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*Published in:*  
Trends in Parasitology

*DOI:*  
[10.1016/j.pt.2009.01.004](https://doi.org/10.1016/j.pt.2009.01.004)

*Publication date:*  
2009

*Document version*  
Early version, also known as pre-print

*Citation for published version (APA):*  
Bergquist, R., Johansen, M. V., & Utzinger, J. (2009). Diagnostic dilemmas in helminthology: what tools to use and when? *Trends in Parasitology*, 25(4), 151-156. <https://doi.org/10.1016/j.pt.2009.01.004>

3 **Diagnostic dilemmas in helminthology: what tools to use and when?**

4

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13

14 **Abstract**

15 Available data regarding the distribution, prevalence and severity of various diseases are  
16 based on the performance and operational characteristics of the diagnostic techniques applied;  
17 a fact particularly apparent in the study of helminth infections. An important lesson learnt  
18 from the efforts to rein in dracunculiasis, lymphatic filariasis and schistosomiasis is that the  
19 diagnostic approach changes as further progress is made towards control and ultimate  
20 elimination of the disease. This insight prompted the opinion presented here, which highlights  
21 diagnostic dilemmas in helminthology related to the stage of control achieved, and sets out  
22 some research needs.

23

24 *Key words:* helminth infections, diagnosis, control, elimination, microscopy, serology,  
25 specificity, sensitivity, prevalence

26

## 27 **Choice of diagnostic assays**

28       New and ambitious goals have been set for the control of infectious diseases in the  
29 developing world by governments and international donor agencies in collaboration with the  
30 World Health Organization (WHO). Significant progress has been made but there is a  
31 tendency to emphasize mainly drug treatment, and also vaccines, while the importance of  
32 quality-assured diagnostic tests is often neglected [1]. Yet, the more successful a control  
33 programme becomes, the more critical is the need for an accurate assessment of the  
34 epidemiological situation.

35       The helminthic diseases require diverse diagnostic approaches. For example, while  
36 serology constitute a valuable adjunct to the clinical diagnosis of echinococcosis,  
37 trichinellosis and toxocariasis [2], the local elimination of various helminth infections such as  
38 dracunculiasis [3], lymphatic filariasis [4,5] and schistosomiasis [4,6,7] highlights the need  
39 for adjusting the diagnostic capability to the different stages of active control.

40       The focus of this opinion article is on schistosomiasis and the main soil-transmitted  
41 helminthiases (ascariasis, hookworm disease and trichuriasis) because these diseases are still  
42 widespread [8-10], while activities to control them have gained momentum due to the World  
43 Health Assembly resolution WHA54.19 of May 2001, which urges member states to regularly  
44 treat at least 75% of school-aged children and other high-risk groups with praziquantel against  
45 schistosomiasis and albendazole/mebendazole against soil-transmitted helminthiases [11].  
46 The food-borne trematodiases (e.g. clonorchiasis, fascioliasis, opisthorchiasis and  
47 paragonimiasis) are also discussed as this group comprises serious, yet truly neglected  
48 tropical diseases which, in addition to their veterinary significance, constitute an emerging  
49 public health threat in many parts of the world [12-16].

50 The choice of a diagnostic assay should be governed by the objective of the activity.  
51 Indeed, the proper diagnosis of an infection is paramount for all aspects of its prevention and  
52 control. Moreover, the evaluation of efficacy and community-effectiveness of interventions,  
53 verification of local disease elimination and early detection of resurgence strongly depends on  
54 reliable diagnostic tools [17,18]. However, while the implementation of a complex diagnostic  
55 approach based on the highest possible combination of sensitivity and specificity can be  
56 defended from a research point of view, even when time-consuming and expensive, an  
57 approach useful in practise is almost always a compromise between quality and quantity as  
58 the techniques needed for large-scale application must be based on cost-effectiveness, i.e.  
59 time and resources required per test, simplicity and robustness. The dilemma represented by  
60 this need for compromise is related to the nature of the infection and the stage of control  
61 achieved.

62 The heart of the matter is the required, continuous adaption of the diagnostic focus to the  
63 state of control, taking into account the prevailing constraints in terms of available resources.  
64 Fig. 1 highlights this by showing the various stages of a hypothetical helminth control  
65 programme juxtaposed with the type of diagnostic tools that must be employed to reach the  
66 set goals.

67

### 68 **From morbidity to post-transmission**

69 In 2002, Engels and colleagues [19] outlined the control of schistosomiasis as a series of  
70 consecutive steps moving from morbidity control to elimination of infection as a public health  
71 threat. This framework has here been expanded to include also the soil-transmitted  
72 helminthiases and the food-borne trematodiases. Underlying reasons are the considerable  
73 geographical overlap of these infections, the similar tools for diagnosis used at the onset of  
74 control activities (e.g. microscopy of stool samples) and the similar public health measures

75 applied (e.g. large-scale administration of anthelmintic drugs when morbidity reduction is  
76 the prime objective) [20,21]. Post-transmission control is not depicted in the figure as this  
77 stage is limited to a relatively small number of patients but it should be realized that it will  
78 require interventions for a prolonged period of time, particularly in the case of schistosomiasis  
79 and the food-borne trematodiasis [22]. The idea to collate this information (Fig. 2) is in line  
80 with the growing emphasis on integrating the control of the so-called neglected tropical  
81 diseases [4,10,23-25]. Currently used techniques are depicted in the boxes to the right in the  
82 figure, while the entries to the left are still tentative.

83

#### 84 **Diagnostic dilemmas**

##### 85 *Morbidity control – questionnaires and standard diagnostic tests*

86 When control of schistosomiasis was first attempted, eradication was the pronounced  
87 goal, at least by some eminent scientists at the time [26]. However, the failure of this  
88 approach was not due to a diagnostic dilemma but depended on the incongruence between  
89 objective and tools. The problem was circumvented by the advent of praziquantel which  
90 permitted **a change of tactics**, i.e. substituting morbidity for transmission as the focus of  
91 control in highly endemic areas [27]. This strategy, relying on mass administration of safe and  
92 efficacious drugs donated or provided at very low cost [4,7,10], is still recommended in  
93 settings where the proportion of those infected surpasses a given threshold (e.g. >50% of  
94 school-aged children infected) [11]. With this diagnostic scenario, cost and simplicity are  
95 more important than sensitivity leading to the utilization of community-based questionnaires  
96 with the results followed-up by standard parasitological examinations of excreta (e.g. stool,  
97 urine and sputum). That these results are not fully reliable with respect to prevalence and give  
98 even less information on the level of transmission must be weighed against the importance of  
99 rapidly identifying those in most need of treatment.

100 Interviewing schoolchildren about blood in the urine has proved generally accurate and  
101 cost-effective for the rapid identification of high-risk communities of urinary schistosomiasis  
102 [28]. While a similar approach, focused on dietary habits (e.g. consumption of raw or  
103 undercooked fish), could be a quick way to identify populations at risk of clonorchiasis [29],  
104 geographical and ethnographical differences present an unforeseen dilemma. For example,  
105 whereas communities suffering from opisthorchiasis in Thailand were able to perform self-  
106 diagnosis leading to treatment-seeking practices, this was not the case in Laos where  
107 opisthorchiasis-specific symptoms were vague [30] leading to the conclusion that the  
108 questionnaire approach must be locally assessed before large-scale implementation. Thus,  
109 parasitological diagnostic tools are still needed for assessing cure after treatment and, in the  
110 longer perspective, dependable disease surveillance.

111 Faecal smears and Kato-Katz thick smears are widely used direct methods for diagnosing  
112 intestinal schistosomiasis, the common soil-transmitted helminthiasis and most food-borne  
113 trematode infections [31,32]. While a strong bias towards false negatives would falsify the  
114 outcome, even a considerable proportion of false positives would not compromise the cost-  
115 effectiveness of this approach since the extra drug expense is marginal in today's prices (e.g.  
116 US\$ 0.10-0.20 for treating a school-aged child with praziquantel) [33,34]. The danger of a  
117 misinterpretation of the epidemiological situation, however, is clearly present and this risk  
118 increases as the numbers and infection intensities are brought down.

119 Some further diagnostic dilemmas with reference to stool examinations at the stage of  
120 morbidity control are worth mentioning. First, because infections with multiple species are the  
121 norm rather than the exception, there is a need for well-trained laboratory technicians and  
122 quality control measures to ascertain accurate, species-specific helminth diagnosis. This issue  
123 is particularly relevant in settings characterized by a high diversity of food-borne trematodes  
124 [35]. Second, while Kato-Katz thick smears should be read shortly after slide preparation

125 (preferably within 30 min) for hookworm eggs which would otherwise have disintegrated,  
126 longer clearing times (sometimes several hours) are warranted for the diagnosis of  
127 *Schistosoma mansoni*, as well as *Ascaris lumbricoides*, *Trichuris trichiura* and food-borne  
128 trematodes. Third, the time required for collecting the stool specimens in the field,  
129 transferring them to the laboratory, and preparing the slides for examination can result in  
130 significant underestimates of hookworm burdens [36]. As a compromise, in settings where  
131 soil-transmitted helminths co-exist with either *S. mansoni* or food-borne trematodes, Kato-  
132 Katz thick smears are often examined 30-60 min after preparation. Fourth, the Kato-Katz  
133 technique is not suitable for the diagnosis of *Strongyloides stercoralis*, which might, at least  
134 partially, explain why this is the most neglected of the soil-transmitted helminths [8,20,37].

135

#### 136 *Transmission control – egg detection subsequently replaced*

137 The need for accurate and precise diagnostic tests increases strongly when the overall  
138 performance decreases towards the low-prevalence end. The standard Kato-Katz technique is  
139 a good example of how this diagnostic process works. Although Kato-Katz is a sound  
140 approach for highly endemic areas [38,39], it is inadequate in situations characterized by a  
141 low infection intensities and few infected people [6,40]. Hence, in the latter case (which is  
142 typical for the transmission control stage), the positive predictive value of the test decreases,  
143 which above all calls for highly sensitive assays but of course also with acceptable specificity.  
144 In this situation, it is obvious that further progress in controlling a disease – and ultimately  
145 local elimination – is jeopardized. FLOTAC<sup>®</sup>, a new technique for stool examination so far  
146 mainly used in the veterinary field, holds promise in relation to this dilemma. Recent studies  
147 found that a single FLOTAC<sup>®</sup> examination is more sensitive than multiple Kato-Katz thick  
148 smears for hookworm diagnosis [41], as well as *A. lumbricoides* and *T. trichiura* diagnosis

149 [42]. In addition, multiple stool (or urine or sputum) examinations and the use of different  
150 methods simultaneously should be considered [37,43-45].

151 **Thus, once** morbidity is under control, further progress demands more sensitive  
152 techniques and when the transmission and surveillance control stages have been reached, cost  
153 might increase as control at these levels not only must consider different kinds of host  
154 (example: schistosomiasis; see Table 1), but also requires even more sensitive approaches. At  
155 this stage, antibody-detection is clearly the preferential, primary approach for monitoring the  
156 human population [39]. Of note, in the Chinese national schistosomiasis control programme,  
157 serology is routinely implemented, usually followed by stool examination of sero-positive  
158 individuals [7]. However, there are many challenges to this course of action. First, antibody-  
159 detection is not quantitative. Second, it fails to distinguish between **current and cured**  
160 infection, although progress has been made to remedy this issue [39]. Third, the high degree  
161 of cross-reactivity with clonorchiasis and paragonimiasis is a problem of particular  
162 importance in China and the countries south of its border where these food-borne trematode  
163 infections are highly endemic [12,13,15]. In areas where antibody-detection is challenged by  
164 significant cross-reactivity, molecular tools should be contemplated in spite of their higher  
165 cost and requirement for speciality laboratories. For example, in Brazil, polymerase chain  
166 reaction (PCR) applied to human faeces found a prevalence of 38.1% in a study of 194  
167 individuals from a *S. mansoni*-endemic area, while triplicate Kato-Katz thick smears achieved  
168 only 30.9% prevalence in the same samples [46]. PCR approaches have also been successfully  
169 developed for a number of other helminths, including food-borne trematodes [47]. Fourth,  
170 integration of this type of serology into national control programmes requires access to  
171 affordable, high-quality reagents or kits, as well as successful methodological standardization  
172 and definition of assay performance. These points might explain why only few countries have  
173 adopted antibody-detection as a key strategy in helminth diagnosis. This notwithstanding, it is



174 likely that antibody-detection will gain in importance as further progress is being made with  
175 controlling helminth infections [39].

176

#### 177 *Post-transmission control – imaging techniques*

178 Recent progress in the use of imaging techniques for helminthic diseases [13,48,49] has  
179 shown that pathology remains a problem long after the infection has been successfully treated.  
180 Based on experience from Japan, surgical and other interventions may increasingly be needed  
181 on an individual basis in settings where transmission of trematode infections has been  
182 interrupted. This is currently a totally neglected problem which needs to be budgeted for as a  
183 final outlay when elimination is in sight.

184

#### 185 **Research needs**

186 Intensity of infection is a key determinant of morbidity, but the relation between egg  
187 excretion in stool (or urine or sputum) and severity of disease is complex [11]. Attempts have  
188 been made to classify helminth infection intensities based on egg counts (Table 2). However,  
189 these classifications are educated guesses at best and new research is warranted to put forth  
190 new or refined infection intensity classes for the helminthiases covered here. Indeed,  
191 morbidity cannot be assessed without clinical examination and sound imaging techniques  
192 [13,48,49]. Nevertheless, there is a possibility that laboratory testing could be a useful  
193 adjunct. For example, a quantitative assay has been developed for schistosomiasis-related  
194 bladder lesions, which relies on the excretion of an eosinophilic cationic protein (ECP) in the  
195 urine [50] and this approach may be possible to use also for faecal investigations [51].

196 While stool examination provides an acceptable measure of the stage of infection in  
197 highly endemic areas, there was originally hope that antigen-detection would do the same at  
198 the other end of the control spectrum, i.e. in areas of very low endemicity. However, this has

199 not been validated as antigen detection techniques are only marginally more sensitive than  
200 stool examination. Although serology and microscopy are complementary, it cannot be  
201 emphasized enough that the integration of serological methods into national control  
202 programmes requires development of accurate, methodologically standardized and easily  
203 applicable assays for the detection of both specific antibodies and antigens.

204 Although, most countries are still far from elimination with respect to the helminthiases  
205 discussed here, it makes sense to already now consider what is required to permit an area or  
206 entire country to be formally declared as eliminated from an infection. Would it suffice to  
207 present a certain number of negative results, over a specified time period, based on an  
208 absolutely specific, highly sensitive assay, such as PCR, in conjunction with negative  
209 serology?

210 The issues discussed here are not the only ones that can introduce failings as large-scale  
211 helminth control programmes continue to advance but the identification of the main  
212 diagnostic obstacles and dilemmas will facilitate the finding of logical, relatively  
213 straightforward ways to address them. The opinions expressed here are intended as an  
214 incitement to further enlargement of the scope of helminth diagnosis leading to multi-country  
215 studies aimed at standardizing protocols for rigorous validation of different diagnostic assays  
216 so that they can be utilized with high levels of confidence at different stages of control  
217 interventions.

218

## 219 **Acknowledgements**

220 We wish to thank Dr Lester Chitsulo for initiating an informal consultation at WHO to  
221 discuss some of the diagnostic dilemmas in helminthology expressed here. J. Utzinger  
222 acknowledges financial support from the Swiss National Science Foundation (project no.  
223 PPOOB--102883; PPOOB--119129).

224

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336

337

338 **Glossary**

339

340 **Accuracy:** the percentage of correct results obtained by a test under evaluation compared with  
341 the results of a reference or 'gold' standard test.

342 **Community effectiveness:** the ability of a particular intervention to alter the natural history  
343 of a particular disease for the better, under actual conditions of practice and use.

344 **Cost-effective:** producing good results for the amount of money spent.

345 **Efficacy:** the ability of an intervention to produce the desired beneficial effect under ideal  
346 circumstances (assessed by randomized controlled trials).

347 **Elimination:** reduction to zero of the incidence of a specific disease/infection caused by a  
348 specific agent in a defined geographical area as a result of deliberate efforts.

349 **Eradication:** permanent reduction to zero of the worldwide incidence of infection caused by a  
350 specific agent as a result of deliberate efforts.

351 **Precision:** the degree to which repeated measurements or calculations show the same or  
352 similar results.

353 **Positive predictive value:** the probability that a positive result accurately indicates the  
354 presence of infection.

355 **Sensitivity:** the proportion of actual positives which are correctly identified as such (i.e. the  
356 percentage of sick people who are identified as having the condition).

357 **Specificity:** the proportion of negatives which are correctly identified (i.e. the percentage of  
358 well people who are identified as not having the condition).

359



360 **Table 1. Characteristics in the diagnostic process at different stages of helminth control**  
 361 **programmes (exemplified by schistosomiasis)**

362

Characteristics	Stage of helminth control programme				
	Morbidity	Prevalence	Transmission	Surveillance	Elimination
Target	• Human host	• Human host	• Human host • Reservoir host • Intermediate host	• Human host • Reservoir host • Intermediate host	• Human host • Reservoir host • Intermediate host
Diagnostic traits	• Simplicity • Low cost	• Sensitivity • Specificity	• High sensitivity • Specificity	• High sensitivity • Specificity	• High sensitivity • High specificity
Suggested approach	• Questionnaire • Microscopy	• Sensitive direct tests	• Antigen detection • Labelled antibody <sup>a</sup>	• Antibody detection	• PCR • Antibody detection
Strength and limitations	• Good indicator of general status • Neglect light infections	• Development of test system not completed	• Antigen detection not sufficiently sensitive • Vector test complicated	• Excellent sensitivity • Cross reactions and specificity problems • Specific titres remain high for long time	• Capable assays • Certified testing • System not yet available

363 <sup>a</sup> applied to the intermediate host

364

365 **Table 2. Classification of infection intensities of different helminths according to egg**  
 366 **counts<sup>a</sup>**

367

Parasite investigated	Unit of measure	Infection intensity			Reference
		Light	Moderate	Heavy	
Schistosomes					
<i>Schistosoma mansoni</i>	EPG	1-99	100-399	≥400	[11]
<i>Schistosoma haematobium</i>	Eggs/10ml urine	1-49	≥50	≥50	[11]
Soil-transmitted helminths					
<i>Ascaris lumbricoides</i>	EPG	1-4999	5000-49999	≥50000	[11]
Hookworm	EPG	1-1999	2000-3999	≥4000	[11]
<i>Trichuris trichiura</i>	EPG	1-999	1000-9999	≥10000	[11]
Food-borne trematodes					
<i>Clonorchis sinensis</i>	EPG	tbd	tbd	tbd	–
<i>Fasciola hepatica</i>	EPG	tbd	tbd	tbd	–
<i>Fasciola gigantica</i>	EPG	tbd	tbd	tbd	–
<i>Opisthorchis viverrini</i>	EPG	1-999	1000-9999	≥10000	[52]
<i>Paragonimus</i> spp.	EPG	tbd	tbd	tbd	–

368 <sup>a</sup> Of note, for most food-borne trematodes, infection intensity thresholds are still lacking

369 EPG, eggs per gram of stool; tbd, to be determined

370 **Figures captions**

371

372 Figure 1. Schematic picture illuminating how falling endemicity levels influence control focus  
373 and diagnostic needs.

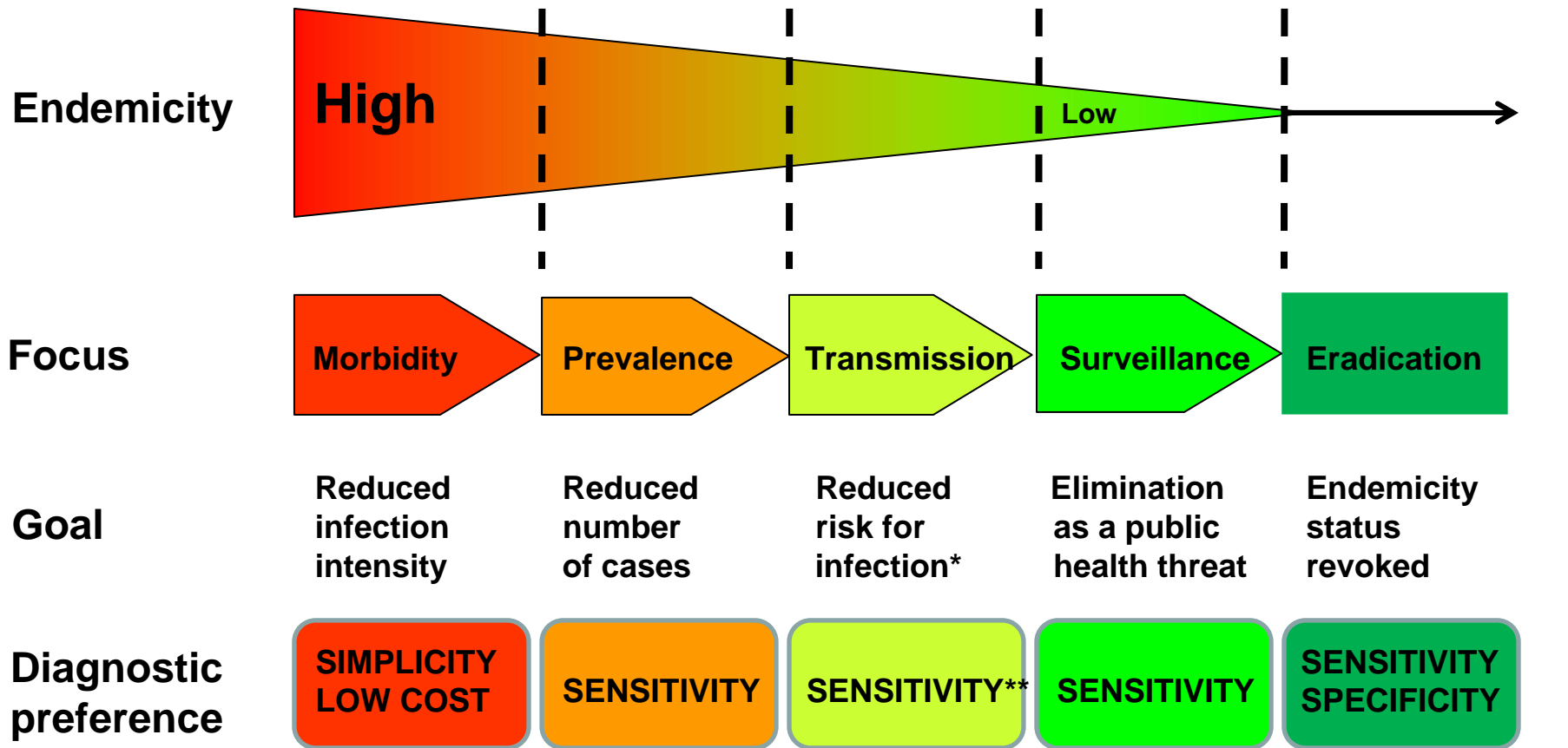
374

375 Figure 2. Current and suggested use of available tools for the diagnosis of major helminth  
376 infections.

377

378

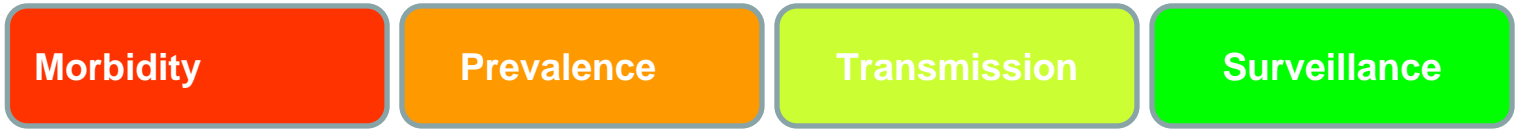
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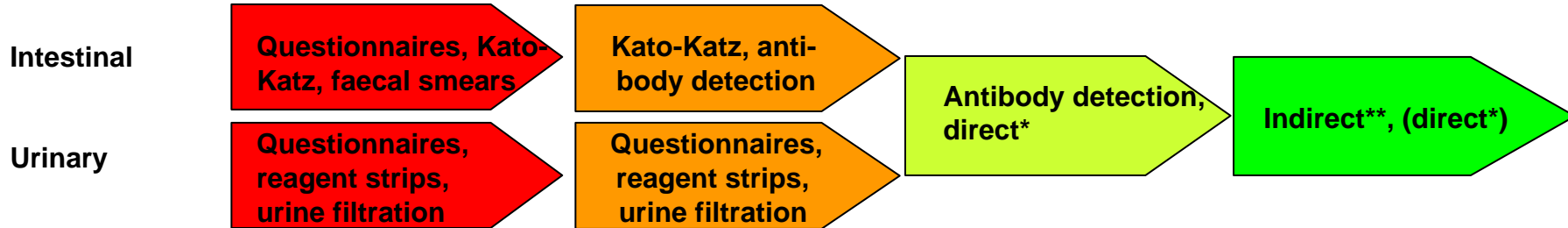
\*less human behavioural risk and/or fewer infected intermediate hosts

\*\* applies also to assays aimed at the intermediate host

**Stage of control**



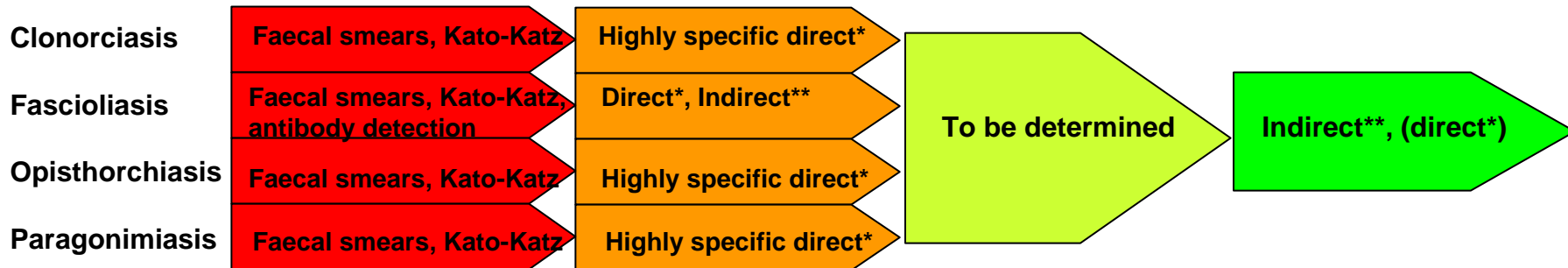
**Schistosomiasis**



**Soil-transmitted helminthiasis**



**Food-borne trematodiasis**



\* Refers to tests used to demonstrate any parasite material in the host circulation, tissues or excreta (whole worms, parasite eggs circulating antigens) directly by microscopy, serology or PCR.

\*\*Refers to results from the use of reagent strips, questionnaires, intradermal tests, clinical examination, imaging and antibody detection.