunch allowance of US$5.
[e] Provision of general items: disposable gloves and plastic-ware.
[f] A contingency allowance to meet costs of any unexpected expenses.

be off-set neutral given its use within a prevalence gathering exercise. Thus, an absolute upper pricing boundary can be firmly set, above which the use of RDTs could not be justified. Pricing at US$1 or US$3 per test is off-set positive, with total savings of US$816.0 and US$408.0, respectively. Given that the example in Figure 1 is but a single patch in the epidemiological quilt of Lake Victoria, for example, if scaled proportionately total savings would be in the region of US$81.6K to US$163.2K. Therefore, in a scenario where the RDT is priced at less than US$3 per test, it would be consistently more cost effective than presumptive treatment of at-risk schools and, for economic reasons alone, could be strongly advocated. Pricing at US$1 per test also opens up another important possibility, that RDTs could be used both in start-point and end-point monitoring if a further US$218 could be re-assigned from the overall budget (i.e. US$43.6K from a total budget for Lake Victoria), thereby off-setting the total costs of conducting the two surveys. If not, then in-country pricing of the RDT at US$0.50 would be required but at this level there is little doubt that RDTs would be consistently justified. Perhaps more importantly, at this pricing their use could lead to an intervention performance indicator, e.g. percentage reduction of disease prevalence by school, as shown in Figure 3. By having such an indicator, both start-point and end-point information could be explicitly defined within the 5-year cycle, which could allow more accurate forecasting of drug requirements over forthcoming decades as well as gathering essential statistics for more informed health advocacy to secure subsequent intervention funds.

(A) Cost of wasted drug = BMDA - PMDA = US$1850

(B) Efficiency (%) of BMDA drug allocation = (BMDA / SMDA *) x 100 = 43%

Efficiency (%) of PMDA drug allocation = (PMDA / SMDA) x 100 = 75%

Figure 2 The budget that could be freed due to better drug targeting could be used to justify implementation of rapid diagnostic tests. (A) From the example shown in Figure 1 and Table 1, the approximate cost of wasted drug is the difference between blanket mass drug administration (BMDA) and prevalence-based mass drug administration (PMDA) following WHO guidelines. (B) Assessment of the efficiency of treatment by BMDA and PMDA set against selected mass drug administration (SMDA). The efficiency of BMDA will always be approximately the same as the aggregated mean prevalence by school of the epidemiological landscape surveyed, i.e. 44% (Table 1). * Note that SMDA is a hypothetical example as to do this would have required logistically unattainable resources and unrealistic financial budgets to determine precisely the infection status of each child.

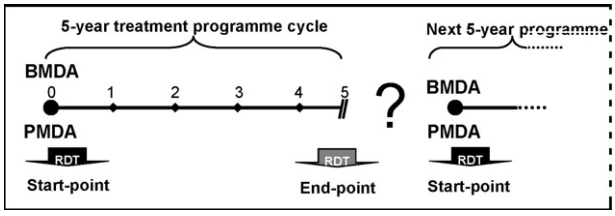

Figure 3 A comparison of the surveillance and evaluation model used in blanket mass drug administration (BMDA) and prevalence-based mass drug administration (PMDA) reveals that PMDA should be favourable for a variety of reasons. First, if rapid diagnostic tests (RDT) priced at US$1.0 per test were incorporated into an initial prevalence mapping exercise by school their immediate use would be off-set positive against the total amount of praziquantel saved by better allocation of treatments. If additional funds were available, or RDTs were priced at US$0.5 per test, then end-point impact mapping of the 5-year programme is also possible. In comparison with BMDA, no such information of impact is gained other than total numbers of treated children through time. If another second round of 5-year funding is envisaged then the initial end-point could be seen as the next start-point (only if a limited amount of time has elapsed, e.g. 1–2 years), otherwise a new start-point assessment is needed. If chemotherapy has had a diminishing effect upon mean aggregated prevalence by school, e.g. is now significantly less than 44%, then the efficiency of BMDA will further decline while the efficiency of PMDA increases.

Please cite this article in press as: Stothard JR. Improving control of African schistosomiasis: towards effective use of rapid diagnostic tests within an appropriate disease surveillance model. *Trans R Soc Trop Med Hyg* (2009), doi:10.1016/j.trstmh.2008.12.012

5. Available rapid diagnostic tests for schistosomiasis

The desirability of a RDT can be encapsulated within the acronym ASSURED (i.e. RDTs should be Affordable, Sensitive, Specific, User-friendly, Rapid and robust, Equipment free and Deliverable to end-users). Presently, RDTs now centralise upon lateral flow immunodiagnostic devices where antigens released from the targeted parasite are detected.[22] Most often, whole blood taken as a fingerprick is used but other bodily fluids, e.g. urine, often contain detectable amounts of parasite antigen. In comparison with other tropical diseases, e.g. malaria and lymphatic filariasis, it is perhaps surprising, given the extensive research into the immunobiology of schistosomiasis, that the choice of commercially available RDTs for this disease is particularly meagre. It should be recognised, however, that there are many implicit difficulties in detecting schistosome infections.[23,24]

For schistosomiasis, attention originally focused upon schistosome antigens present in patient serum,[25] then later urine, which led to a simple-to-use ELISA dipstick specific for schistosome circulating cathodic antigen (CCA) in urine. In reality, CCA is a cocktail of secreted proteins released from the gut of adult worms that share carbohydrate polysaccharide epitopes. Since the schistosome gut is blind-ended, worms typically vomit their digested blood meals daily and these products, together with CCA, enter the host blood vasculature system. Schistosome CCA is then excreted by the kidney into the urine at amounts detectable by antigen capture methods. Further refinements in anti-CCA antibody formulations led to lateral flow urine-CCA dipstick,[26] which became commercially available in 2003 entitled the 'schistosomiasis one step test' produced by the European Veterinary Laboratory (Woerden, The Netherlands; see http://www.evlonline.nl). From a field perspective, collection of urine samples is much easier than stool collection, thus the urine-CCA dipstick facilitates particularly rapid specimen collection for examination at each school.

As CCA antigens are genus cross-specific, the 'schistosomiasis one step test' was not designed to discriminate between urinary and/or intestinal schistosomiasis, which, from a control perspective, has the advantage of capturing, but not identifying, both forms of disease in a single test.[26] While the test had gone to market it was not fully evaluated to US Food and Drug Administration (FDA) standards for use in the disease-endemic setting and was therefore supplied for research purposes only. A variety of *ad hoc* evaluation studies followed and found, unexpectedly, that the dipstick totally failed to detect *S. haematobium* infections[27] or that the sensitivity for urinary schistosomiasis was poor.[28] On the other hand, the diagnostic performance of the dipstick for intestinal schistosomiasis was very good,[27] which has also been corroborated in different epidemiological settings.[29] Another important facet of this RDT is its ability to track the intensity of *S. mansoni* infections, as proportionality between CCA concentration and excreted eggs was strongly correlated.[27] A RDT that can record intensity of infection is particularly useful for assessing a decline in individual host worm burdens as well as identifying locations where transmission is particularly high.

The reported observations on urinary schistosomiasis prompted a subsequent reformulation of this test by the Department of Parasitology, Leiden University Medical Center (Leiden, The Netherlands) and eventual production with a different commercial supplier, namely Rapid Medical Diagnostics (South Africa), but a recent evaluation of the test has still shown that the detection of urinary schistosomiasis, at least on Zanzibar, was poor (J.R. Stothard et al., unpublished data). There are a variety of reasons why the dipstick is not performing, but a potentially serious concern is that subtle differences in the antigenicity of CCA from populations of *S. haematobium* from different regions may be a likely confounder.

6. Present barriers against use of existing rapid diagnostic tests

A formidable barrier in the use of a schistosomiasis RDT is that there is presently no reliable RDT capable of detecting both disease forms simultaneously. This is a serious set back as even if the test was proven to perform well in some locations, it could incorrectly document the prevalence of schistosomiasis, especially co-infections, if the present reformulated urine-CCA dipstick was applied without additional in-country evaluations. Whilst it may be possible to supplement the performance of the test by conjoint use of reagent strips for detection of microhaematuria, this would not be advisable as it would complicate sampling protocols, which should be kept as simple as possible.

Another major hurdle limiting any further use, even within a monoendemic area for intestinal schistosomiasis, is the current cost of each CCA dipstick, presently retailing at between US$2.6 and US$4.6.[27] This pricing is contingent upon numbers requested/packaging requirements and does not cover freighting or local taxes. Careful consideration is therefore needed to determine whether the performance, and more importantly cost-effective application, can be justified. Compossible scenarios in the framework stipulated above would suggest that this pricing is too high for any sustainable future, as presently it would be off-set negative against the possible saving of PZQ. At the same time as fixing in-country prices, the likely total economic revenue to be generated from the RDTs has to be financially attractive for the diagnostic industry otherwise their retail market is barren. Given that most people afflicted with schistosomiasis cannot and could not afford to buy PZQ treatments, the possibility of any private retail within the endemic area is slim. From another perspective, as the SCI has created and fostered a demand for production of PZQ within the pharmaceutical sector, a similar atmosphere is therefore needed for sustained commercial production of RDTs. It can only be hoped that with future large-scale donor funding for control of neglected tropical diseases, e.g. from the United States Agency for International Development (USAID), this aspect is more carefully nurtured otherwise monitoring and surveillance activities, which are necessary to ensure donor funds are wisely spent, will remain incomplete and stunted.

Please cite this article in press as: Stothard JR. Improving control of African schistosomiasis: towards effective use of rapid diagnostic tests within an appropriate disease surveillance model. *Trans R Soc Trop Med Hyg* (2009), doi:10.1016/j.trstmh.2008.12.012

7. Future rapid diagnostic test technologies in the pipeline

In a review such as this it is important to speculate what future technologies could work in synergy or even replace antigen/serological methods. It is certain that any future schistosomiasis-specific RDT will likely depend upon inspection of biomarkers obtained from a patient's urine. Detection of parasite DNA in host urine through PCR is still being explored with quantitative real-time PCR with a variety of fluorescent-labelled reporter probes.[30] Assays that have the capacity to detect either species of schistosome are emerging but adaptation of these methods to the field setting will be particularly challenging. With this intention, lateral flow oligochromatographic techniques are being developed with a goal to downgrade the laboratory equipment into a more 'outdoor' setting.[31] The price of each oligochromatographic dipstick, however, has yet to be set and the necessary time taken to obtain test results remains speculative, neither of which make for appealing or enduring solutions.

As yet, direct detection of parasite DNA with complementary oligonucleotide probes is not possible, thus the initial PCR step cannot be avoided. As an alternative to conventional PCR, loop-mediated isothermal amplification (LAMP) could be particularly attractive, as being pioneered for the diagnosis of trypanosomiasis,[32] given its high sensitivity and, if coupled with visual detection of turbidity within each LAMP reaction, negating the need for an expensive photometer, could be one way forward. None the less, as with all PCR-based methods, care should be taken with possibilities for cross-contamination, which could be a key challenge for quality control if such methods were set in routine practice. In so doing, this could significantly alter the cost effectiveness of PCR approaches if replicate tests were needed on a regular basis to cross-verify initial findings.

8. Concluding remarks

To promote the sustainable future use of RDTs for use in the control of schistosomiasis, a reliable non-invasive test capable of detection, and differentiation, of both forms of the disease is required. The tests also have to be endorsed by the WHO and their use set within an umbrella policy document setting out best practice. In addition to this, a key ingredient for sustainability will be in correctly setting the price per test; when set against the cost of drug wastage, an in-country price of less than US$3 per test could make the RDT immediately affordable. Ideally, if tests were no more than US$0.50 per test then these could play an additional role in both start-point and end-point monitoring of the control programme itself. Gathering such information would promote transparency, which in turn could potentially better secure further donor funds by an explicit demonstration of reducing disease burdens through time. The challenge is now for the commercial sector to bring to market a RDT that fulfils these requirements.

Acknowledgements: The author would like to thank all those with whom he has worked with on schistosomiasis during the last decade. In particular, he would like to thank especially David Rollinson, Vaughan Southgate and the late David Brown of the Natural History Museum, UK, and Alan Fenwick, Imperial College London, UK, all of whom he has had the privilege of learning from. The author is also indebted to friends and colleagues linked with the SCI and DBL in Africa, especially Bertrand and Elisabeth Sellin, Thomas Kristensen, Narcis Kabatereine, Amadou Garba, Louis Albert Tucheume-Tuchente and the late Ali Foum Mgeni. He is grateful for the long-term advice and guidance from several colleagues within the WHO.

Funding: The author's research has received funding from the Wellcome Trust, European Union (EU-CONTRAST) and the Bill & Melinda Gates Foundation.

Conflicts of interest: None declared.

Ethical approval: Not required.

References

1. Brown DS. *Freshwater snails of Africa and their medical importance*. London: Taylor & Francis; 1994.
2. Jordan P, Webbe G. *Human schistosomiasis*. London: William Heinemann Medical Books Ltd.; 1969.
3. Brooker S, Rowlands M, Haller L, Savioli L, Bundy DAP. Towards an atlas of human helminth infection in sub-Saharan Africa: the use of geographical information systems (GIS). *Parasitol Today* 2000;**16**:303–7.
4. Van Der Werf MJ, De Vlas SJ, Brooker S, Looman CWN, Nagelkerke NJD, Habbema JDF, et al. Quantification of clinical morbidity associated with schistosome infection in sub-Saharan Africa. *Acta Trop* 2003;**86**:125–39.
5. Tchinda JP, Tchuente LAT, Fomena A. *Schistosoma intercalatum* and soil transmitted helminthiasis in Eseka town in Cameroon. *Am J Trop Med Hyg* 2005;**73**(6 Suppl):163. Abstract 497.
6. Webster BL, Tchuente LAT, Southgate VR. A single-strand conformation polymorphism (SSCP) approach for investigating genetic interactions of *Schistosoma haematobium* and *Schistosoma guineensis* in Loum, Cameroon. *Parasitol Res* 2007;**100**:739–45.
7. French MD, Rollinson D, Basanez MG, Mgeni AF, Khamis IS, Stothard JR. School-based control of urinary schistosomiasis on Zanzibar, Tanzania: monitoring micro-haematuria with reagent strips as a rapid urological assessment. *J Pediatr Urol* 2007;**3**:364–8.
8. Odogwu SE, Ramamurthy NK, Kabatereine NB, Kazibwe F, Tukahebwa E, Webster JP, et al. *Schistosoma mansoni* in infants (aged < 3 years) along the Ugandan shoreline of Lake Victoria. *Ann Trop Med Parasitol* 2006;**100**:315–26.
9. Brooker S. Spatial epidemiology of human schistosomiasis in Africa: risk models, transmission dynamics and control. *Trans R Soc Trop Med Hyg* 2007;**101**:1–8.
10. Brooker S, Hay SI, Issae W, Hall A, Kihamia CM, Lwambo NJS, et al. Predicting the distribution of urinary schistosomiasis in Tanzania using satellite sensor data. *Trop Med Int Health* 2001;**6**:998–1007.
11. Clements ACA, Brooker S, Nyandindi U, Fenwick A, Blair L. Bayesian spatial analysis of a national urinary schistosomiasis questionnaire to assist geographic targeting of schistosomiasis control in Tanzania, East Africa. *Int J Parasitol* 2008;**38**:401–15.
12. Stothard JR, Mgeni AF, Khamis S, Seto E, Ramsan M, Hubbard SJ, et al. New insights into the transmission biology of urinary schistosomiasis in Zanzibar. *Trans R Soc Trop Med Hyg* 2002;**96**:470–5.

Please cite this article in press as: Stothard JR. Improving control of African schistosomiasis: towards effective use of rapid diagnostic tests within an appropriate disease surveillance model. *Trans R Soc Trop Med Hyg* (2009), doi:10.1016/j.trstmh.2008.12.012

13. Brooker S, Kabatereine NB, Myatt M, Stothard JR, Fenwick A. Rapid assessment of *Schistosoma mansoni*: the validity, applicability and cost-effectiveness of the Lot Quality Assurance Sampling method in Uganda. *Trop Med Int Health* 2005;**10**:647–58.
14. Stothard JR, Kabatereine NB, Tukahebwa EM, Kazibwe F, Mathieson W, Webster JP, et al. Field evaluation of the Meade Readiview handheld microscope for diagnosis of intestinal schistosomiasis in Ugandan school children. *Am J Trop Med Hyg* 2005;**73**:949–55.
15. Hotez PJ, Molyneux DH, Fenwick A, Kumaresan J, Sachs SE, Sachs JD, et al. Control of neglected tropical diseases. *N Engl J Med* 2007;**357**:1018–27.
16. Fenwick A. New initiatives against Africa's worms. *Trans R Soc Trop Med Hyg* 2006;**100**:200–7.
17. Kabatereine NB, Brooker S, Tukahebwa EM, Kazibwe F, Onapa AW. Epidemiology and geography of *Schistosoma mansoni* in Uganda: implications for planning control. *Trop Med Int Health* 2004;**9**:372–80.
18. Kabatereine NB, Tukahebwa E, Kazibwe F, Namwangye H, Zaramba S, Brooker S, et al. Progress towards countrywide control of schistosomiasis and soil-transmitted helminthiasis in Uganda. *Trans R Soc Trop Med Hyg* 2006;**100**:208–15.
19. Montresor A, Crompton DWT, Bundy DAP, Hall A, Savioli L. *Guidelines for the evaluation of soil-transmitted helminthiasis and schistosomiasis at community level: a guide for managers of control programmes*. Geneva: World Health Organization; 1998.
20. Montresor A, Crompton DWT, Gyorkos TW, Savioli L. *Helminth control in school-age children: a guide for managers of control programmes*. Geneva: World Health Organization; 2002.
21. Brooker S, Kabatereine NB, Fleming F, Devlin N. Cost and cost-effectiveness of nationwide school-based helminth control in Uganda: intra-country variation and effects of scaling-up. *Health Policy Plan* 2008;**23**:24–35.
22. Banoo S, Bell D, Bossuyt P, Herring A, Mabey D, Poole F, et al. Evaluation of diagnostic tests for infectious diseases: general principles. *Nat Rev Microbiol* 2006;**4**(12 Suppl):S20–32.
23. Doenhoff MJ, Chiodini PL, Hamilton JV. Specific and sensitive diagnosis of schistosome infection: can it be done with antibodies? *Trends Parasitol* 2004;**20**:35–9.
24. Wilson RA, Van Dam GJ, Kariuki TM, Farah IO, Deelder AM, Coulson PS. The detection limits for estimates of infection intensity in schistosomiasis mansoni established by a study in non-human primates. *Int J Parasitol* 2006;**36**:1241–4.
25. Al-Sherbiny MM, Osman AM, Hancock K, Deelder AM, Tsang VCW. Application of immunodiagnostic assays: detection of antibodies and circulating antigens in human schistosomiasis and correlation with clinical findings. *Am J Trop Med Hyg* 1999;**60**:960–6.
26. Van Dam GJ, Wichers JH, Ferreira TMF, Ghati D, Van Amerongen A, Deelder AM. Diagnosis of schistosomiasis by reagent strip test for detection of circulating cathodic antigen. *J Clin Microbiol* 2004;**42**:5458–61.
27. Stothard JR, Kabatereine NB, Tukahebwa EM, Kazibwe F, Rollinson D, Mathieson W, et al. Use of circulating cathodic antigen (CCA) dipsticks for detection of intestinal and urinary schistosomiasis. *Acta Trop* 2006;**97**:219–28.
28. Ayele B, Erko B, Legesse M, Hailu A, Medhin G. Evaluation of circulating cathodic antigen (CCA) strip for diagnosis of urinary schistosomiasis in Hassoba school children, Afar, Ethiopia. *Parasite* 2008;**15**:69–75.
29. Legesse M, Erko B. Field-based evaluation of a reagent strip test for diagnosis of *Schistosoma mansoni* by detecting circulating cathodic antigen in urine before and after chemotherapy. *Trans R Soc Trop Med Hyg* 2007;**101**:668–73.
30. Ten Hove RJ, Verweij JJ, Vereecken K, Polman K, Dieye L, Van Lieshout L. Multiplex real-time PCR for the detection and quantification of *Schistosoma mansoni* and *S. haematobium* infection in stool samples collected in northern Senegal. *Trans R Soc Trop Med Hyg* 2008;**102**:179–85.
31. Akinwale OP, Laurent T, Mertens P, Leclipteux T, Rollinson D, Kane R, et al. Detection of schistosomes polymerase chain reaction amplified DNA by oligochromatographic dipstick. *Mol Biochem Parasitol* 2008;**160**:167–70.
32. Njiru ZK, Mikosza ASJ, Matovu E, Enyaru JCK, Ouma JO, Kibona SN, et al. African trypanosomiasis: sensitive and rapid detection of the sub-genus *Trypanozoon* by loop-mediated isothermal amplification (LAMP) of parasite DNA. *Int J Parasitol* 2008;**38**:589–99.

Please cite this article in press as: Stothard JR. Improving control of African schistosomiasis: towards effective use of rapid diagnostic tests within an appropriate disease surveillance model. *Trans R Soc Trop Med Hyg* (2009), doi:10.1016/j.trstmh.2008.12.012