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UNCERTAINTIES IN THE EPIDEMIOLOGY AND CONTROL OF SCHISTOSOMIASIS

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Abstract. In this paper, gaps in our understanding of the dynamics of infection, transmission, pathology, and control of schistosomiasis, and the possible contribution of modeling are briefly discussed. The measurement of prevalences and intensities of infection by egg counts has shortcomings; a recently developed model of egg count variations contributes to a better interpretation of survey data, and suggests that true prevalences and worm loads in endemic communities may be considerably underestimated. The question as to whether schistosome populations are regulated by host-dependent or transmission-related factors is still being debated; recent scientific advances and operational control experiences tend to favor the first mechanism, with important implications for control and research strategies. However, there is still a lack of field data to feed models of the dynamics of transmission. We still know little about the dynamics and even the importance of schistosomiasis morbidity, although more objective data are now becoming available through ultrasound studies. Models of the development of early- and late-stage morbidity could substantially contribute to more cost-effective strategies of passive and active chemotherapy. Modeling can also contribute to a better understanding and improvement of results of ongoing control efforts, particularly concerning the impact of repeated chemotherapy, and its complex interaction with many biological and social factors on infection, transmission, and morbidity.

Major gaps in our understanding of the dynamics of infection, transmission, pathology, and control of schistosomiasis continue to hamper the development of cost-effective control strategies, as well as the rational orientation of research. Many fundamental questions are, in fact, hardly acknowledged or even addressed. In this paper, some of these gaps and the possible contribution of modeling to their solution are briefly discussed from the viewpoint of the field epidemiologist. Each schistosome species has its own specific biological and epidemiologic aspects, but most of the problems discussed in this report are relevant to all human schistosomes.

INFECTION

Measurement of infection. Most concepts in the epidemiology and control of schistosome populations are based on measurements of prevalence and intensity of infection/reinfection using fecal or urine egg counts. Egg counts as a measurement of worm loads must be interpreted with some caution, however. First, even though the level of egg excretion in a community may be relatively stable, there are important day-to-day fluctuations on the individual level.[1,2] Second, with common egg count techniques, some inherent inaccuracies cannot be avoided. Even under ideal circumstances, the weight of stool samples calibrated with Kato templates easily varies up to 50% and more (Polderman AM and others, unpublished data). The distribution of *Schistosoma haematobium* eggs in urine samples, even if thoroughly mixed, is far from homogeneous.[3] Under field conditions, variations in the consistency of stools, the concentration and time of collection of urine samples, the quality of the preparation and of the clearing of slides, and errors in microscopy and recording add further to the inherent inaccuracy.[3–5] Third, even if reliable individual egg counts can be obtained, e.g., by repeated examinations, their validity as a measure of worm burden remains questionable. The relationship between worm loads and egg counts found in the few available autopsy studies is far from linear.[6,7] The evolution of this host-parasite relationship with age after treatment, reinfection, and through the development of immunity is even less clear.

Even as a qualitative measure of infection, commonly applied screening methods do not provide accurate information because many light infections are missed. Prevalences can be considerably underestimated, particularly in communities and in age groups with low egg counts; the sensitivity of screening decreases further after chemotherapy and as infections become less intense.[8,9] This affects the most simple epidemiologic data, such as age-related prevalences (Figure 1) or the change in prevalences after treatment.

To better understand the relationship between parasite populations and their hosts, and how it is affected by control interventions, a more accurate measure of worm burden would be most useful.[10] The issue gains even more importance in view of the evaluation of possible vaccine candidates, the dual effect of which on both worm burdens and worm fecundity cannot be distinguished by egg counts.[11] New immunodiagnostic approaches, such as the detection of circulating antigens, may provide a valuable additional tool in this respect but do not yet detect all light infections.[12]

Modeling of infection. The problem of accurately estimating prevalences can also be approached statistically. Based on a series of empirical observations and common biological assumptions, both interindividual and intra-individual variations in egg counts and the underlying processes related to worm burdens have recently been combined in one stochastic model, allowing assessment of the real number of infections in a community.[13] The results suggest that the underestimation of prevalences by common egg count techniques may be even more important than indicated by empirical data. Repeated examination does improve sensitivity, but new infections must be expected to show up even after dozens of negative egg counts.[9] This has important implications in research, e.g., for the interpretation of immunoepidemiologic data and mechanisms; examples are false-positive results in serologic surveys, and the assumed nonconcomitant nature of acquired resistance in the absence of infection as determined by negative egg counts.[14–16] For

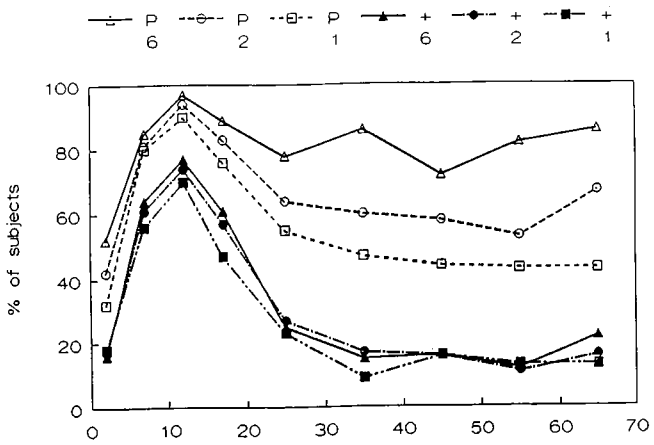

FIGURE 1. Evolution of the prevalences (P) and of the prevalence of infections with egg counts greater than 100 eggs per gram (epg) of feces (+) in Gihungwe, Burundi, with a single Kato slide (1), duplicate slides from one stool sample (2), or three duplicate slides from three stool samples (6). The age-dependent convexity of the curve decreases with increased sensitivity of the screening methods. △ = prevalence of infection measured with six (three stool samples) 25-mg Kato slides; ○ = prevalence of infection measured with duplicate 25-mg Kato slides (one stool sample); □ = prevalence of infection measured with one 25-mg Kato slide; ▲ = prevalence of infection with an epg > 100 measured with six (three stool samples) 25-mg Kato slides; ● = prevalence of infection with an epg > 100 measured with duplicate 25-mg Kato slides (one stool sample); ■ = prevalence of infection with an epg > 100 measured with one 25-mg Kato slide.

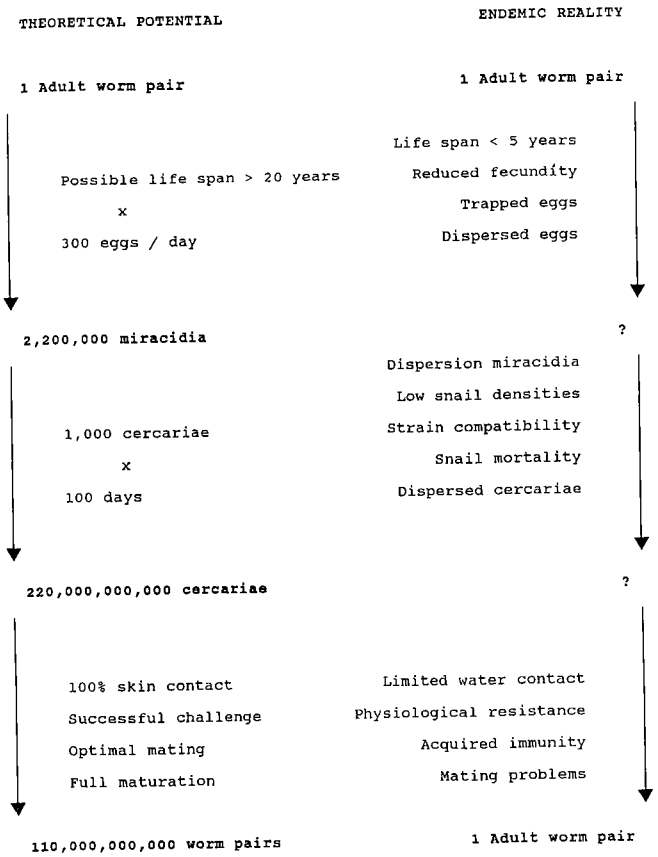

FIGURE 2. Theoretical reproduction potential of an adult schistosome couple, and factors affecting the dilution of this potential to a rate of one.

control purposes, the model would imply that selective population chemotherapy would always leave a substantial number of infected persons untreated, who would remain at risk of pathology and continue to contribute to transmission.[9] As a practical application, the model can be used to derive charts that allow estimation of true prevalences from observed survey data.[17,18]

This egg count model further suggests that for epidemiologic observations and biological assumptions about worm fecundity to be consistent, most people in endemic communities would have to harbor hundreds of worm pairs, rather than the few or dozens found in the few available autopsy series.[6,7,13,19] This would imply that even a 99% effective drug would leave at least a few worms alive in most treated people, at least if the worm killing pattern were random in each patient, a largely unexplored question so far. In this case, even indiscriminate mass treatment would leave many subjects with light infections. Although much validation is still needed, the above described work illustrates how modeling on the basis of available knowledge can lead to new insights, intriguing questions, and practical applications.

TRANSMISSION AND IMMUNITY

Population dynamics of schistosomes. If the reproduction potential of schistosomes were fully exploited, each adult couple would generate a staggeringly large offspring (Figure 2). In a stable endemic situation, the average reproductive rate would equal one. Thus, strong, yet finely tuned regulatory mechanisms must be at work, which resulting from evolutionary adaptation between two complex organisms can be expected to be multiple and intricately interfering. The relative contribution of ecologic and host-related factors to this equilibrium between schistosomes and their hosts is the subject of a long-standing debate that is far from being settled.[14,15,20,21]

In a very simplified way, two models of dilution of the transmission potential to an equilibrium transmission outcome, i.e., the rate at which adult worms are successfully established, can be envisaged (Figure 3). In one extreme model, this reduction would be a gradual process through the transmission cycle, governed by proportional rules. A reduction of any transmission factor, e.g., community egg output by selective or mass treatment, snail populations by molluscicide, human exposure by providing safe water supply, would then all ultimately result in a reduction of the transmission outcome, and thus of incidence and infection/reinfection rates in the population. This notion is actually reflected in many practical and theoretical considerations of current control strategies.[22,23] In the second model, one or several stages of multiplication, e.g., egg production by female worms, cercarial production in snails, would provide expansion points, followed by one or more bottlenecks, e.g., the limited number of snails available, human resistance to infection/reinfection (Figure 3). In this case, the ultimate transmission outcome would not necessarily be proportional to, or even dependent on, the transmission potential, but rather be determined by the size of the bottlenecks. Consequently, the impact of transmission control measures on the

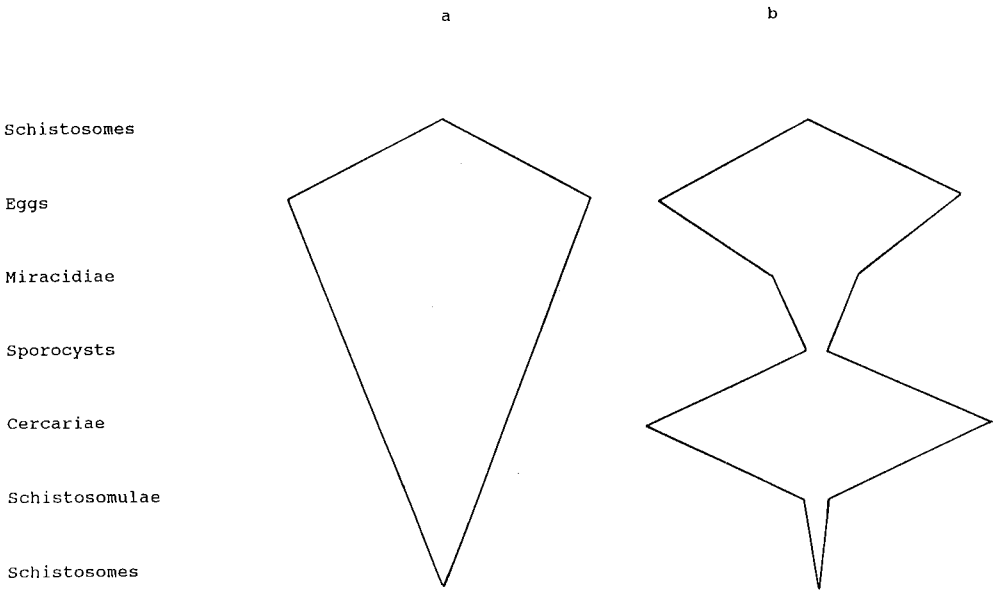

FIGURE 3. Simplified representation of two models of dilution of transmission potential: **a** a gradual reduction through the transmission cycle and **b** a possible series of expansion points and bottlenecks.

transmission outcome would be much less direct. A few infected people and a few snails may then provide sufficient transmission potential for maintaining (and re-establishing after mass treatment) a schistosome population at its equilibrium level. Biologically, such processes may be helped, e.g., by chemotactic attraction of miracidia by snails, and their enormous multiplication into cercariae. At another level in the cycle, cercarial densities may be much higher than needed for maintaining the parasite populations; innate or acquired human resistance may cut off the excess of transmission to a level determined by the host, rather than by the level of transmission itself.[15,20] Although schistosome populations are probably regulated by a complex interaction of both host- and transmission-related mechanisms, control experiences and epidemiologic experiments do in fact support a host-determined bottleneck model. Most programs of population-based treatment are confronted with continued transmission and reinfection, even if combined with extensive snail control.[8,24–28] In areas in which both community egg output and snail populations were reduced to less than 5% of precontrol values, no substantial lasting impact on the transmission outcome could, in fact, be demonstrated. Also, reinfection/exposure studies, reviewed elsewhere in this issue, show the importance of host-determined regulation of parasite populations.[15,29]

Modeling population dynamics. Obviously, it would be useful to develop models which put more emphasis on host factors to fit observed data from real-life operational control programs. The consequences of host regulation for research and control strategies are indeed far-reaching. First, the lack of success in controlling infection/reinfection by molluscicide may become explainable by ecologic mechanisms, besides the many practical and logistic problems that affect the efficacy and feasibility of this strategy. Second, transmission-related rationales for targeting certain groups for treatment because they are the most important source of contamination, or for treating animal reservoirs in the control of *S. japonicum,* may lack a sound epidemiologic basis. Third, if any impact on the transmission outcome would be expected from population-based treatment, then nearly complete population coverage would be required. The follow-up of prevalences (as the proportion of subjects excreting any number of eggs and thus potentially contributing to transmission), in addition to intensities, would gain new significance. Fourth, host regulation would considerably strengthen the argument for investment in vaccine research.

Unfortunately, the opposing views on the issue of regulatory mechanisms merely illustrate our lack of biological knowledge. It remains difficult to test any models of transmission and transmission control because valid field data on many aspects are incomplete or simply lacking. Modeling can, at least, help to identify these knowledge gaps and to define research priorities accordingly.

Contamination. Very few studies have been made of the dynamics of water contamination by schistosome eggs. We have no indication of the proportion of eggs that reach the water, hatch, and infect a snail, or how these dynamics are affected by heterogeneity in time and space, sociocultural, and ecologic factors. Some observations, such as the unexpectedly high proportion of bisexual miracidial infections in individual snails, remain unexplained.[30]

Snail dynamics. The dynamics of snail populations of schistosomes have been studied in more detail both by field biologists and modelers.[10] However, commonly applied methods for measuring snail populations and snail infection rates are in fact crude and insensitive, and the available data are relatively unreliable.[31,32] Usually, only a small and varying proportion of the actual number of (infected) snails is sampled; a whole range of possible sources of variation, including erratic heterogeneity in time and space, have to be considered.[33,34] The impact of these variations and sampling biases on observations and hypotheses would actually be an interesting subject for modeling on its own, comparable to the above-described egg count variation model.

Larval dynamics. Because of their short life span, the importance of the larval stages as determinants of transmission is supposed to be limited.[22] In modeling these stages, one is again confronted with a lack of useful biologic data and of reliable, practical field methods. The use of sentinel snails or mice is cumbersome. The results from studies reported so far vary widely, from a few to hundreds of adult worms recovered from mice exposed to natural habitats.[30,35,36] Direct cercariometric and miracidiometric methods have been applied in only a few field studies so far, but they appear to be as cumbersome and have not yet been used in a comprehensive study of the transmission dynamics of schistosomes.[37,38] Snail infection rates are often used as a kind of composite index of both miracidial and cercarial densities, but seldom in a comprehensive approach to transmission dynamics. High snail infection rates have been associated with high levels of human infection/reinfection in some studies, but in others no relationship could be shown; this is particularly the case in situations in which snail control measures have been implemented.[8,25,26,28,30,35] Systematic field studies on the relationship between densities and infection rates in snails and those in humans, however simplistic the subject may seem, would still be highly useful.

Exposure and immunity. A better understanding of the dynamics of larval stages is also essential for a better interpretation of studies on exposure and immunity. As indicated by the above-mentioned mouse exposure studies, we have little idea of the average cercarial challenge to an individual in a given endemic situation: is this a few, dozens, or hundreds a day, a month, a year? Does this challenge usually happen in monosexual space/time clusters, or rather as a random event? Consequently, is cercarial challenge indeed proportional to time and body surface exposed, as assumed in immunity/exposure studies.[14]

Regarding immunity, there is now evidence that effective resistance to infection/reinfection develops after 5–15 years of exposure.[14,15,29] Many aspects of the complex immunologic process remain unclear or hypothetical; exposure and immunity probably do interact to different degrees depending on the level of endemicity.[14,22] As discussed above, some basic assumptions of the studies have not yet been fully substantiated, such as the measurement of the presence and intensity of infection by egg counts, the proportional relationship between the cumulative number of cercariae penetrating the skin, and the number, duration, and extent of water contacts. Furthermore, the hypothesis of slowly acquired immunity does not explain all observations related to the regulation of parasite populations, e.g., why egg counts in treated children return to pretreatment levels in a few months or years, whereas it took 5–10 years to build up the initial infection. Recent studies in a newly exposed community in northern Senegal provide conflicting results: both egg counts and circulating antigen levels (supposedly a more direct measure of worm burdens) strongly decrease in adults, in spite of the assumed lack of immunity; compatible observations have been made in Burundi.[39–41] Apparently, water contact patterns determine the age-related distribution of parasites in recently established foci, although this would not exclude, after an intriguing transition phase from the epidemic to the endemic stage, a predominant role of immunity in older foci. The increasing number of situations in which due to ecologic modifications or migrations, entire communities are newly exposed to transmission provide a sad but unique opportunity to study how immune-related resistance develops. However, to analyze the complex interaction between transmission and exposure in this build-up of immunity, a mathematical framework is probably a prerequisite.

MORBIDITY

Measurement of morbidity. As reviewed elsewhere in detail, we still know surprisingly little about the dynamics and even the importance of morbidity associated with schistosome infections.[42–44] An association between morbidity and intensity of infection at the group or community level has been described in several studies. The frequency of high egg counts is often used as a surrogate indicator of morbidity by control workers as well as modelers.[23,24,45] However, in many morbidity studies, the correlation between egg counts and morbidity was absent, limited, or present in selected age groups only; at the individual level, it is even less consistent.[46] This can be explained by the inadequacy of individual egg counts as a measure of worm burden. Moreover, common indicators of morbidity, such as hepatomegaly in schistosomiasis mansoni, are unreliable for the assessment of functional disease.[44,46,47] Modern ultrasound techniques, although also measuring anatomical rather than functional morbidity, provide more objective data.[48]

Modeling of morbidity. As such data become increasingly available, they should be used to model a more consistent relationship between prevalence, intensity, and disease. Such a model should also take into account the time lag between heavy infection and pathology; a first attempt in this direction is described elsewhere in this supplement.[49] However, the assumptions remain hypothetical because field data on this subject are extremely scarce, and may remain so. The availability of praziquantel has indeed made it ethically unacceptable to study the natural history of disease in a longitudinal way. Even so, well-designed cross-sectional studies can provide useful information; in the Sudan for example, comparison of age-related patterns of infection intensities and liver fibrosis allowed an estimation that there is a time lag of about five years between peak intensity and the development of severe liver disease.[50] To what extent other factors in the geographic variation of morbidity patterns, such as immunogenetic and ethnic differences, concomitant infections, endemic histories, and the dynamics of infection (e.g., many light versus a few heavy exposures in a lifetime) can be modeled remains to be seen.[46,51] At least, a consistent infection/morbidity model would allow abnormal morbidity patterns to be objectively recognized, and orient research to identify risk factors accordingly.

CONTROL

Clearly, many questions still have to be answered before simulation models for the epidemiology of schistosomiasis can be fully tested and practically applied for control purposes. However, modeling can make practical contributions to the evaluation and improvement of existing programs.

Impact on infection. One problem to be tackled is the analysis of factors affecting the outcome of repeated che-

motherapy. In several countries where population-based chemotherapy has been applied for several years, it has been observed that prevalences decreased dramatically after the first treatment(s), but then tended to stabilize in spite of repeated treatment.[8,24,26,27] This stabilization is probably the result of several factors, including treatment failures, reinfection, insensitivity of screening, incomplete coverage and compliance, and immigration.[28] Without a mathematical framework, it is virtually impossible to quantify the relative contribution of each of these interacting factors, and to predict the outcome of modifications, e.g., by improving screening sensitivity, coverage, compliance or drug efficacy.

Impact on transmission. A second practical example concerns the impact of population-based treatment on transmission and reinfection. Early models, supported by field data, predicted that even almost complete sanitation, let alone a temporary and partial reduction of community egg output by selective treatment, would not be able to interrupt transmission.[52] Due to the focality in time and space of transmission, field studies on this subject are difficult and tedious; the few efforts reported so far indicate that treatment alone has only a limited, if any, effect on the rates of reinfection.[53] Even if such an impact would in theory be possible, it is questionable whether it could be achieved under operational conditions, when coverage and compliance are seldom optimal and untreated immigrants or temporary residents reintroduce and maintain transmission. The persistence of transmission and reinfection in most control programs tends to confirm this doubt.[8,24,26,27] Designing treatment strategies as a function of transmission control has considerable cost implications; fitting the results from control programs to various hypothetical levels of impact could help to substantiate or refute the soundness of such approaches.

Impact on morbidity. As a third example, a model for morbidity that distinguishes early- and late-stage morbidity and incorporates the time lag between both can help to optimize the timing of treatment.[47] Even more importantly, such a model may allow estimation of the probability that an individual would seek and receive treatment for early symptomatic disease, thereby avoiding the development of late, insidious pathology, and by what measures these probabilities can be increased. This would help health care planners to decide whether active intervention is needed at all, or whether or how far morbidity control can be achieved by improvement of passive case detection through primary health care.[43] In situations in which active intervention would be desirable, a morbidity model could also indicate that simple infection and/or early morbidity parameters can be used to select target groups at risk for severe chronic pathology, to define threshold levels for intervention, and to determine the optimal timing and frequency of re-treatment. Cost-effectiveness modeling, as discussed elsewhere in this supplement, could then complete the necessary basis for a rational selection of control strategies.[45]

CONCLUSIONS

This overview has attempted to demonstrate that many basic questions remain unanswered and unaddressed in the dynamics and control of schistosome populations. The formal approaches of modelers can help field epidemiologists to identify the knowledge gaps, sometimes provide part of the answers, and orient further research. As our scientific knowledge and control experiences grow, the complexity of the interactions of biological, sociocultural, and economic factors become increasingly apparent, as does the need for collaboration between field workers and modelers.

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