volume 17 no 3 pp 402–403 March 2012

Letter to the Editors

Response to: accuracy of circulating cathodic antigen tests for rapid mapping of *Schistosoma mansoni* and *S. haematobium* infections in Southern Sudan by RA Ashton *et al.* (2011) *Trop Med Int Health* 16, pp. 1099–1103

Dear Editors,

All researchers involved in schistosomiasis field projects are struggling with the fact that the currently available and widely used microscopical methods have very limited sensitivity and need to be performed repeatedly, preferably on multiple samples, to reach sensitivities higher than 80%. Indeed, it has been well documented in various studies that the sensitivity of a single Kato-Katz will typically range between 25% and 50% – particularly when the slides are observed within 1 h after preparation – (Utzinger *et al.* 2001; Booth *et al.* 2003). Therefore, a new and more sensitive field-applicable test that should be robust, simple to use, cheap and based on the analysis of non-invasively obtained patient material (i.e. urine or faeces rather than blood) is urgently needed. However, any new test can in a schistosomiasis low-endemic region only be realistically evaluated if extensive microscopy has been performed on multiple samples to create a reliable 'parasitological gold standard'. Otherwise, owing to the high percentage of false-negative egg counts, any conclusion on the specificity of a new test would be unfounded. The study of Ashton *et al.* (2011), in which the accuracy of a novel point-of-care test based on the detection of schistosome antigen CCA in urine (CCA-POC test) has been evaluated, clearly shows this serious methodological flaw and this is not sufficiently highlighted by the authors. Despite this limitation, the data could still be used if a proper way of analysis is applied, as indicated below.

The available literature (some of which has been cited in the article) shows that the CCA-POC test shows characteristics which are similar to that of the CCA-ELISA from which it has been derived (Van Dam *et al.* 2004). The CCA-ELISA has been extensively evaluated and applied in many studies showing a high sensitivity for *Schistosoma mansoni* infections, a limited and variable sensitivity for *S. haematobium* infections, a specificity which is typically over 95%, and – importantly – significantly less day-to-day variation than stool egg counts (De Jonge *et al.* 1988, 1989; Kremsner *et al.* 1994; Van Lieshout *et al.* 2000). So what in our opinion *should* have been done, given the limitations of the microscopy data set, is to determine the sensitivities of the Kato-Katz and CCA-POC each *vs.* a combined diagnostic 'gold' standard in which a case is considered infection-positive by either egg- or CCA-positivity (Ebrahim *et al.* 1997; Midzi *et al.* 2009; Glinz *et al.* 2010; Knopp *et al.* 2011). A preliminary analysis based on the data provided in the article shows that for *S. mansoni* infections this would result in sensitivities for microscopy and CCA-POC of 56% and 94%, respectively. For the *S. haematobium* infections, these would be 62% and 61%, respectively. For *S. mansoni* the 'true' prevalence would then be 44% and for *S. haematobium* 42%. These results are well in line with common findings presented by others as cited in (Utzinger *et al.* 2011).

Alternatively, for the *S. mansoni* infections, the 'pocket chart' model that has been developed and evaluated extensively by De Vlas *et al.* (1993) could have been applied. This mathematical model predicts ('extrapolates') the true prevalence in a given population based on single egg count determinations. This mathematical model has been evaluated in many studies and proven to provide very reliable results. Although in the study of Ashton *et al.* (2011) the individual egg counts are not presented, it is mentioned that the majority of the infections were of light intensity. When the pocket chart is used to extrapolate the true prevalence from the observed prevalence (24.5%) assuming that the geometric mean egg counts were between 40 and 100 epg, this results in true prevalences ranging between 45% and 70%, which corresponds well with the 44% shown by the combined gold standard (Figure 1).

These two different approaches in interpreting the data would undoubtedly have altered the conclusion on the usability of the CCA-POC test for schistosomiasis mapping, in particular with respect to *S. mansoni*. Apart from this incorrect conclusion, we find it rather disheartening to note that despite a wealth of literature on this specific topic the inherent shortcomings of a single Kato-Katz assay for evaluating new diagnostic tests are still not been properly taken into consideration by part of the scientific community.

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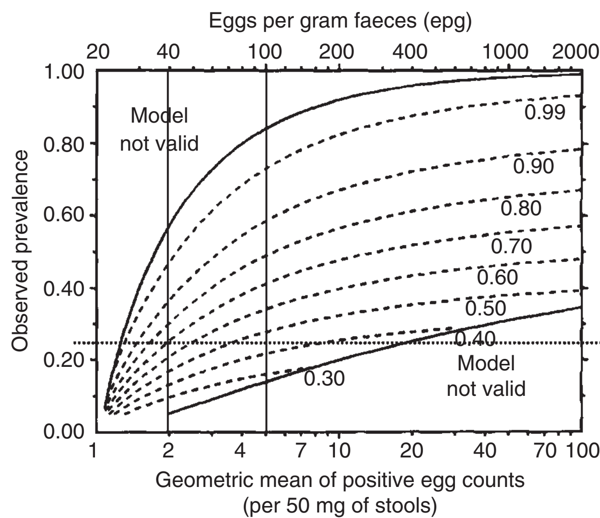

Figure 1 Estimation of true *S. mansoni* prevalence according to (De Vlas *et al.* 1993). The dotted line represents the observed prevalence (24.5%) based on a single egg count. The region between the solid lines corresponds to the light intensity infections (with geometric mean between 40 and 100 epg) and the lines cross the dotted line at the true (predicted) prevalences of 70% and 45%.

Apart form this major criticism, we disagree with the authors' citation of the article by (Midzi *et al.* 2009), in which one of us (GJvD) is a co-author, as showing 'poor performance for detecting *S. haematobium*'. This article reported 88% sensitivity and it was concluded that the CCA-POC test had an acceptable place in field diagnosis of *S. haematobium*. We also disagree with the conclusion that the Hemastix® would have 'superior specificity' over the CCA-POC test in this mixed infection region as that the latter assay will detect preferably *S. mansoni* infections which are completely missed by the Hemastix®.

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