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ESTIMATING THE INTENSITY OF INFECTION WITH *SCHISTOSOMA JAPONICUM* IN VILLAGERS OF LEYTE, PHILIPPINES. PART I: A BAYESIAN CUMULATIVE LOGIT MODEL. THE SCHISTOSOMIASIS TRANSMISSION & ECOLOGY PROJECT (STEP)

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Abstract. Intensity profiles for helminths are used to describe population infection status, monitor effectiveness of control programs, and provide accurate data to validate transmission models. This study aims to accurately predict age/gender specific intensity profiles of endemic schistosomiasis japonica infection in the Philippines. Poor sensitivity of the Kato-Katz test and large heterogeneity in infection levels across villages complicate these predictions. Data from 1,989 individuals living in three endemic villages were analyzed with a Bayesian cumulative-logit model adjusting for nonproportional odds, variation between villages, and measurement error. The posterior uncertainty regarding the proportion of individuals in each egg category was high compared with that estimated using a model ignoring measurement error and villages' heterogeneity. The intensity profiles were very different in children less than 7 years old compared with older children and adults. This model could easily be adapted to other parasitic infections or outcomes where an analysis by category would be recommended.

INTRODUCTION

Schistosoma japonicum is a trematode parasite of enormous public health importance in Asia,[1–2] where an estimated 1.5 million individuals are infected and a further 60–75 million are at risk.[3] In the Philippines in particular, 6.7 million people are at risk and 1.8 million are considered directly exposed to the parasite.[4] Infection with *S. japonicum* has been linked to increased work loss and decreased physical capacity,[5–6] as well as nutritional and cognitive deficits in children.[7] The parasite can infect all mammals although there may be variation in their efficiency as definitive hosts.[8] Infected mammals contaminate the water with their feces that containing the parasite eggs that infect in turn the intermediate hosts (*Oncomenalia hupensis quadrasi*). Larvae from the parasite are then shed into the water where mammals can get infected. By the very nature of this transmission cycle, it is likely that individuals living in the same local area and sharing common water contact patterns will have a risk of infection more similar than individuals living in different areas. This clustering can lead to heterogeneity in the level and intensity of infection even within relatively small geographical regions, which, in turn, complicates targeting of treatment and prevention programs.

From 1975 to 1997, estimated human schistosomiasis prevalence in the Philippines decreased from 17.3% to reach a new equilibrium of 4.7% due to regular use of praziquantel starting in 1980 combined with both active and passive case detection.[4] However, as documented by Aligui and Yu and others,[9,10] the sensitivity of the tests used for national schistosomiasis screening is low and decreases with the intensity of infection. Therefore, the true national prevalence is likely to be higher than reported. Regional prevalence estimates have also been shown to be very heterogeneous—varying as a function of geography, ecology, as well as age and sex.[11] In addition to the prevalence, an accurate measure of the intensity of infection with *S. japonicum* is essential to evaluating the transmission dynamics of the infection. This is because individuals more heavily infected will contaminate the environment with more eggs than lightly infected individuals. Also, hepatic morbidity associated with *S. japonicum* in the Philippines appears to be linked to chronic untreated infections rather than the intensity of infection as observed with *Schistosoma mansoni*, thus the importance of accurately measuring the intensity of even light infection.[12] Finally, the intensity of infection can be used to assess the effectiveness of public health intervention. In effect, the intensity of infection within those affected is an important measure of intervention effectiveness and of the endemic state of an infection; the prevalence alone is not sufficient for public health decision making.[13] Misclassifications errors between categories at the extremes of a continuum are not unique to helminthic infections. They can also pose a challenge in other areas of medicine such as, for example, measuring cognitive levels, measuring birth weights to define very and low birth weight babies. Neuhaus[14] and Paulino and others[15] have adjusted for misclassification errors in research in the area of human papilloma virus (HPV) infection, using methods very similar to those proposed here.

Our objective here is to develop a statistical model to enable reliable prediction, in an endemic situation, of age/gender intensity "profiles" of schistosomiasis infection, adjusting for the measurement error of the Kato-Katz test and acknowledging the potential heterogeneity in infection due, in part, to differing occupational water contact and ecological patterns between communities within the same region. For each age/gender stratum, we predict the probability that an individual is in each of four contiguous egg categories. These four probabilities then make up the intensity profile for that stratum. In addition to providing reliable estimates of schis-

tosomiasis prevalence in this area, the stratum-specific profile estimates are used subsequently to inform the transmission dynamics.[16]

In the current paper, we adopt a Bayesian model-based approach that has the flexibility to acknowledge all sources of uncertainty. In particular, our model incorporates the uncertainties 1) surrounding the estimates of the sensitivity and specificity of the Kato-Katz test, 2) due to missing covariate data, and 3) due to the heterogeneity in intensity of infection patterns between communities.

MATERIALS AND METHODS

Description of the data. The data were collected as part of an 8-year follow-up study of individuals living in three rural villages in northeastern Leyte, Philippines. The primary objective was to evaluate the impact of an annual community-based case-finding and praziquantel treatment program on the epidemiology and transmission of *S. japonicum*.[17] The villages were specifically chosen to represent different socio-economical and ecological systems. They were also selected to represent the range of prevalence of *S. japonicum* previously observed in the Philippines. Between 1981 and 1988, each villager aged over 1 year was asked to provide one stool sample to the research team for parasitological examination. Individuals found positive were treated with a single dose of praziquantel. Because the goal of the current analysis was to develop a model for the intensity of infection with *S. japonicum* in an endemic situation (no recent previous treatment), only data from the first sampling taking place in November 1981 in two villages and in March 1982 in a third village will be used. At that time, 2,264 individuals provided a stool sample for parasitological examination among whom 275 provided a sample only then, and were therefore never seen again between 1982 and 1988. Those individuals did not differ in their intensity of infection or gender distributions, but compared with the individuals providing more than one stool specimen, those aged between 13 and 21 years from Villages 2 and 3 were overrepresented and were treated less frequently if found positive at the stool examination. Based on this and on the observations of the principal investigator at the time (R.O.), it is suspected that some individuals from other villages may have come to the first examination to get free treatment or may have emigrated for educational or occupational purposes. These individuals are thus likely to misrepresent the level of infection found in the three villages selected for the study. Therefore, the data analysis will be limited to the 1,989 individuals with more than one parasitological test during the 8-year follow-up.

Parasitological examination. Each stool sample was analyzed with a duplicate 50-mg Kato-Katz thick smear method.[17] Positive samples were independently reviewed by two microscopists. In addition, 10% of all slides were reviewed by an expert microscopist, with an agreement of over 99%. The number of eggs found on each slide was multiplied by 10 to obtain an estimate of the number of eggs per gram (epg). The results were divided into four groups of infection: not infected (0 epg), lightly infected (1–100 epg), moderately infected (101–800 epg) and very heavily infected (> 800 epg). We have used a modified classification to the one recommended by the WHO to better reflect the impact of heavily infected individuals on the transmission dynamics of the infection.[18]

The Kato-Katz method has been shown to have a low sensitivity, especially for individuals lightly infected, as reviewed by Aligui.[9] Because it is less likely that a person at least moderately infected would be misclassified by the Kato-Katz test, our model accounts only for misclassification errors between the lowest infection categories (no infection and light infection). Public health control programs in the Philippines still largely rely on the prevalence of infection to decide which villages should be targeted for closer control, so that misclassification between the two lowest categories leads to bias in prevalence estimates with important public health impact. Further, because egg counts follow a negative binomial distribution,[13] most individuals are not infected or very lightly infected, so that most of the misclassification occurs here. It has been shown that *S. japonicum* eggs tend to be more numerous at the surface of the stool than in the center, leading to additional variability if the stool is not stirred before analysis.[19] In a study comparing various methods to adjust prevalence estimates of *S. japonicum*, the sensitivity and specificity of a single stool Kato-Katz analysis were assumed to range between 0.41 and 0.69, and 0.90 and 1.00, respectively. These estimates were based on a review of the literature and allow for error associated with inter-microscopist variation.[9]

Statistical analysis. Individuals were categorized into three age groups: 0–6 years (Age group 1); 7–13 years (Age group 2), and > 13 years (Age group 3). These age categories were chosen to represent groups of homogeneous water contact patterns among young children, school children, and adolescents and adults. The distribution of intensity of infection was similar within age groups over 13 years old.

Full details of the statistical model are presented in the Appendix. Briefly, our outcome is the true but unobserved egg category of each individual in their respective age/sex/village stratum. The outcome is modeled with four values corresponding to epg $= 0$, $0 <$ epg ≤ 100, $100 <$ epg ≤ 800, and epg > 800, respectively, so that we model the probability (π) that an individual is in each egg category. We used a cumulative logit model[20–22] to directly model these cumulative probabilities over the four categories. For example, for individuals in each age/sex/village stratum, we would first look at the probability of being at least slightly infected compared with not being infected. In a second stage, we would look at the probability of being at least moderately infected compared with slightly infected or not infected, and so on. By subtracting probabilities in adjacent categories, the probability for each egg category is available.

Incorporating the misclassification error. As discussed above, the Kato-Katz method can lead to misclassification of samples, and our model was extended to account for this misclassification. Details are given in the Appendix.

Missing values. Twenty individuals had no age data recorded. Evidence from the field and from the nonmissing data from these individuals suggest that this covariate information was missing completely at random, its absence being unrelated to the data we analyzed. We used multiple imputation for the missing ages in relative proportion to the age distribution in the remaining population.[23] The posterior estimates of the intensity profiles fully incorporate the additional uncertainty arising from the missing age values.

The proportional odds assumption. Although relatively flexible in its incorporation of misclassification error and covariate information, the above model makes one particularly strong assumption: that of proportional odds. This means that the effect of each covariate is assumed to be the same across cumulative categories. For example, the odds ratio (OR) of being at least slightly infected (compared with not infected) in young children compared with adults would be exactly the same as the OR of being at least moderately infected (compared with being slightly infected or not infected) in young children compared with adults. This means that being an adult compared with a child has a constant effect on increasing intensities of infection, for example, but this does not appear to be the case. In particular, the odds of having egg count greater than a particular category in individuals in young children (0–7) relative to older children or adults appears to differ markedly as a function of the intensity of infection. The proportional odds assumption, however, does appear reasonable with respect to gender (data not shown). Therefore, the proportional odds assumption was relaxed for the effect of age on the intensity of infection (see the Appendix for details).

Prior distributions. In any Bayesian analysis, information in the data is combined with any information about parameter values known prior to analysis of the current data set. When little information is available, non-informative prior distributions can be used, which in practice mean that the information in the data will dominate any final inferences. We used non-informative prior distributions for almost all parameters in our model, but there is little information in the study data about the sensitivity and specificity of the Kato-Katz test.[24] We therefore used informative prior distributions for these two parameters, and assessed the sensitivity of our results to alternative prior distributions reflecting more optimistic and more pessimistic views regarding the performance of the test. In particular, we assumed the sensitivity of the Kato-Katz test, to have a mean of 0.55, and 99% Bayesian Credible Interval (BCI; Bayesian analogue of standard confidence intervals) of 0.41, 0.69. For the specificity, we assumed a mean of 0.95 and 99% BCI of 0.87, 1.00. As a robustness check to these prior assumptions, we used an "optimistic" prior with mean sensitivity 0.65 (99% BCI: 0.51, 0.77) and mean specificity 0.99 (99% BCI: 0.95, 1.00). In contrast, the pessimistic priors assume the sensitivity has mean 0.45 (99% BCI: 0.32, 0.58) and the specificity has mean 0.86 (99% BCI: 0.79, 0.95). The variation in results across these three different prior distributions (displayed in Figure 1) will reflect how dependent our results are on the choice of prior.

Estimation. Inferences are based on the joint posterior distribution of the model unknowns, as given in the appendix. The posterior distribution is analytically intractable and so we use Markov chain Monte Carlo (MCMC) methods, specifically the Gibbs sampler, to obtain samples from the marginal posteriors of the parameters. (See Gilks and others[25] and references therein for a description and properties of the algorithm.) All computations have been carried out in WinBUGS and are based on 10,000 iterations following convergence.[26]

Prediction and model verification. We obtained predictions of the patterns of intensity by age and gender, adjusted for known misclassification error and the variability between villages by using the MCMC samples plugged into the relevant

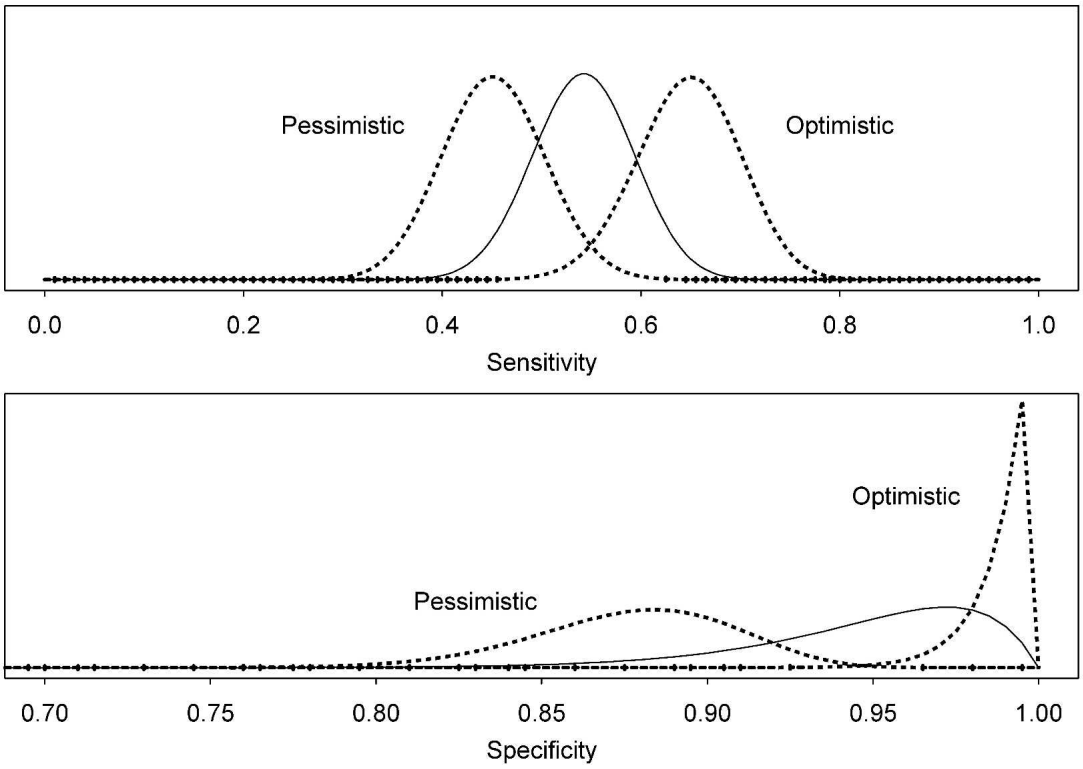

FIGURE 1. Assumed priors for the sensitivity and specificity of the Kato-Katz diagnostic test representing the misclassification error between noninfected and lightly infected categories. Shown are our assumed priors (solid lines) and those reflecting optimism and pessimism regarding the properties of the test (dotted lines).

prediction equations from our model. In this way, we are not only able to predict patterns likely to be seen in the future if our model is correct, but we are also able to compare these predictions from our model to the actual data we observed, as a further check on the validity of our model. Full details are provided in the Appendix.

RESULTS

Figure 2 shows the predicted probabilities of being in each egg category by age and sex after adjusting for known misclassification error and acknowledging the heterogeneity in infection patterns between villages. The posterior uncertainty regarding the proportion of individuals in each egg category, as indicated by the width of the 95% BCI in the left full lines, is considerably higher than that estimated under a model which ignores the measurement error and heterogeneity between villages, indicated by the dotted lines. We believe that the former better reflects what is in fact known about the underlying state of the infection. The largest 95% BCIs are seen with the first two egg categories, which is to be expected as this is where the misclassification occurs. These estimates will be used to inform our model for the transmission dynamics. Since there is still much unknown about the dynamics of schistomiasis japonica,[27] it is important that potential transmission mechanisms are not ruled out simply because they are not consistent with overly precise, biased estimates. For subjects 0–6 years old, the point estimates under the different approaches are similar (Figure 2) but for the 7–12 years and the > 13 years age groups, acknowledging the misclassification error, and between village heterogeneity, results in a decreased estimate of the probability of being uninfected and an increased probability of being lightly infected.

As illustrated in Figure 3, we observed no clinically important changes in our estimates when we used optimistic and pessimistic priors compared with the results reported above for our initial priors. All three priors result in very similar point estimates for the probability of infection in each age and sex stratum. The optimistic priors result in slightly narrower 95% BCI, simply because it has more precise values initially. Therefore, our results are robust across a reasonable range of prior information on the sensitivity and specificity of the Kato-Katz test. In the sequel, only results using these initial priors will be presented.

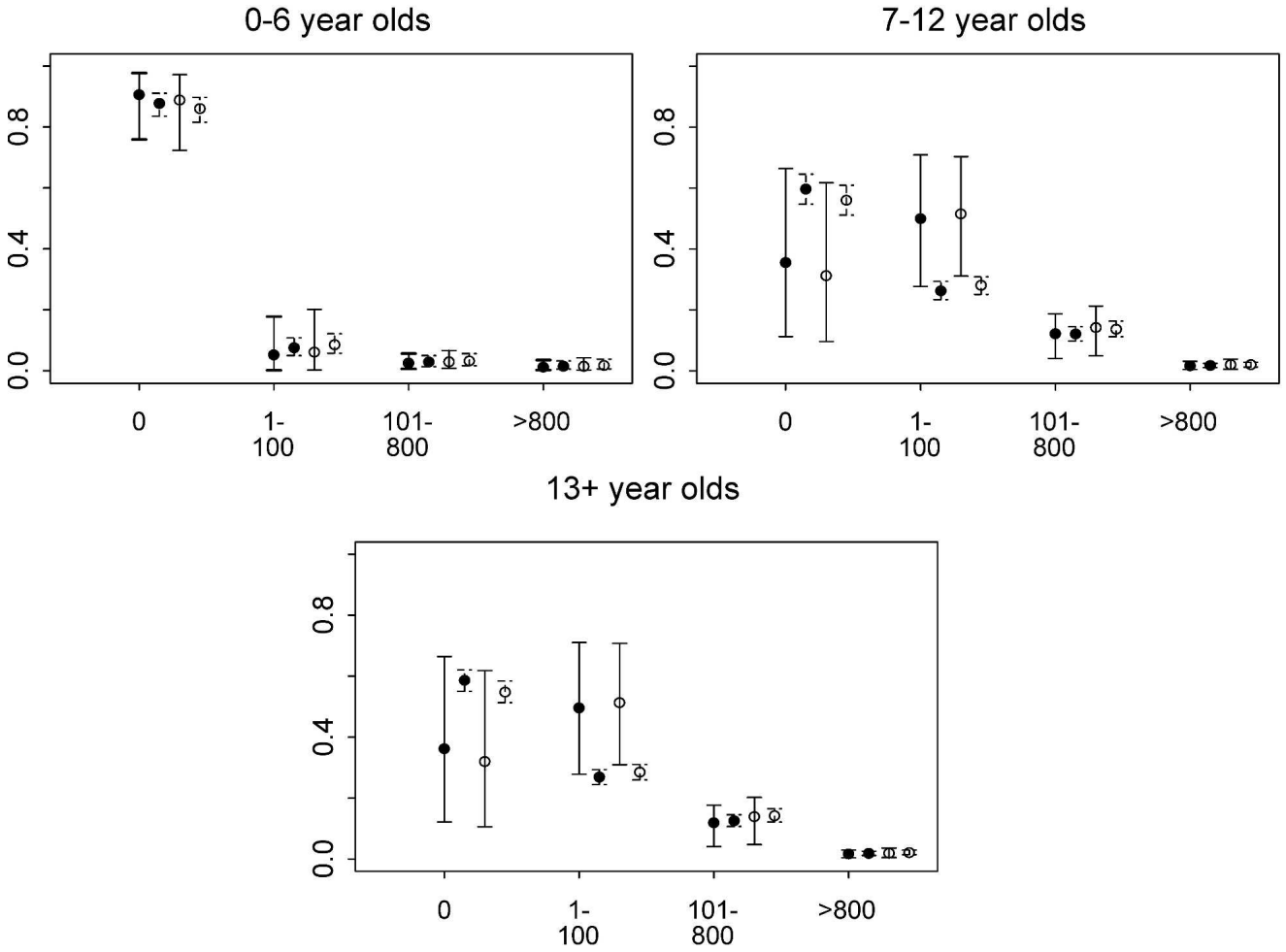

FIGURE 2. Estimated median probability and 95% Bayesian credible interval (95% BCI) of schistosomiasis infection in four egg categories (noninfected, lightly infected, moderately infected, heavily infected) by age group, sex (empty circle = males, full circles = females), and model used. For each gender, the full line represents the average probability and its 95% BCI under a model adjusting for measurement error and heterogeneity in infection between villages; the dotted line represents the average probability and its 95% confidence interval under an erroneous model that does not acknowledge the measurement error or heterogeneity in infection between villages.

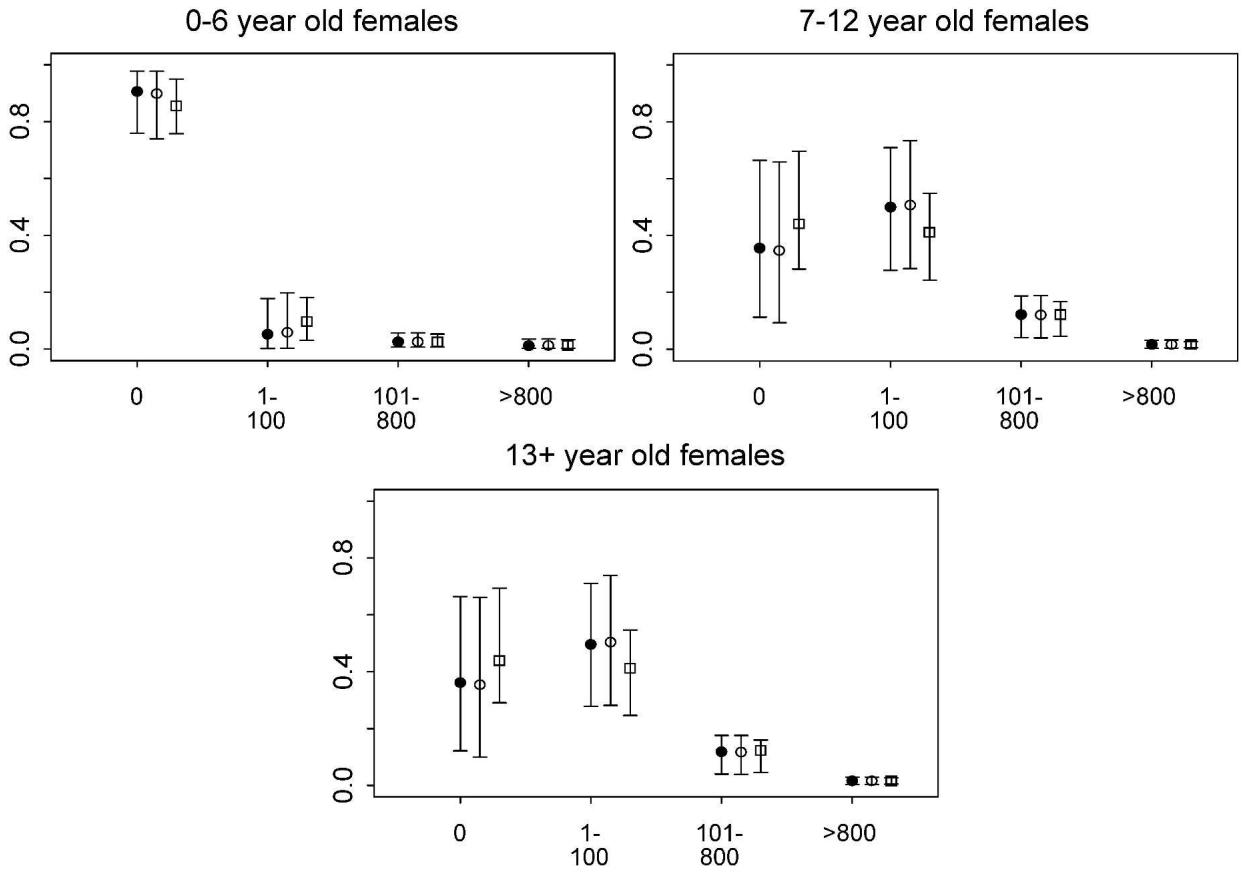

FIGURE 3. Estimated median probability and 95% Bayesian credible interval (95% BCI) of schistosomiasis infection in four egg categories (noninfected, lightly infected, moderately infected, heavily infected) for females by age group, assuming our default prior for the sensitivity and specificity of the Kato-Katz test (full circles, left line), the pessimistic prior (empty circles, middle line), and the optimistic prior (empty squares, right line).

Table 1 illustrates the odds ratios between epg categories comparing the three different age groups. These crude comparisons clearly indicate that the proportional odds assumption is not met when comparing age groups. A number of interesting observations emerge from examining the odds ratios (ORs) presented in Table 2. The ORs for sex and village are roughly proportional, whereas the ones for age change according to the intensity of infection, which reflects the nonproportionality of the odds. The ORs for age reflect what was seen in Table 1 with the crude estimates, which is that those 0–6 years old are less infected than older individuals except when heavily infected. It also reflects that those 13+ years old have the same ORs compared with those 7–12 years old across epg categories. There is some evidence for a gender effect, with the OR being below 1, indicating a global shift of probability toward lesser intensities among females. Also ap-

TABLE 1

Empirical, crude odds ratios of *S. japonicum* infection according to the eggs per gram (epg) counts (with associated 95% confidence intervals)

Age group	Reference age group	epg > 0*	epg > 100†	epg > 800‡
0–6	7–12	0.10 (0.07, 0.15)	0.27 (0.16, 0.48)	0.715 (0.27, 1.90)
0–6	13+	0.08 (0.05, 0.12)	0.31 (0.17, 0.56)	1.16 (0.35, 3.82)
7–12	13+	0.76 (0.56, 1.02)	1.14 (0.77, 1.70)	1.62 (0.58, 4.57)

* epg > 0: the OR compares individuals infected to individuals not infected.
† epg > 100: the OR compares individuals infected with more than 100 eggs per gram to individuals with 100 eggs per gram or less.
‡ epg > 800: the OR compares individuals infected with more than 800 eggs per gram to individuals with 800 eggs per gram or less.

TABLE 2

Posterior estimates and 95% Bayesian credible intervals for odds ratios of interest

Category	Reference	epg > 0	epg > 100	epg > 800
Age 0–6	Age 7–12	0.06 (0.01, 0.14)	0.28 (0.15, 0.48)	0.85 (0.31, 1.99)
Age 0–6	Age 13+	0.0 (0.02, 0.14)	0.29 (0.16, 0.48)	0.88 (0.32, 2.02)
Age 7–12	Age 13+	1.04 (0.79, 1.37)	1.04 (0.79, 1.37)	1.04 (0.79, 1.37)
Female	Male		0.82 (0.65, 1.05)	
Village 2	Village 3		1.30 (0.96, 1.81)	
Village 1	Village 3		0.42 (0.28, 0.63)	
Village 1	Village 2		0.33 (0.19, 0.50)	

For variables gender and village, the proportional odds assumptions was met, meaning that the effect of these covariates remains constant across cumulative egg categories. epg, eggs per gram.

parent is the heterogeneity between villages. Relative to Village 3, the odds of infection (of any intensity) are lower in Village 1 (OR = 0.42, 95% BCI: 0.28, 0.63) and possibly raised in Village 2 (OR = 1.30, 95% BCI: 0.96, 1.81).

As Figure 2 and Table 2 show, the epg profiles do not present clinically important differences in individuals aged 7 years and above of the same gender. However, a very different pattern of intensity of infection is estimated in infant and young children (0–6 years old).

Model validity. The lines in Figure 4 shows the median posterior predictions with their 95% BCI of the epg categories stratified by age and village for females. The crosses show the crude observations of these estimates. A similar picture emerges for males (not shown). These predictions are obtained by conditioning on both the cumulative logit model, the misclassification error model and the demographic composition of the villages (through the nonproportional odds component of the model)—they are, therefore, what we would expect to have observed "on the ground" if our model were correct. Even though we should expect some observations to fall outside the 95% BCI due to the poor sensitivity of the single stool Kato-Katz test, most observations do not differ greatly in practical terms. Hence, the model appears to well capture the overall pattern of infection intensity across the age groups.

DISCUSSION

Intensity profiles for helminthic infection provide an easily interpretable summary of the intensity of infection within a given population and can be used to monitor the effectiveness of control programs or to provide accurate data to validate dynamic transmission models. This model could easily be adapted to other infections with macroparasites or outcomes where an analysis by category would be easier to interpret and where misclassifications errors are likely (e.g., onchocercaiasis, malaria, insulin levels, birth weights, gestational ages, etc.).

The intensity profiles themselves can be derived in a number of ways. One approach is to assume a distributional form, say negative binomial, for the raw egg counts of individuals within a specific risk category, and then compute the required probabilities conditional on this assumption. The latter reduces to computing the proportion of the distribution between appropriate cut-points—in our case (0,1,100,800). Rather than assuming a distributional form for the egg counts, we prefer to model the probabilities directly. As well as affording a little more flexibility in the form of the underlying intensity profiles, the major advantage of this approach in the current context is the ease with which the misclassification error can be incorporated. Our model was robust to the

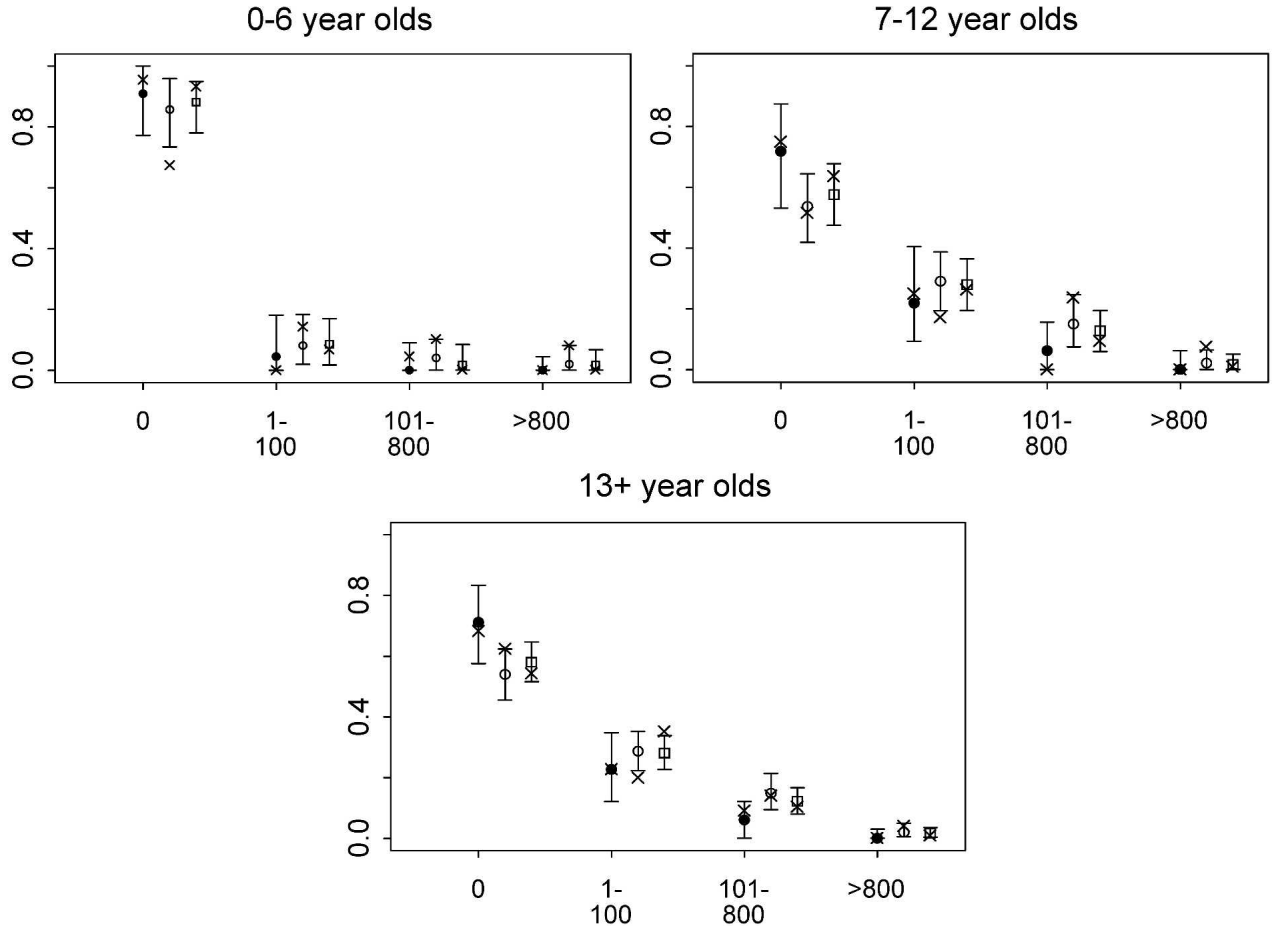

FIGURE 4. Observed prevalence of schistosomiasis japonicum within each egg category and age stratum for women (cross) and median posterior predictive estimates and 95% Bayesian credible interval (95% BCI) of the same quantities under the nonproportional odds model (bars). The three bars within each stratum represent the predictive distributions for each of Village 1 (full circle, left line), Village 2 (empty circle, middle line), and Village 3 (empty square, right line).

use of different prior distributions to adjust for the measurement error of the single stool Kato-Katz examination. Although widely advocated in the statistical literature, this is the first time (to our knowledge) that this specific approach has been adopted in the context of intensity of helminthic infections (a medline search with MeSH terms "helminthes" and "parasite egg count" found 3,314 publications, none of which had used this approach).

Cumulative logit models can be fitted within the classic estimation framework, see Agresti and Natarajan for details,[21] but we find the Bayesian approach more attractive for a number of reasons. First, inferences do not rely on asymptotic arguments that break down in the face of sparse data. In addition, the Bayesian approach does not demand the maximization of complex likelihoods and so many models not estimable using a classic approach become feasible using a Bayesian approach. Most importantly, however, it affords far greater flexibility, allowing us to extend our model to acknowledge appropriately the clustering of infection within villages and the misclassification error inherent in the Kato-Katz test. Others have also used a Bayesian generalized linear model to adjust for similar misclassification errors,[15] and Neuhaus has shown that not adjusting for such errors can lead to bias not only in the prevalence estimates, but also to the regression coefficients themselves.[14] In parasitology, adjusting for misclassification error for estimating the prevalence of helminthic infection has been used in a few instances in human epidemiologic studies and veterinary epidemiologic studies,[9,28–31] but not in combination with multivariate regressions or for prediction purposes.

Our model confirms the frequently observed higher prevalence of infection in males and agrees for what had been reported for *S. japonicum* in the Philippines and China.[1,32–35] This is most likely due to the fact that, in this population, females have less water contact than males.[9] However, the odds of infection in males compared with that in females are the same for all intensity of infection thresholds. In other words, males are consistently 22% more likely to be at least lightly infected, at least moderately infected or at least heavily infected compared with females. Thus, even though males are in general more infected than females, the distribution of individuals in each intensity of infection group is similar for the two genders. It may be that males and females progress through heavier intensities of infection with a similar rate. This was not the case when age groups were compared. The intensity and prevalence of infection increased with age, which is also consistent with what has been reported from the Philippines and China.[1,32–35] However, the rate with which the intensity of infection increases is different between very young children (0–6 years old) and older children and adults. Young children are less likely than older age groups to be infected or at least moderately infected, but the odds of being heavily infected (compared with non-heavily infected) is similar in all age groups. This may be because there are only a very small number of heavily infected individuals in all age groups. It also shows that infection really starts occurring between the ages of 7 and 13 years and remains similar afterwards. This is consistent with the usually observed increase in intensity and prevalence of infection in teenagers followed by a plateau.[1,32] Again, this age difference is most likely due to differences in the frequency of water contacts but could also be linked to puberty.[7,36]

Despite the advantages outlined above, there are a number of limitations to our analysis within the specific context of the Leyte example. First, we have assumed misclassification occurs only between egg classes 1 and 2, although the model could be extended to allow more complex misclassification error mechanism. This choice was based on the experience that, in parasitological analysis, identifying a few eggs is always more challenging than counting several eggs. However, there may still be some errors between the other categories of egg counts, even though we believe that these would be minor. In a study on *Schistosoma mansoni* conducted in Burundi, it was clearly shown that the estimates of prevalence of moderate and heavy infections remained very similar when stools were sampled at days 1, 3, 5, 8, 10, 32, and 37, whereas the cumulative prevalence of light infection increased from 29.5% in Day 1 to 45.9% in Day 37.[37] Second, our estimation of the pattern of heterogeneity between communities is based on information from only three villages and makes the assumption that these villages represent the range of prevalences and intensities that would be found in the field. The villages were sampled based on the judgment of the principal investigator of the 1981 study (R.O.). Even though this was not a random sample, we believe our results represent a significant improvement over previous approaches in which all heterogeneity was ignored.

APPENDIX: DESCRIPTION OF OUR STATISTICAL MODEL

Let t_{ij} denote the true but unobserved egg category of individual j in age/gender stratum i (i.e., strata 1–3 and 4–6, respectively, categorize men and women in Age groups 1–3), and let $\boldsymbol{X}_{ij}$ denote the associated vector of individual-specific covariates, $i = 1, \ldots, 6, j = 1, \ldots, N_i$, where N_i is the number of subjects in stratum i. So, for example, an 8-year-old boy from Village 1 would be in age-gender stratum $i = 2$ with vector covariates age group = 2, gender = 0, and village = 0. The response variable can take one of four values 1, 2, 3, or 4 corresponding to epg = 0, $0 <$ epg ≤ 100, $100 <$ epg ≤ 800, and epg > 800, respectively. We model the probability (π_{ijk}) that individual j, stratum i, is in egg category k given their covariates values, X_{ij}, represented by

$$\pi_{ijk} = \Pr\{t_{ij} = k | \boldsymbol{X}_{ij}\}, i = 1, \ldots, I; j = 1, \ldots, N_i, k = 1, \ldots, 4$$

We use a hierarchical cumulative logit model[20–22] to directly model the cumulative probabilities,

$$q_{ijk} = \Pr\{t_{ij} > k | \boldsymbol{X}_{ij}\} = \sum_{k+1}^{4} \pi_{ijk}$$

where q_{ijk} denotes the probability that individual j, stratum i has egg load greater than that defined by category k. At the first level of our hierarchical model, we assume a linear model for the logit of these cumulative probabilities,

$$\text{logit}(q_{ijk}) = \log\left(\frac{q_{ijk}}{1 - q_{ijk}}\right) = \mu_{ij} - \theta_k \quad (1)$$

where the θ_k are such that $\theta_k > \theta_{k-1}$, k=1, . . , 4 and $\theta_0 = \infty$, and where μ_{ij} is the overall mean within each category. Because infection intensity varies with age, gender and village, at the second level of our hierarchical model, we set

$$\mu_{ij} = \alpha + \beta_a I_{\{age_{ij}=\alpha\}} + \gamma\, I_{\{sex_{ij}=female\}} + \delta_v I_{(village_{ij}=v)} \quad (2)$$

where $i = 1, \ldots, 6$; $a = 1,2,3$; $v = 1,2,3$; and $I_{f.j}$ is an indicator function that takes the value 1 if the logical expression in brackets is true, and zero otherwise. Age group 1 and Village 3 are taken as the baseline, giving $\beta_1 = 0$, $\delta_3 = 0$. As an example, the probability that the 8-year-old boy from Village 1 is at least lightly infected ($k > 1$) would be given by $\text{logit}^{-1}(\alpha + \beta_2 + \delta_1 - \theta_1)$.

Incorporating the misclassification error. Let y_{ij} denote the recorded (observed) egg category of individual j, stratum i, and Ψ and Φ the specificity and sensitivity of the Kato-Katz test, respectively. Modeling misclassification between categories 1 and 2, we have

$$\Pr\{y_{ij} = 1\} = \Pr\{y_{ij} = 1 | t_{ij} = 1\}\pi_{ij1} + P\{y_{ij} = 1 | t_{ij} = 2\}\pi_{ij2} = \Psi\pi_{ij1} + (1 - \Phi)\pi_{ij2} \quad (3)$$

$$\Pr\{y_{ij} = 2\} = \Pr\{y_{ij} = 2 | t_{ij} = 1\}\pi_{ij1} + P\{y_{ij} = 2 | t_{ij} = 2\}\pi_{ij2} = (1 - \Psi)\pi_{ij1} + \Phi\pi_{ij2} \quad (4)$$

$$\Pr\{y_{ij} = 3\} = \pi_{ij3} \quad (5)$$

$$\Pr\{y_{ij} = 4\} = \pi_{ij4} \quad (6)$$

Relaxing the proportional odds assumption. One way to incorporate non-proportional odds is to allow the cut points (θ_k) to vary with age. Specifically, we allow independent cut points θ_k^* ($k = 1,2,3$) for Age group 1 (0–6 years), where θ_2^* to ensure the model is identifiable. Consider individuals L and M. Under our model, the ratio of their respective odds of being in egg category greater than k is now a function of k and so varies across cumulative categories,

$$OR = \frac{\Pr\{t_{iL} > k\}/(1 - \Pr\{t_{iL} > k\})}{\Pr\{t_{iM} > k\}/(1 - \Pr\{t_{iM} > k\})} = \frac{\exp(\text{logit}(q_{iLk}))}{\exp(\text{logit}(q_{iMk}))} = \exp((\alpha + \delta_2 - \theta_k^*) - (\alpha + \beta_2 + \delta_2 - \theta_k)) = \exp(\theta_k - \beta_2 - \theta_k^*) \quad (7)$$

Prior distributions. As discussed in our "Materials and Methods" section, informative prior distributions are specified for Ψ and Φ, reflecting the available *a priori* knowledge.[9] in particular, we used

$$\Psi \sim Beta(72,4)$$

$$\Phi \sim Beta(52,44)$$

As these priors will not be significantly updated by our data, we assess the sensitivity of our results to alternative prior hypotheses reflecting more optimistic and more pessimistic views regarding the performance of the Kato-Katz test.[23] Specifically, the optimistic priors ($\Psi \sim Beta[100,1]$, $\Phi \sim Beta[55,30]$) reflect a view that the sensitivity has mean 0.65 and the specificity has mean 0.99. In contrast, the pessimistic priors ($\Psi \sim Beta[100,14]$, $\Phi \sim Beta[42,51]$) assume the sensitivity has mean 0.45 and the specificity has mean 0.86. These priors are displayed in Figure 1.

To complete the model specification, we assume diffuse $N(0,10^4)$ hyper-priors for each of the model unknowns: γ, α, δ_1, δ_2, β_1 and β_2. The cut-points are assumed *a priori* to be uniformly distributed over a wide range, bounded above or below (as appropriate) by zero to ensure the strict ordering $\theta_1 < \theta_2 < \theta_3$: $\theta_1, \theta_1^* \sim U[-10,0]$; $\theta_1, \theta_1^* \sim U[0,10]$.

Estimation. Inferences are based on the joint posterior distribution of the model unknowns,

$$p(\underline{\pi},\underline{\theta},\underline{\beta},\underline{\delta},\gamma,\alpha,\Phi,\Psi|\underline{y}) \propto p(\underline{y}|\underline{\pi},\Phi,\Psi)p(\underline{\pi}|\underline{\theta},\underline{\beta},\underline{\delta},\gamma,\alpha)\, p(\underline{\theta},\underline{\beta},\underline{\delta},\gamma,\alpha,\Phi,\Psi)$$

where $\underline{y} = \{y_{ij}\}$, $\underline{\pi} = \{\pi_{ijk}\}$, $\underline{\theta} = (\theta_1,\theta_3,\theta_1^*,\theta_3^*)$, $\underline{\beta} = (\beta_1,\beta_2)$, $\underline{\delta} = (\delta_1,\delta_2)$ and the likelihood function $p(\underline{y}|\underline{\pi},\Psi,\Phi)$ is given by

$$p(\underline{y}|\underline{\pi},\Phi,\Psi) = \prod_{i,j}\{(\Psi\pi_{ij1} + (1 - \Phi)\pi_{ij2})I_{\{y_{ij}=1\}} + ((1 - \Psi)\pi_{ij1} + \Phi\pi_{ij2})I_{\{y_{ij}=2\}} + \pi_{ij3}I_{\{y_{ij}=3\}} + \pi_{ij4}I_{\{y_{ij}=4\}}\}. \quad (8)$$

The resulting posterior distribution is analytically intractable and so we use Markov chain Monte Carlo (MCMC) methods, specifically the Gibbs sampler, to obtain samples from the marginal posteriors of the parameters.

Prediction. The primary aim of this analysis is to provide reliable and robust prediction of patterns of intensity by age and gender, adjusted for known misclassification error and the variability between villages (see below). One way to achieve this, and the approach taken in the current paper, is to empirically "mix" over villages when predicting from the model. Thus, at each iteration of the MCMC sampler, we draw village $v = 1$, 2, or 3 with equal probability and predict the intensity profile for a given age/gender stratum conditional on this drawn value of v. Averaging over iterations within a stratum provides the required predictions of the intensity profiles for that specific stratum. The latter incorporates appropriately the between-village variability in infection intensity—effectively we are integrating over the effect of village—without having to assume a specific distributional form for the between-village heterogeneity. If information were available on a greater number of villages, an alternative approach to that above would be to assume a random village effect with, say, a normal random effects distribution and at each iteration draw a new village effect from this random effects distribution. Again, within the Bayesian estimation framework, this elaboration could easily be incorporated. Such predictions also allow us to compare data the model predicts with the data that actually occurred. If our model fits well, these two sets of data (i.e., the real data set and predictions of future data from our model) should not be too different.

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REFERENCES

1. Ross AG, Yuesheng L, Sleigh AS, Yi L, Williams GM, Wu WZ, Xinsong L, Yongkang H, McManus DP, 1997. Epidemiologic features of *Schistosoma japonicum* among fishermen and other occupational groups in the Dongting Lake region (Hunan Province) of China. *Am J Trop Med Hyg 57:* 302–308.
2. Zhou X, Acosta L, Willingham AL III, Leonardo LR, Minggang C, Aligui G, Zheng F, Olveda R, 2002. Regional Network for Research, Surveillance and Control of Asian Schistosomiasis (RNAS). *Acta Trop 82:* 305–311.
3. Chitsulo L, Engels D, Montresor A, Savioli L, 2000. The global status of schistosomiasis and its control. *Acta Trop 77:* 41–51.
4. Leonardo RL, Acosta LP, Olveda RM, Aligui GDL, 2002. Difficulties and strategies in the control of schistosomiasis in the Philippines. *Acta Trop 82:* 295–299.
5. Blas BL, Tormis LG, Portillo LA. The schistosomiasis control component of the national system improvement project in Leyte, Philippines. Part III. An attempt to study the economic loss arising from *Schistosoma japonicum* infection. Proceedings of SEAMEO-TROPMED seminar. 13–16 June 1988. Surat Thani, Thailand.
6. Wu X-H, Wang T-P, Lu D-B, Hu H-T, Gao Z-B, Zhu C-G, Fang G-R, He Y-C, Mei Q-J, Wu W-D, Ge J-H, Zheng J, 2002. Studies of impact on physical fitness and working capacity of patients with advanced *Schistosoma japonica* in Susing County, Anhui Province. *Acta Trop 82:* 247–252.
7. McGarvey ST, 2000. Schistosomiasis: impact on childhood and adolescent growth, malnutrition, and morbidity. *Sem Pediatr Infect Dis 11:* 269–274.
8. He YX, Salafsky B, Ramaswamy K, 2001. Host-parasite relationships of *Schistosoma japonicum* in mammalian hosts. *Trends Parasitol 17:* 320–324.
9. Aligui GL, 1997. *Quantifying Human Schistosoma japonicum Infection and Exposure: Errors in Field Diagnosis and Uncertainties in Exposure Measurements*. PhD Thesis. Brown University, RI.
10. Yu JM, de Vlas SJ, Yuan HC, Gryseels B, 1998. Variations in fecal *Schistosoma japonicum* egg counts. *Am J Trop Med Hyg 59:* 370–375.
11. Blas BL, Bautista ES, Lipayon IL, 1990. *An Atlas on the Endemicity of Schistosomiasis japonica in The Philippines.* Manila, The Philippines: Schistosomiasis Control Service, Department of Health.
12. Olds GR, Olveda R, Wu G, Wiest P, McGarvey S, Aligui G, Zhang S, Ramirez B, Daniel B, Peters P, Romulo R, Fevidal P, Tiu W, Yuan J, Domingo E, Blas B, 1996. Immunity and morbidity in schistosomiasis japonicum infection. *Am J Trop Med Hyg 55* (*5 Suppl*): 121–126.
13. Anderson RM, May RM, 1989. Indirectly transmitted helminths. Anderson RM, May RM, eds. *Infectious Diseases of Humans: Dynamics and Control*. Oxford, UK: Oxford University Press, 550–589.
14. Neuhaus JM, 1999. Bias and efficiency loss due to misclassified responses in binary regression. *Biometrika 86:* 843–855.
15. Paulino CD, Soares P, Neuhaus J, 2003. Binomial regression with misclassification. *Biometrics 59:* 670–675.
16. McGarvey ST. 2002. NIH-funded "Ecology and transmission of Schistosomiasis japonica in the Philippines" project. *Ecology and Transmission of Schistosomiasis in the Philippines. Proceedings of a Stake Holders Meeting on an NIH-Supported Research Project*. Tacloban, Leyte, Philippines. 18–20 October 2001. Geneva: World Health Organization.
17. Olveda RM, Daniel BL, Ramirez BD, Aligui GD, Acosta LP, Fevidal P, Tiu E, de Veyra F, Peters PA, Romulo R, Domingo E, Wiest PM, Olds GR, 1996. Schistosomiasis japonica in the Philippines: the long-term impact of population-based chemotherapy on infection, transmission, and morbidity. *J Infect Dis 174:* 163–172.
18. Montresor A, Crompton DWT, Bundy DAP, Savioli L, 1998. *Guidelines for the Evaluation of Soil-Transmitted Helminthiasis and Schistosomiasis at Community Level. A Guide for Managers of Control Programmes*. Geneva: World Health Organization. WHO/CTD/SIP/98.1.
19. Ye XP, Donnelly CA, Anderson RM, Fu YL, Agnew A, 1998. The distribution of *Schistosoma japonicum* eggs in faeces and the effect of stirring faecal specimens. *Ann Trop Med Parasitol 92:* 181–185.
20. Ananth CV, Kleinbaum DG, 1997. Regression models for ordinal responses: a review of methods and applications. *Int J Epidemiol 26:* 1323–1333.
21. Agresti A, Natarajan R, 2001. Modeling clustered ordinal categorical data: a survey. *Int Stat Rev 69:* 345–371.
22. Lunn DJ, Wakefield J, Racine-Poon A, 2001. Cumulative logit models for ordinal data: a case study involving allergic rhinitis severity scores. *Stat Med 20:* 2261–2285.
23. Rubin DB, 1987. *Multiple Imputation for Non-Response Survey*. New York: John Wiley & Sons.
24. Spiegelhalter DJ, Freedman LS, Parmar MKB, 1994. Bayesian approaches to randomized trials. *J R Stat Soc Ser A Stat Soc 157:* 357–416.
25. Gilks W, Spiegelhalter DJ, Richardson SR, 1996. *Markov Chain Monte Carlo in Practice*. London: Chapman and Hall.
26. Spiegelhalter DJ, Thomas A, Best NG, 2000. WinBUGS version 1.3. Available at http://www.mrc-bsu.cam.ac.uk/bugs/.
27. McGarvey S, Zhou XN, Willingham AL, Feng Z, Olveda R, 1999. The epidemiology and host-parasite relationships of *Schistosoma japonicum* in definitive hosts. *Parasitol Today 15:* 214–215.
28. Joseph L, Gyorkos TW, Coupal L, 1995. Bayesian estimation of disease prevalence and the parameters of diagnostic tests in the absence of a gold standard. *Am J Epidemiol 141:* 263–272.
29. Hubbard A, Liang S, Maszle D, Qiu D, Gu X, Spear RC, 2002. Estimating the distribution of worm burden and egg excretion of *Schistosoma japonicum* by risk group in Sichuan Province, China. *Parasitology 125:* 221–231.
30. Pouedet MS, Zoli AP, Nguekam JP, Vondou L, Assana E, Speybroeck N, Berkvens D, Dorny P, Brandt J, Geerts S, 2002. Epidemiological survey of swine cysticercosis in two rural communities of West-Cameroon. *Vet Parasitol 106:* 45–54.
31. Frossling J, Bonnett B, Lindberg A, Bjorkman C, 2003. Validation of a *Neospora caninum* iscom ELISA without a gold standard. *Prev Vet Med 57:* 141–153.
32. Workshop WHO, 1980. Quantitative aspects of the epidemiology of *Schistosoma japonicum* infection in a rural community of Luzon, Philippines. *Bull World Health Organ 58:* 629–638.
33. McGarvey ST, Aligui G, Daniel B, Peters P, Olveda R, Olds GR, 1992. Child growth and schistosomiasis japonica in Northeastern Leyte, The Philippines: cross-sectional results. *Am J Trop Med Hyg 46:* 571–581.
34. Tiglao TV, Camacho AC, 1983. Water contact behaviour among humans in Leyte, Philippines. *Southeast Asian J Trop Med Public Health 14:* 18–24.
35. Li Y, Sleigh AC, Williams GM, Ross AGP, Li Y, Forsyth SJ, Tanner M, McManus DP, 2000. Measuring exposure to *Schistosoma japonicum* in China. III. Activity diaries, snail and human infection, transmission ecology and options for control. *Acta Trop 75:* 279–289.
36. McGarvey ST, Aligui G, Kurtis JD, Willingham AL III, Carabin H, Olveda R, 2004. Multidisciplinary perspectives on *Schistosoma japonicum*. In Mascie-Taylor N, Peters J, McGarvey ST, eds. *The Changing Face of Disease: Implications for Society.* New York: Taylor & Francis, 114–129.
37. Engels D, Sinzinkayo E, Gryseels B, 1996. Day-to-day egg count fluctuation in *Schistosoma mansoni* infection and its operational implications. *Am J Trop Med Hyg 54:* 319–324.