Emerging Patterns of Hookworm Infection: Influence of Aging on the Intensity of *Necator* Infection in Hainan Province, People's Republic of China

Jeffrey Bethony,[1] Jizhang Chen,[2] Shaoxiong Lin,[2] Shuhua Xiao,[3] Bin Zhan,[1,3] Shangwen Li,[2] Haichou Xue,[3] Fuying Xing,[2] Debbie Humphries,[4] Wang Yan,[1] Grace Chen,[1] Virginia Foster,[1] John M. Hawdon,[1] and Peter J. Hotez[1]

[1]George Washington University, Washington, D.C.; [2]Hainan Institute of Parasitic Diseases, Haikou, and [3]Institute of Parasitic Diseases, Chinese Academy of Preventive Medicine, Shanghai, China; and [4]Yale University School of Medicine, New Haven, Connecticut

We examined risk factors associated with *Necator americanus* infection among persons aged ⩾50 years in Hainan Province, People's Republic of China. Age and sex made the most important contributions to the variation in infection intensity (28%–30%), with age alone responsible for 27% of this variation. When stratified by 20-year age intervals, the influence of shared residence was 23% for persons aged ⩾50 years and 27% for those aged <20 years, who had the highest and lowest levels of infection intensity, respectively. This points to shared residence as a means of capturing the complex relationship between aging and shared socioeconomic, environmental, and behavioral factors that influence transmission of *Necator* infection. None of the other 26 personal or 32 household risk factors were found to be significant. The importance of aging in *Necator* infection reveals an emerging public health problem among the elderly population of developing countries.

Human hookworm infection is endemic in the People's Republic of China [1, 2]. According to the Chinese nationwide parasite survey, in which examinations of fecal specimens were conducted for 1,477,742 persons in all provinces during 1988–1992, 194 million cases of hookworm infection were estimated to have occurred [1, 3]. This nationwide survey found that the South

China Sea island province of Hainan had the highest prevalence of hookworm infection in the People's Republic of China (60%) [4]. Data obtained in 1997 and 1998 from South China indicate that infection remains endemic [2, 5–9]. A 1998 survey of the prevalence and intensity of *Necator* hookworm infection in Hainan Province confirmed the high prevalence of infection, with *Necator americanus* found to be the predominant hookworm [9].

Increasing evidence suggests that *N. americanus* infections in humans exhibit distinct epidemiological patterns from infections with other soil-transmitted helminthiases [10, 11]. The prevalence and intensity of infection with *Ascaris* and *Trichuris* species typically peak during middle and late childhood [12]. This pattern has provided the justification for anthelminthic chemotherapy programs that target school-aged children (5–14 years of age). Although peak prevalence and intensity of infection for hookworm still occur among children in many tropical areas [13, 14], we report an emerging pattern of infection among elderly persons in

Hainan province, where peak prevalence and infection intensities occur in persons aged ⩾50 years.

PATIENTS AND METHODS

Study sample. The village of Daocong is located on the north of Hainan Island. Eight hundred eight persons were registered with the Daocong Village administration. District public health revealed that Daocong had not had a deworming program since 1979. A survey given at the time of study recruitment revealed that 50 persons had received treatment for helminthic infection from private sources within the past 5 years. These persons were excluded from the analysis sample. Full participation was 67% (509 persons; figure 1). The 249 persons who did not participate in the study did not differ from study participants with regard to age $(P = .30)$, sex $(P = .35)$, occupation $(P = .43)$, or area of residence within the village $(P = .40)$.

The relationship between sex and age is shown in table 1. The mean age was 31.33 years (95% CI, 30–33 years) and ranged from 2 to 89 years. No significant difference $(P = .24)$ was found between the mean age of female subjects (32.57 years; 95% CI, 29.90–35.23 years) and the mean age of male subjects (30.34 years; 95% CI, 27.70–32.97 years). The largest imbalance in the proportion of male to female subjects occurred in the 20–29-year interval, with 65% more female $(n = 41)$ than male subjects $(n = 25)$.

Of the residences, 127 (72%) had members who provided all of the parasitological, demographic, personal survey, and household survey data. The households included in the analysis ranged in size from 1 to 9 inhabitants, with a mean of 4.01 persons per household (95% CI, 3.69–4.32; table 2). Nearly two-thirds (83 households [65%]) of the households included ⩾4 inhabitants.

Table 3 shows selected covariates from a 27-item instrument, which was administered to each participant; proxy responses for the individual surveys were accepted by parents for children aged <6 years. Table 3 also shows the selected effects for a 36-item household survey administered to the principal male or female resident of the household. The largest occupational group was agricultural worker (67% of persons), followed by secondary school student (21% of persons), primary school student (11% of persons), and non–agricultural worker (1% of persons). Forty-three percent of persons lived in households with latrines. The most common crops grown by households in the study area were rice (98% of households) and vegetables (95% of households). Chemical fertilization predominated, with 93% of persons residing in household reporting its use, followed by use of cattle dung (54%). Only 5% of persons lived in households that reported use of night soil (i.e., human feces). Most houses grew crops for subsistence (56%), with a large percentage (42%) growing them for commercial use. There were many reports of indiscriminate defecation, especially of defecation around the "peridomestic environment" (56% of persons).

All research was performed in accordance with the ethical standards of the Yale University Human Investigations Committee (protocol 10932), the Internal Review Board of the George Washington University Medical Center (protocol
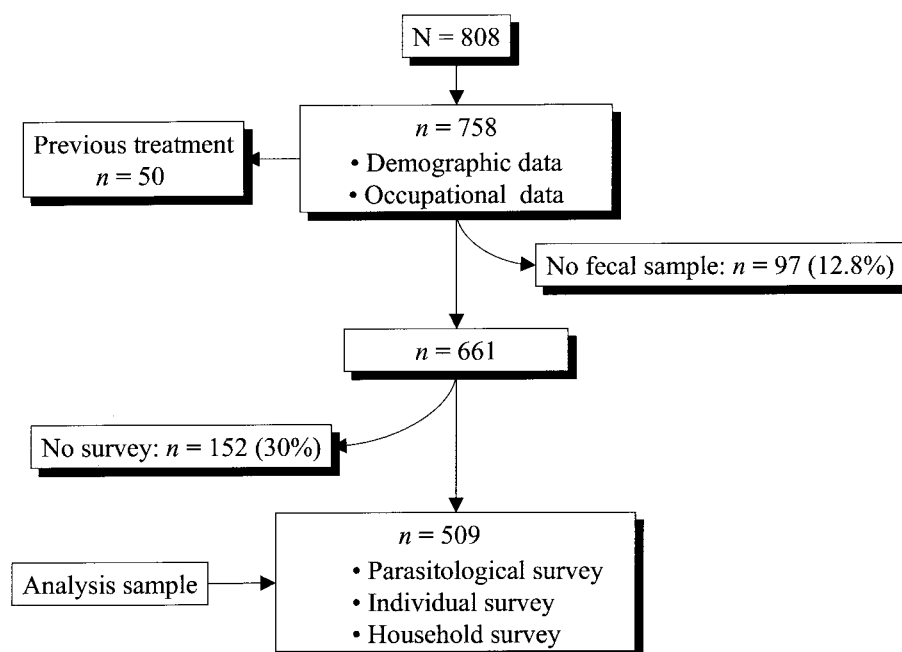
Figure 1. Assembly of study sample for study of hookworm infection in Daocong Village, Hainan Province, People's Republic of China

Table 1. Distribution of subjects by sex and by 10-year age intervals in study of hookworm infection, Daocong Village, Hainan Province, People's Republic of China, 1999 ($n = 509$).

Age, years	No. of subjects		
	Male	Female	Total
2–9	51	45	96
10–19	57	39	96
20–29	25	41	66
30–39	38	38	76
40–49	34	32	66
50–59	15	19	34
60–69	25	21	46
≥70	11	18	29

080004), and the Institute of Parasitic Diseases through a single project assurance from the National Institutes of Health.

Parasitological testing methods. Fecal samples were requested from all residents aged >2 years. The presence of intestinal nematode eggs was determined by saline float. For persons whose fecal sample tested positive, 3 subsequent fecal samples were obtained over the course of 3 days. Two slides from each day's fecal sample were prepared ≤24 h after receipt by use of the Kato-Katz thick smear technique [15]. Hookworm species *(Ancylostoma duodenale* or *N. americanus)* were determined by morphological identification of third-stage larvae reared from eggs by coproculture.

Statistical methods. Data were entered into a pedigree-based data management system, Pedigree Data Management System (PEDSYS) [16], which facilitated assembly of the household matrix needed for the variance-components analysis of shared residence. To meet the required normal distribution for the variance-components analysis, we logarithmically (ln) transformed the variable egg count per gram (epg) of feces plus 1 (ln epg). The $\ln(x+1)$ transformation normalized the variable, markedly reducing the kurtosis (-1.493 ± 0.216) and the skewness (0.172 ± 0.108). The variable "ln epg" was used in all subsequent statistical analysis.

Student's *t* test was used to determine significant differences in mean values for normally distributed continuous variables for 2 independent effects. Analysis of variance was used to test the mean differences of continuous variables when an effect consisted of >1 group (e.g., 10-year age intervals). Bonferroni post hoc tests, with a significance level of .05, were used for multiple testing. A χ^2 test was used to test the significance of proportions of persons with positive and negative results of tests for the presence of eggs. A Pearson product moment correlation was used for all correlations.

A variance-component analysis was used to test the effects of covariates and shared residence on fecal egg counts during

Necator infection. Detailed development of the variance-component method [17–20] is outlined in the Appendix. Special reference to the use of this method for estimating the effects of shared residence on intensity of helminthic infection has been described elsewhere [20]. All analyses were done with the sequential oligogenic linkage analysis routines (SOLAR) general variance-component analysis package [21, 22].

RESULTS

The relationships between age and prevalence of infection and between age and intensity of infection were different for each of the soil-transmitted helminthic infections examined. The proportion of infected persons positive for hookworm eggs was 56% (95% CI, 51%–60%; $n = 285$) and peaked in the ≥80-year-old age group (86%; 95% CI, 72%–99%; $P < .001$). Figure 2 shows that male and female subjects had similar patterns of *Necator* prevalence by 10-year age intervals. The highest prevalence was observed in the oldest women and men, with a significantly higher ($P = .02$) proportion of women (61%) than men (50%) testing positive for eggs. Figure 3 shows that, in contrast to the intensity of *Necator* infection, the peak intensity for *Ascaris* infection (665; 95% CI, 109–1220) and *Trichuris* infection (242; 95% CI, 242–363) occurred during the first decade of life (1–9 years of age).

The mean egg count per gram of stool for *Necator* infection in the sample was 971 (95% CI, 639–1304). The range of egg counts was 24–66,432 epg. Again, the peak egg counts occurred among persons in the oldest age intervals. Female subjects (1332 epg; 95% CI, 724–1939 epg) had significantly ($P = .034$) higher egg counts than did male subjects (615 epg; 95% CI, 340–890 epg). Analysis of variance showed that egg counts were significantly different ($P < .001$) among the age intervals and that the 4 oldest age intervals were significantly different ($P < .05$) from the younger age intervals but not different from each other.

Table 2. Distribution of subjects by household in a study of hookworm infection, Daocong Village, Hainan Province, People's Republic of China, 1999 ($n = 509$).

Size of household, no. of persons	No. of households	No. of persons
1	9	9
2	23	46
3	12	36
4	37	148
5	23	115
6	14	84
7	5	35
9	4	36
Total	127	509

Table 3. Selection of individual ($n = 509$) and household ($n = 127$) risk factors for *Necator* infection, Daocong Village, Hainan Province, People's Republic of China, 1999.

| Variable	Value
Individual data, no. (%) of subjects	
Occupation[a]	
Agriculture	341 (67)
Secondary school student	107 (21)
Primary school student	61 (12)
Place of defecation	
Household latrine	219 (43)
Public latrine	56 (11)
Household's agricultural fields	209 (41)
Neighboring agricultural fields	25 (5)
Peridomestic environment	285 (56)
Neighboring peridomestic environment	31 (6)
Method of feces disposal	
No method	504 (99)
Wash away feces	41 (8)
Hand washing after defecation[a]	
Never	280 (55)
Wash with soap	229 (45)
Frequency of wearing footwear outdoors[a]	
Never	214 (42)
Sometimes	173 (34)
Usually	61 (12)
Always	25 (5)
No response	36 (7)
Kind of footwear worn outdoors	
Slippers	402 (79)
Open-toed sandals	117 (23)
Cloth shoes	15 (3)
Household data, no. (%) of households	
Contains latrine	229 (45)
Crops grown	
Rice	499 (98)
Vegetables	484 (95)
Sugar cane	341 (67)
Sweet potatoes	280 (55)
Fruit	280 (55)
Fertilizer used	
Chemical	473 (93)
Animal dung	275 (54)
Combination	56 (11)
Human feces	25 (5)
Household economy	
Subsistence	285 (56)
Commercial	214 (42)
Subsistence and commercial	10 (2)

[a] Mutually exclusive categories.

Similar patterns were seen in the relationship between age and intensity of infection in both sexes.

Figure 4 depicts the linear relationship between intensity of infection and age ($r = .62$; $P = .001$) for persons whose stool specimens tested positive for eggs, and table 4 presents the variance-components analysis of age and sex on infection intensity for a series of 5 nested models. The models are as follows: (1) sporadic, (2) sex, (3) age, (4) age and sex, and (5) age, sex, and the interaction term sex by age (sex × age). The "sporadic" model of variation incorporates only the contribution of random effects. Models 2–5 retain this effect and introduce an effect due to the specified covariate(s). The sex (model 2) and age (model 3) models were significantly better than the sporadic model, with sex accounting for 2% ($P = .003$) and age accounting for 27% ($P < .0001$) of the variation in ln epg. The inclusion of the terms age and sex together were significantly better than the sex ($P < .001$) or age models ($P = .006$), accounting for 29% of the variation in infection intensity. Finally, the addition of the interaction term (sex × age) accounted for 30% of the variation in egg counts and significantly improved the model ($P = .0019$). We also estimated the effects of models with age included as 10-year age classes represented by ordinal, nonquantitative variables and 10-year age class represented by a series of binary (0/1) dummy variables (data not shown). These 2 methods did not lead to different results when age was used as a continuous variable.

Formal likelihood-ratio tests for the effect of shared household on intensity infection are outlined in table 5. A significant effect was found for shared residence (model 1), with 16% of the variation in egg counts due to residence in the same house. Model 2 shows the effects of shared residence on egg counts when the sample is stratified by sex: nearly identical proportions of variation (16%) were observed for female and male subjects ($P = .026$ and $P = .031$, respectively). Model 3 shows the effects of shared residence when the sample is stratified by 20-year age categories. A substantial (27%) and significant ($P < .001$) effect for shared residence was found among persons aged <20 years. Similarly, a substantial (23%) and significant ($P = .0204$) effect for shared residence was found for persons aged ≥50 years. No significant differences in the variation of infection intensity were found for such traditional variables as defecation practices or footwear use, even though 42% claimed never to wear footwear outdoors.

DISCUSSION

The World Health Organization estimates that ~2 billion people worldwide are infected with soil-transmitted helminths and that ~300 million experience severe morbidity caused by high worm burdens [23]. School-aged children are considered the group most at risk for the morbidity associated with soil-transmitted
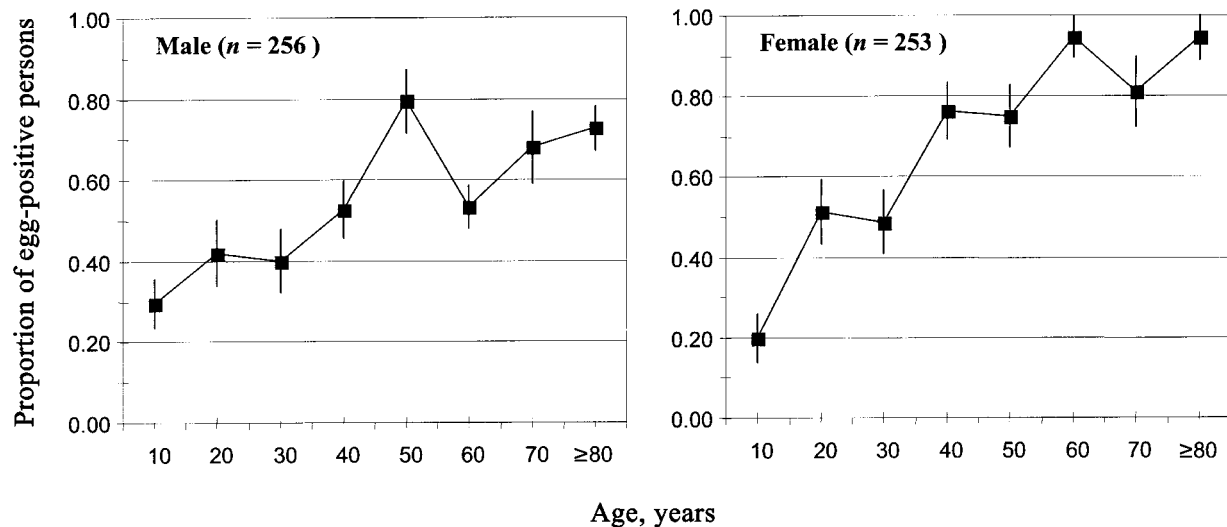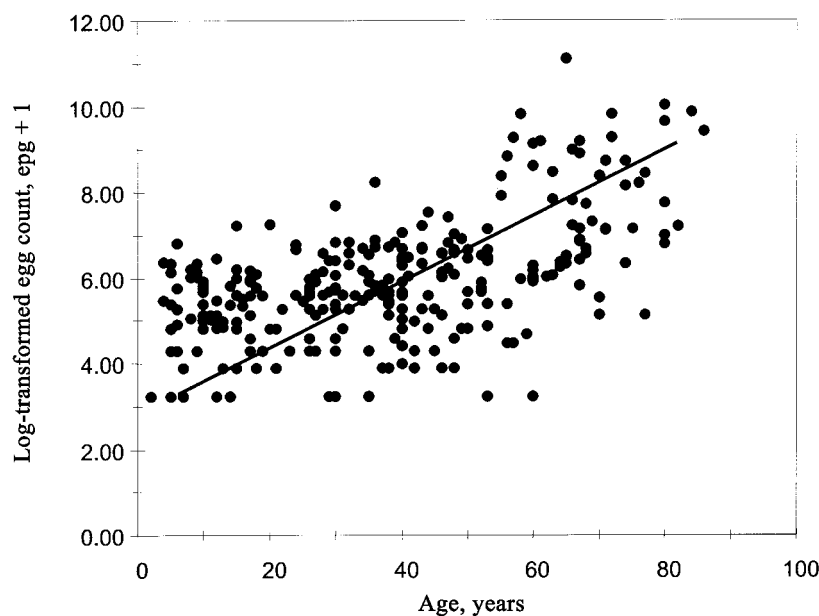
Figure 2. Relationship between proportion of persons whose stool specimens tested positive for hookworm eggs and 10-year age intervals, by sex, Daocong Village, Hainan Province, People's Republic of China ($n = 509$).

helminthiases. Chronic infections with soil-transmitted helminths during childhood result in stunting of linear growth [13, 24, 25], reduced physical fitness [26, 27], lower educational achievement [28], slowed mental development, and impaired cognitive function [29]. On the basis of these observations, the World Health Organization has designed simple and comprehensive guidelines to reduce the impact of soil-transmitted helminthiases, which include the recommendation of regular administration of anthelminthic chemotherapy among children aged 5–14 years [30].

An increasing body of evidence, however, suggests that the hookworms no longer exhibit age distributions similar to those of the other major soil-transmitted helminths (*Ascaris* and *Trichuris* species) [10, 11]. *Ascaris* and *Trichuris* worm burdens typically peak in school-aged children and decrease in adulthood [12]. In contrast, although childhood hookworm infection and clinical hookworm disease remain a pediatric problem in some regions [13, 14, 24–26, 31], our data used a variance-component method to show that hookworm infection prevalence and intensity rates increase with age, with elderly patients
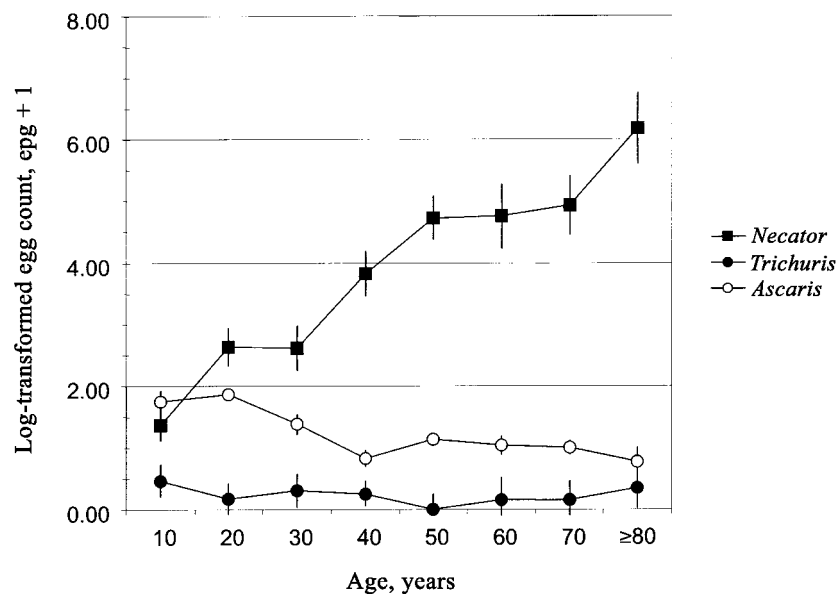
Figure 3. Relationship between age and infection intensity for *Necator, Ascaris,* and *Trichuris* infection, Daocong Village, Hainan Province, People's Republic of China. Bars indicate SEs for each age interval ($n = 509$). epg, Eggs per gram of feces.

Figure 4. Relationship between age in years and log-transformed egg counts (eggs per gram of feces [epg]) for persons whose stool specimens tested positive for eggs, Daocong Village, Hainan Province, People's Republic of China (*n* = 285). Diagonal line indicates trend line from least squares regression.

having the highest prevalence and intensity of infection in areas of endemicity. Especially striking is the strong correlation (r = .62; P = .001) between age and egg counts shown in figure 4. Similar patterns for infection have been observed areas where *N. americanus* is endemic in China [6, 9] and Southeast Asia [32].

The association between increasing age and increasing prevalence and intensity of infection reveals an important public health problem for developing countries, because the elderly population is seldom mentioned as a group at high risk for either infection or the consequent morbidity associated with high worm burdens. As such, we wanted to quantify the extent to which age affected the variation in *Necator* infection intensity and to identify risk factors associated with aging and high levels of infection. The study's strength was the use of a variance-components methodology [17] to accomplish this task. The variance-component approach is highly flexible, and virtually any aspect of exposure than can be articulated and measured

Table 4. Maximum likelihood estimates to determine proportion of variance in log-transformed egg counts per gram of feces during *Necator* infection in series of nested models, Daocong Village, Hainan Province, People's Republic of China, 1999.

Model	β	Proportion (SE)	Log-transformed likelihood	χ^2	P
Model 1: sporadic	—	—	−853.940	—	—
Model 2: sex	.839	.02 (.03)	−849.658	8.56	.003
Model 3: age	.061	.27 (.03)	−805.590	96.57	<.001
Model 4					
Sex	.772	.29 (.04)	−801.764	95.79	<.001[a]
Age	.060			7.65	.006[b]
Model 5					
Sex	.720	.30 (.04)	−796.924	9.68	.002[c]
Age	.043	—	—	—	—
Sex × age	.043	—	—	—	—

[a] Compared with model 2.
[b] Compared with model 3.
[c] Compared with model 4.

Table 5. Maximum likelihood estimate of proportion of variance in log-transformed egg counts due to shared residence, stratified by sex and age, Daocong Village, Hainan Province, People's Republic of China, 1999 ($n = 509$).

Household model	n	Proportion (SE)	Log-transformed likelihood	χ^2	P
Model 1: household	509	.16 (.05)	−845.338	16.50	<.001
Model 2					
Male	246	.16 (.07)	−417.500	4.98	.026
Female	253	.16 (.08)	−426.968	4.48	.031
Model 3					
<20	192	.27 (.08)	−341.289	11.32	.001
15–49	208	.15 (.07)	−411.847	4.46	.034
≥50	106	.23 (.07)	−281.056	5.37	.020

can be modeled and its effect size on the dependent variable evaluated. Moreover, the variance-components method gives an unbiased estimation of the size of each effect modeled, enabling us to rank the importance of an effect in terms of its contribution to the total variance. For example, variance-components analysis has been used to study the effect of common sibship environments (e.g., sharing parents) or common parent-offspring environments in some genetic studies. Environmental measures based on distance between households or cohabitation history have also been investigated [33–37]. In the present study, our specification of household (**H**) represents a simple aggregate measure of shared residence in a single dwelling, in addition to the more specific aspects of shared physical environment (e.g., fertilizer used) that are investigated.

In the present study, variance-components analysis revealed that age and sex made the most important contributions to infection intensity (28%–30%), with age alone responsible for 27% of this variation. The significance of a model that includes the product term sex × age (model 5) points to the statistical interaction between these 2 effects on the variation in infection intensity and, thus, to a possible biological interaction between aging and sex on *Necator* egg counts (e.g., hormones).

Other studies have found a similar relationship between aging and *Necator* infection, especially in Asia [6, 9, 32]. To our knowledge, ours is the first study to have identified individual or household risk factors, including shared residence, that may contribute to the association between aging and infection intensity. Shared residence accounted for 16% of the variance in egg counts (table 5). Interestingly, when stratified by 20-year age intervals, the proportion of variation due to shared residence was 23% for persons aged ≥50 years and increased to 27% for those aged <20 years. These are the age groups in the sample with the heaviest and lightest infection, respectively. The strong household aggregation among members of these age groups may indicate a number of shared risk factors not captured by the current survey instrument, such as similar hygienic behavior or defecation practices.

None of the covariates from the individual or household survey contributed significantly to variation in infection intensity. Even traditional risk factors for hookworm infection were not found to be significant. Although 42% of persons claimed not to wear footwear outdoors, there was no significant difference in the rate of hookworm infection between those who wore footwear outdoors and those who did not. The use of night soil did not influence hookworm transmission. However, in contrast to other parts of China [2], night soil is not widely used as a fertilizer, as it is in the Sichuan Province of the People's Republic of China or in Vietnam [6, 32, 38].

The influence of aging on the prevalence and intensity of *Necator* infection has important public health consequences. The morbidity associated with hookworm infection is not just related to the number of worms in a host, but also to "the duration of infection and to the background health status of the host" [30, p. 281]. The nutritional and background health statuses of elderly persons in developing countries are often poor [39], which makes these persons vulnerable to the morbidity associated with chronic and heavy hookworm infection. Furthermore, although developing countries are experiencing an unprecedented growth in the size of their elderly populations [40], those countries are still plagued with the diseases of the developing world [41, 42]. Our observation of increased prevalence and intensity of *Necator* infection in the elderly population of Daocong Village points to 1 such example and the need for further study into the reasons for this emerging pattern of infection.

APPENDIX

VARIANCE-COMPONENT ANALYSIS FOR INFECTIOUS DISEASES

In brief (see [20] for detailed explanation), let $y = (y_1, \ldots, y_n)$ denote the vector of quantitative trait values for a collection

of n persons. In a model of multivariate normality [18] for the trait vector $\boldsymbol{y}$ the logarithm (ln) likelihood l of the sample is given by $l = -\frac{n}{2}\ln(2\pi) - \frac{1}{2}\ln|\boldsymbol{\Sigma}| - \frac{1}{2}(\boldsymbol{y}-\boldsymbol{\mu})'\boldsymbol{\Sigma}^{-1}(\boldsymbol{y}-\boldsymbol{\mu})$, where $\boldsymbol{\mu}$ and $\boldsymbol{\Sigma}$ are, respectively, the mean and variance-covariance matrix for $\boldsymbol{y}$. Covariate effects are introduced by modeling the trait mean vector as $\boldsymbol{\mu} = \boldsymbol{\gamma} + \boldsymbol{A\beta}$, where $\boldsymbol{\gamma}$ is the overall trait mean; $\boldsymbol{A}$ is an $n \times m$ design matrix for the trait whose n rows contain m covariates, such as age, sex, and any other demographic, socioeconomic, physical environmental, or behavioral indices for each individual; and $\boldsymbol{\beta}$ is an m-vector of regression coefficients for the selected covariates.

The covariance matrix $\boldsymbol{\Sigma}$ depends on the specific effects and interactions to be modeled. In general, $\boldsymbol{\Sigma}$ takes the form $\boldsymbol{\Sigma} = \sum_j \boldsymbol{\Omega}_j \sigma_j^2$, where the parameter σ_j^2 is a scalar variance-component and $\boldsymbol{\Omega}_j$ is the corresponding structuring matrix representing the expected pattern of covariation. Minimally, $\boldsymbol{\Sigma}$ must contain a term reflecting random, individual-specific environmental variation. This "sporadic" model can be written $\boldsymbol{\Sigma} = \boldsymbol{I}\sigma_e^2$, where $\boldsymbol{I}_n$ is the $n \times n$ matrix and σ_e^2 is the variance due to random, individual-specific environmental effects. Additional environmental factors are expected to be important, however. For example, the contribution of shared household to variation in the dependent variable can be modeled by introducing the term $\boldsymbol{H}$ (household), where $\boldsymbol{H}$ is a matrix whose ij-th element $h_{ij} = 1$ if individuals i, j live in the same house and $h_{ij} = 0$ otherwise. The associated parameter σ_h^2 represents the variance in the dependent variable that is attributable to the effect specified by $\boldsymbol{H}$. The total trait covariance for this "household" model is then $\boldsymbol{\Sigma} = \boldsymbol{H}\sigma_h^2 + \boldsymbol{I}\sigma_e^2$

The statistical significance of any modeled effect is tested by comparing the likelihood L_0 of the null model in which the effect is absent with the likelihood L_1 of a model in which the effect is estimated. Under standard conditions, the likelihood ratio statistic $\lambda = -2\ln(L_0 - L_1)$ is asymptotically distributed as a χ^2 variable with degrees of freedom equal to the difference in the number of free parameters between the 2 models. With variance-component models, however, the likelihood-ratio test is often made under nonstandard conditions—some parameters may fail to exist under the null hypothesis, or some parameters have their true value under the null hypothesis on a boundary of the parameter space defined by the alternative hypothesis. In these cases, the distribution of the likelihood ratio statistic under the null hypothesis is a complex mixture of χ^2 distributions, with mixing proportions determined by the geometry of the parameter space [19]. All analyses were done with the sequential oligogenic linkage analysis routines (SOLAR) general variance-component analysis package [21, 22].

References

1. Hotez PJ, Feng Z, Xu LQ, et al. Emerging and reemerging helminthiases and the public health of China. Emerg Infect Dis **1997**; 3:303–10.

2. Hotez PJ. China's hookworms. China Quarterly (in press).

3. Yu SH, Xu LQ, Jiang ZX, et al. Special report, nationwide survey of human parasites in China. Southeast Asian J Trop Med Public Health **1994**; 25:4–10.

4. Xu LQ, Yu SH, Jiang ZX, et al. Soil-transmitted helminthiases: nationwide survey in China. Bull World Health Organ **1995**; 73:507–13.

5. Sun FH, Wu ZX, Qian YX, et al. Epidemiology of human intestinal nematode infections Wujiang and Pizhou Counties, Jiangsu Province, China. Southeast Asian J Trop Med Public Health **1998**; 29:605–10.

6. Liu CH, Zhang XR, Qiu DC, et al. Epidemiology of human hookworm infections among adult villagers in Hejiang and Santai Counties, Sichuan Province, China. Acta Trop **1999**; 73:243–9.

7. Wang Y, Shen GG, Wu WT, et al. Epidemiology of human ancylostomiasis among rural villagers in Nanlin County (Zhongzhou Village), Anhui Province, China: age-associated prevalence, intensity, and hookworm species identification. Southeast Asian J Trop Med Public Health **1999**; 30:692–7.

8. Zhan LL, Zhang BX, Tao H, et al. Epidemiology of human geohelminth infections (ascariasis, trichuriasis and necatoriasis) in Lushui and Puer Counties, Yunnan Province, China. Southeast Asian J Trop Med Public Health **2000**; 31:448–53.

9. Gandhi NS, Chen JZ, Koshnood K, et al. Epidemiology of *Necator americanus* hookworm infections in Xiulongkan Village, Hainan Province, China: high prevalence and intensity among middle-aged and elderly residents. J Parasitol **2001**; 87:739–43.

10. Bundy DAP. Is hookworm just another geohelminth? In: Schad GA, Warren KS, eds. Hookworm disease: current status and new directions. London: Taylor and Francis, **1990**:147–64.

11. Chan MS, Bradley M, Bundy DA. Transmission patterns and the epidemiology of hookworm infection. Int J Epidemiol **1997**; 26:1392–400.

12. Anderson RM. Mathematical models in the study of the epidemiology and control of acariasis in man. In: Crompton DWT, Nesheim MC, Pawlowski ZS, eds. Ascariasis and its public health significance. London: Taylor & Francis, **1985**:39–67.

13. Stephenson LS, Latham MC, Kurz KM, Kinoti SN, Brigham H. Treatment with a single dose of albendazole improves growth of Kenyan schoolchildren with hookworm, *Trichuris trichiura,* and *Ascaris lumbricoides* infection. Am J Trop Med Hyg **1989**; 41:78–87.

14. Labiano-Abello N, Canese J, Velazquez JM, Hawdon JM, Wilson ML, Hotez PJ. Epidemiology of hookworm infection in Itagua, Paraguay: a cross sectional study. Mem Inst Oswaldo Cruz **1999**; 94:583–6.

15. Katz N, Chaves A, Pelligrino JP. A simple device for quantitative stool thick-smear technique in *Schistosoma mansoni.* Rev Inst Med Trop Sao Paulo **1972**; 14:397–400.

16. Dyke B. PEDSYS. PGL technical report no. 2. San Antonio, TX: Southwest Foundation for Biomedical Research, **1989**.

17. Searle SR, Casella G, McCulloch CE. Variance components. New York: John Wiley & Sons, **1992**.

18. Lange K. Cohabitation, convergence, and environmental covariances. Am J Med Genet **1986**; 24:483–91.

19. Hopper JL, Mathews JD. Extensions to multivariate normal models for pedigree analysis. Ann Hum Genet **1982**; 46:373–83.

20. Bethony J, Williams JT, Kloos H, et al. Exposure to *Schistosoma mansoni* infection in a rural area in Brazil. II: Household risk factors. Trop Med Int Health **2001**; 6:136–42.

21. Almasy L, Blangero J. Multipoint quantitative-trait linkage analysis in general pedigrees. Am J Hum Genet **1998**; 62:1198–211.

22. Blangero J, Almasy L. Multipoint oligogenic linkage analysis of quantitative traits. Genetic Epidemiol **1997**; 14:959–64.

23. World Health Organization. 107th Session of WHO's executive board. Available at: http://www.who.int/inf-pr-2001/en/pr2001-03.html.

24. Hotez PJ. Hookworm disease in children. Pediatr Infect Dis J **1989**; 8:516–20.

25. Hotez PJ. Pediatric geohelminth infections: trichuriasis, ascariasis, and hookworm infections. Semin Pediatr Infect Dis **2000**; 11:236–44.

26. Stephenson LS, Latham MC, Kinoti SN, Kurz KM, Brigham H. Improvements in physical fitness of Kenyan schoolboys infected with

hookworm, *Trichuris trichiura* and *Ascaris lumbricoides,* following a single dose of albendazole. Trans R Soc Trop Med Hyg **1990**; 84:277–82.

27. Smilie WG, Augustine DL. Hookworm infestation: the effect of varying intensities on the physical condition of school children. Am J Dis Child **1926**; 31:151–68.

28. Montresor A, Ramsan M, Chwaya HM, et al. School enrollment in Zanzibar linked to children's age and helminth infections. Trop Med Int Health **2001**; 6:227–31.

29. Drake LJ, Jukes MCH, Sternberg RJ, Bunday DAP. Geohelminth infections (ascariasis, trichuriasis, and hookworm): cognitive and developmental impacts. Semin Pediatr Infect Dis **2000**; 11:245–51.

30. Albonico M, Crompton DW, Savioli L. Control strategies for human intestinal nematode infections. Adv Parasitol **1999**; 42:277–341.

31. Nawalinski TA, Schad GA, Chowdhury AB. Population biology of hookworms in children in rural West Bengal. I. General parasitological observations. Am J Trop Med Hyg **1978**; 27:1152–61.

32. Humphries DL, Stephenson LS, Pearce EJ, The PH, Dan HT, Khanh LT. The use of human feces for fertilizer is associated with increased intensity of hookworm infection in Vietnamese women. Trans R Soc Trop Med Hyg **1997**; 91:518–20.

33. Astemborski JA, Beaty TH, Cohen BH. Variance components analysis of forced expiration in families. Am J Med Genet **1985**; 21:741–53.

34. Hopper JCP. Covariation between family members as a function of cohabitation history. Behav Genet **1983**; 13:459–71.

35. Hopper JL, et al. Genetic analysis of systolic blood pressure in Melbourne families. Clin Exp Pharmacol Physiol **1982**; 9:247–52.

36. Lange K. Cohabitation, convergence, and environmental covariances. Am J Med Genet **1986**; 24:483–91.

37. Clifford CA, et al. A genetic and environmental analysis of a twin family study of alcohol use, anxiety, and depression. Genet Epidemiol **1984**; 1:63–79.

38. Chang K. Studies on hookworm disease in Szechwan Province, West China. Am J Hyg Monogr Ser **1949**; 19:1–152.

39. Tucker KL, Buranapin S. Nutrition and aging in developing countries. J Nutr **2001**; 131:2417–23.

40. Howson CP. Perspectives and needs for health in the 21st century: 20th-century paradigms in 21st-century science. J Hum Virol **2000**; 3: 94–103.

41. Holden C. New populations of old add to poor nation's burdens. Science **1996**; 273:46–8.

42. Lloyd-Sherlock P. Population ageing in developed and developing regions: implications for health policy. Soc Sci Med **2000**; 51:887–95.