

## ACUTE DISEASE EPISODES IN A *WUCHERERIA BANCROFTI*-ENDEMIC AREA OF PAPUA NEW GUINEA

NEAL D. E. ALEXANDER, ROBERT T. PERRY, ZACHARY B. DIMBER, PHILLIP J. HYUN, MICHAEL P. ALPERS, AND  
JAMES W. KAZURA

*Papua New Guinea Institute of Medical Research, Goroka and Maprik, Papua New Guinea;  
Case Western Reserve School of Medicine, Cleveland, Ohio*

**Abstract.** Acute disease episodes of Bancroftian filariasis were monitored prospectively in a rural area of Papua New Guinea. The frequency and duration of episodes were recorded for the leg, arm, scrotum, and breast. A very high incidence of acute disease was observed; 0.31 episodes per person-year in the leg alone. Incidence generally increased with age, except in the breast, where episodes were concentrated in the reproductive age range. Males had slightly higher incidence than females in the leg and arm. Chronic disease was strongly associated with acute disease incidence in all locations. Microfilaremia had a statistically significant association with acute disease in the leg, arm, and breast, but not the scrotum. This study again demonstrates the high burden of acute manifestations of lymphatic filariasis, and provides new information on risk factors, which may lead to better understanding of etiology and control prospects.

Lymphatic filariasis is a disfiguring disease whose global prevalence is currently estimated as 2%,<sup>1</sup> with resultant annual morbidity estimated as four million disability-adjusted life years.<sup>2</sup> Chronic and acute disease manifestations affect the limbs, breasts, genitals, and other parts of the body.<sup>3</sup> The acute form of disease typically involves lymphadenitis and lymphangitis, known collectively as adenolymphangitis. Most studies have been single cross-sectional surveys, so 'what has happened before patients are seen is largely unknown, and what will happen subsequently also remains speculative.'<sup>4</sup> This is particularly true for acute disease because, by definition, the symptoms are of shorter duration and therefore less likely to be identified during a cross-sectional survey. This led the World Health Organization to recognize that 'Longitudinal observations should be carried out to yield further insight into the natural history of filarial infection and disease.'<sup>5</sup>

Acute filarial disease can prevent normal activities and be totally incapacitating.<sup>6,7</sup> In an area of intense infection and transmission of Bancroftian filariasis,<sup>8,9</sup> we are longitudinally monitoring acute episodes as part of a randomized drug trial.<sup>10</sup> This is done prospectively at a local level throughout the study area. In addition to the fundamental epidemiologic information which this provides, annual surveys allow us to evaluate clinical and parasitologic risk factors for acute disease. This paper describes the results of the initial pretreatment year.

### MATERIALS AND METHODS

**Study population.** The study was conducted in part of Urat and Urim census districts in a rural area of East Sepik Province, Papua New Guinea. The epidemiologic and entomologic characteristics of the study area have been described elsewhere.<sup>8,9</sup>

**Ethical approval.** The study was approved by Medical Research Advisory Committee of Papua New Guinea, and by the Institutional Review Board of University Hospitals of Cleveland. Informed consent was obtained from all adult participants, and from parents or guardians of minors.

**Recording of morbidity through village reporter system.** A proforma questionnaire for community-based record-

ing of acute morbid episodes was written in Melanesian Pidgin (the local lingua franca), including questions on swelling of the leg, groin, arm, armpit, scrotum, and breast. Episodes were included in the analysis only if fever occurred in addition to swelling. We did not expect recall to be accurate to within one day, so, for each anatomic location, the form contained four questions on swelling that day, the previous day, the day before that, and any other day in the previous week.

The form was administered by local people employed as full time reporters. To help maintain compliance and confidence in the work, each reporter was selected from a shortlist drawn up by the community where they would work. Each reporter's schedule involves visiting each person in their area once a week, according to a map indicating their daily schedule. To record the actual coverage, each reporter has a reporter book, which is a bound computer printout detailing everyone in their area. The reporter books are replaced every four weeks to update demographic variables such as births, deaths, and change of residence. Each person in the book has a box for each of the four weeks, where the reporter indicates whether or not they were interviewed, and, if so, whether or not they were sick in the previous week. If they were sick, the reporter then completes a morbidity questionnaire. We have disregarded data from the initial training period, and the current report covers the year from June 1, 1993 to May 31, 1994.

Comparison of the acute morbidity results with microfilarial counts and chronic disease status is based on the second annual cross-sectional survey of those at least 5 years of age, which was done in 1994,<sup>10</sup> and was the first to cover all the villages in which baseline morbidity surveillance was done.

**Statistical methods.** Disease incidence rates were analyzed by Poisson regression, with the empirical scale factor being used to inflate standard errors and confidence intervals, to allow for excess variability.<sup>11,12</sup> This can be used for single variable analysis, or to adjust for confounding by fitting multivariable models.

### RESULTS

Morbidity surveillance was done on 2,500 person-years occurring in the calendar year from June 1, 1993. A total of

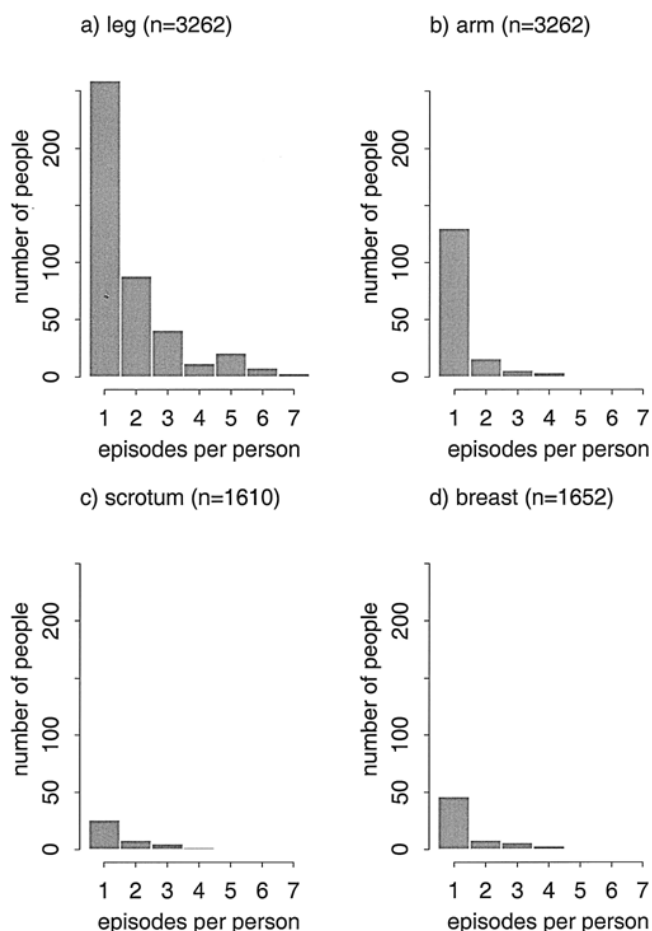


FIGURE 1. Number of acute episodes per person, over one calendar year, in **a**, leg, **b**, arm, **c**, scrotum, and **d**, breast.

3,262 people were interviewed: 1,610 males and 1,652 females. Episodes involving the groin were pooled with those involving other parts of the leg. Thus, some episodes involve both symptoms, although such concurrence was rare. Without pooling, single-symptom episodes followed similar patterns. Episodes involving the arm and armpit were pooled in a similar way. Figure 1 shows the number of episodes per person for the different anatomic locations. Most people did not report any episodes (87% even for the leg, which was the most common location). Among those with any episodes, most reported only one.

Figure 2 shows the duration of the episodes for the different anatomic locations. Consecutive reports of acute disease were assumed to refer to a single episode if the interval was no more than two weeks. Most episodes lasted no more than one week, although the distribution was skewed, with a few episodes lasting much longer. The leg was by far the most common anatomic location, accounting for 69% of all episodes. The mean duration of episodes involving the arm or breast was about a week: those involving the leg or scrotum lasted an average of about two and a half weeks.

Tables 1–4 show the acute episodes broken down by age group, sex, chronic disease, and microfilarial intensity. In each of these four tables, the first set of columns gives the number of episodes and the number of person-years of surveillance for each category of each risk factor, together with

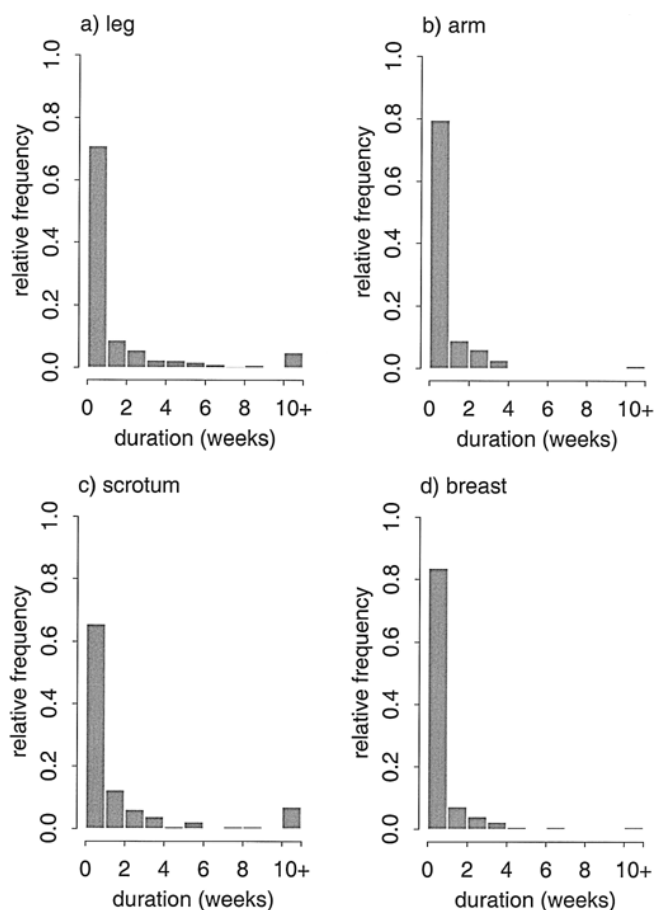


FIGURE 2. Duration of acute episodes in **a**, leg, **b**, arm, **c**, scrotum, and **d**, breast. The numbers of episodes by site are 780, 196, 65, and 92, respectively. The mean durations are 2.3, 1.1, 2.8, and 1.0 weeks, respectively.

the resulting incidence rate. The second set of columns are raw univariate rate ratios with 95% confidence intervals calculated as described above. The third set of columns are the rate ratios and confidence intervals from a multivariable regression model including all potential risk factors in the table. Those less than five years of age cannot be included in the multivariable model because they were not examined during the cross-sectional survey. Rate ratios of incidence in the leg and arm are calculated relative to the youngest age group; however, since there were very few such episodes at that age in the scrotum or breast, these rate ratios are calculated relative to an adult age group.

Acute episodes in the leg (Table 1) increased with age; rapidly at first, before levelling off and finally decreasing slightly. Males had a slightly higher incidence than females. Incidence was also higher in those with microfilariae. Chronic disease was strongly associated with increased incidence, and its rate ratio was far larger than those of the other potential risk factors. The estimates from the multiple regression model follow a generally similar pattern to the raw rate ratios. Patterns of incidence in the arm (Table 2) are roughly similar to those in the leg, although the associations with chronic edema and microfilariaemia are stronger, and the peak incidence is at a younger age.

Incidence of acute disease in the scrotum (Table 3) also

TABLE 1  
Risk factors for acute episodes in the leg\*

	Episodes/person-years (incidence rate)	Raw incidence rate ratio (95% CI)	Adjusted† incidence rate ratio (95% CI)‡
Age (years)			
0–9.99	85/813 (0.10)	1	1
10–19.99	115/543 (0.21)	2.03 (1.35–3.04)	1.49 (0.93–2.41)
20–29.99	170/434 (0.39)	3.74 (2.57–5.46)	2.34 (1.48–3.72)
30–39.99	125/257 (0.49)	4.65 (3.12–6.93)	2.63 (1.62–4.28)
40–49.99	142/190 (0.75)	7.14 (4.84–10.55)	3.09 (1.90–5.03)
≥50	143/263 (0.54)	5.21 (3.53–7.69)	2.31 (1.43–3.75)
Sex			
Female	385/1,270 (0.30)	1	1
Male	395/1,231 (0.32)	1.06 (0.86–1.31)	1.38 (1.12–1.70)
Chronic disease‡			
Absent	446/1,796 (0.25)	1	1
Present	211/67 (3.14)	12.6 (10.2–15.6)	10.8 (8.55–13.6)
Microfilariae/ml‡			
None	208/849 (0.25)	1	1
1–999	264/591 (0.45)	1.82 (1.38–2.40)	1.35 (1.06–1.72)
≥1,000	168/363 (0.46)	1.89 (1.39–2.56)	1.59 (1.20–2.09)
Total	780/2,500 (0.31)		

\* CI = confidence interval.

† Using a Poisson multiple regression model with the four explanatory variables in the table.

‡ Based only on those people examined in the cross-sectional survey.

increases with age, although without a decrease at the highest values. As in the other tables, chronic disease has the strongest effect on incidence, but the effect of microfilaremia is weaker. Incidence in the breast (Table 4) showed a different age pattern to that in the other anatomic locations, with a peak in the reproductive ages. Chronic disease was again the strongest risk factor, but there was also a strong positive association with microfilaremia.

The regression models shown in Tables 1–4 do not include interactions between risk factors, some of which help shed light on the disease process. In the arm and scrotum,

there were statistically significant interactions between age and microfilarial density ( $P = 0.023$  and  $P = 0.0015$ , respectively). The peak of acute disease incidence occurred at a younger age in microfilaremic individuals than in amicrofilaremic ones. A similar pattern was seen in the leg, although the differences were not statistically significant. This suggests that heavier infections lead initially to higher incidence of acute disease, but eventually induce a reaction that reduces the incidence more effectively at higher ages than in those people with lighter infections. No interactions except between age and microfilarial density were significant

TABLE 2  
Risk factors for acute episodes in the arm\*

	Episodes/person-years (incidence rate)	Raw incidence rate ratio (95% CI)	Adjusted incidence rate ratio (95% CI)†
Age (years)			
0–9.99	34/813 (0.04)	1	1
10–19.99	21/543 (0.04)	0.92 (0.48–1.78)	1.16 (0.47–2.88)
20–29.99	48/434 (0.11)	2.64 (1.56–4.48)	2.58 (1.12–5.95)
30–39.99	42/257 (0.16)	3.90 (2.27–6.73)	4.45 (1.93–10.3)
40–49.99	26/190 (0.14)	3.27 (1.77–6.04)	2.12 (0.82–5.48)
≥50	25/263 (0.10)	2.28 (1.22–4.24)	2.52 (1.03–6.16)
Sex			
Female	93/1,270 (0.07)	1	1
Male	103/1,231 (0.08)	1.14 (0.81–1.62)	1.17 (0.81–1.70)
Chronic disease†			
Absent	129/1,856 (0.07)	1	1
Present	13/7 (1.77)	25.5 (13.6–47.9)	19.1 (9.87–37.0)
Microfilariae/ml†			
None	27/849 (0.03)	1	1
1–999	70/591 (0.12)	3.72 (2.27–6.09)	2.78 (1.71–4.54)
≥1,000	39/363 (0.11)	3.37 (1.95–5.82)	2.42 (1.40–4.17)
Total	196/2,500 (0.08)		

\* CI = confidence interval.

† Based only on those people examined in the cross-sectional survey.

TABLE 3  
Risk factors for acute episodes in the scrotum\*

	Episodes/person-years (incidence rate)		Raw incidence rate ratio (95% CI)	Adjusted incidence rate ratio (95% CI)†
Age (years)				
0–9.99	4/424	(0.01)	0.10 (0.03–0.36)	0.38 (0.06–2.34)
10–19.99	3/272	(0.01)	0.12 (0.03–0.48)	0.18 (0.03–1.02)
20–29.99	10/192	(0.05)	0.56 (0.22–1.44)	0.51 (0.18–1.42)
30–39.99	11/118	(0.09)	1	1
40–49.99	14/88	(0.16)	1.71 (0.71–4.09)	0.51 (0.18–1.43)
≥50	23/136	(0.17)	1.81 (0.82–4.02)	1.05 (0.45–2.48)
Chronic disease†				
Absent	12/805	(0.01)	1	1
Present	42/95	(0.44)	29.8 (13.8–64.2)	17.5 (7.67–39.9)
Microfilariae/ml†				
None	10/388	(0.03)	1	1
1–999	20/282	(0.07)	2.75 (0.96–7.85)	1.18 (0.49–2.87)
≥1,000	19/199	(0.10)	3.70 (1.28–10.7)	1.05 (0.43–2.62)
Total	65/1,231	(0.05)		

\* CI = confidence interval.

† Based only on those people examined in the cross-sectional survey.

in the leg, arm or scrotum. In the breast, that interaction was not significant, but the two involving chronic disease were significant. More specifically, the excess incidence in those with chronic disease was greater in the middle age groups, and also at higher microfilarial densities. This may indicate that the development over time of acute pathology in the breast is subject to influences, such as lactation, not pertaining elsewhere.

Comparing the four anatomic locations, acute disease incidence generally increased with age, sometimes with a decrease in the highest ages. However, in the breast, acute disease was strongly concentrated in the reproductive ages. Incidence in the arm and leg was roughly similar in the two sexes, but slightly higher in males. In all four anatomic locations, acute episodes were more frequent in those people with coincident chronic disease: this was the factor with the greatest excess risk, and the most statistically significant. The relationship with microfilarial density is more compli-

cated, being dependent on age, and somewhat different in the four locations. However, in general, microfilaremia is positively associated with acute disease.

Finally, if episodes are defined only in terms of swelling, without requiring concurrent fever, then febrile episodes make up roughly two-thirds of the total (Table 5). Episodes in the breast were the most likely to include fever, and those in the scrotum the least likely. If the above analysis is done on the broader definition of acute disease, the results are generally similar but the associations with chronic disease and microfilaremia are slightly weaker.

#### DISCUSSION

Acute disease is one of the major burdens of lymphatic filariasis, but understanding of its epidemiology has been hindered by a lack of pertinent studies.<sup>5</sup> Its short-term episodic morbidity requires prospective community-based sur-

TABLE 4  
Risk factors for acute episodes in the breast\*

	Episodes/person-years (incidence rate)		Raw incidence rate ratio (95% CI)	Adjusted incidence rate ratios (95% CI)†
Age (years)				
0–9.99	0/389	(0.00)	0.00 (0.00–22.4)	0.00 (0.00–498)
10–19.99	12/271	(0.04)	0.22 (0.11–0.46)	0.29 (0.13–0.66)
20–29.99	43/242	(0.18)	0.88 (0.52–1.48)	0.87 (0.50–1.52)
30–39.99	28/139	(0.20)	1	1
40–49.99	5/102	(0.05)	0.24 (0.09–0.68)	0.19 (0.07–0.54)
≥50	4/126	(0.03)	0.16 (0.05–0.49)	0.19 (0.06–0.61)
Chronic disease†				
Absent	55/908	(0.06)	1	1
Present	32/55	(0.58)	9.59 (5.66–16.3)	7.27 (4.42–12.0)
Microfilariae/ml†				
None	22/461	(0.05)	1	1
1–999	35/309	(0.11)	2.37 (1.18–4.77)	2.16 (1.20–3.88)
≥1,000	28/165	(0.17)	3.57 (1.71–7.42)	3.69 (1.96–6.96)
Total	92/1,270	(0.07)		

\* CI = confidence interval.

† Based only on those people examined in the cross-sectional survey.

TABLE 5  
Number (%) of episodes with fever\*

	Location				Total
	Leg	Arm	Scrotum	Breast	
Fever present	780 (64.9)	196 (60.9)	65 (50.8)	92 (74.8)	1,133 (63.9)
Fever absent	421	126	63	31	641
Total	1,201	322	128	123	1,774

\* Fever data were missing for three episodes in the leg and one in the arm.

veillance, which has not been done for Bancroftian filariasis until recently in India<sup>13</sup> and Ghana.<sup>14,15</sup> In addition, one study has been done of Brugian filariasis,<sup>16</sup> although it only included a subset of the population at risk. Some other studies have been based on recall of clinic patients.<sup>6,17</sup> The most important contribution of the current study is the estimation of risks associated with microfilarial density and chronic disease.

The fact that our data were collected by people with no medical qualifications, after only a few weeks training, warrants a critical review. Adenolymphangitis has several possible causes, such as cuts or other lesions in extremities distal to the inguinal and axillary nodes. Its specificity as a sign of filariasis has been questioned,<sup>18</sup> and we did record a large number of episodes in people who tested negative for microfilaremia. As in other studies, we cannot reasonably expect all the observed episodes to be ultimately filarial in etiology. On the other hand, microfilarial density was positively associated with acute disease incidence in the leg, arm and breast. Moreover, Kar and others<sup>19</sup> observed microfilaremia status to change during the course of an acute attack, leading them to hypothesize that filarial adenolymphangitis could be an inflammatory response to parturition of adult female worms.

The incidence is high compared with those in most other studies, in particular the 0.1 episodes per person-year found in India<sup>13</sup> and Ghana,<sup>14</sup> but comparable with the 0.37 per person-year in a *Brugia malayi*-endemic area.<sup>16</sup> These differences will be partly due to differences in episode definitions. For example, we did not require episodes to last at least three days, as was done in Ghana as part of World Health Organization criteria.<sup>14</sup> Therefore, given the high intensity of infection<sup>8</sup> and transmission<sup>9</sup> in this area, the rate of 0.31 episodes per person-year in the leg alone is not anomalously large. The restriction of each reporter's work to their own home district introduced a confounding with other spatial factors such as transmission intensity, and is undoubtedly a weakness of the study. A design in which each reporter worked in different areas at different times would have been less prone to bias. This would, for example, have tended to even out any differences in response rates resulting from differences in the reporters' communication skills. However, the large distances to cover on foot, and the likely resistance of the population to giving rather intimate information to strangers, would have made this impossible to implement in practice. Moreover, maps of acute disease (Alexander N, unpublished data) do not show excessively pronounced changes in incidence at reporter area boundaries. There were more episodes at the start of the year, which may have been partly due to initial enthusiasm and curiosity among those participating in the study. However, there is no

reason to believe that this introduced a bias among the risk factors examined. It has been suggested that acute episodes may be precipitated by infective mosquito bites.<sup>14</sup> However, to investigate such a relationship in the present study would require a complicated analysis, taking account of temporal autocorrelations and the spatial distribution of the entomologic surveillance sites.

The most basic feature of acute filarial disease in this study is its very high frequency. This area of Papua New Guinea ranks as one of most heavily burdened by filariasis to be recorded, in terms of acute disease as well as transmission and microfilarial density. The tendency of acute disease incidence in the leg, arm, and scrotum to increase with age is similar to the overall patterns found previously.<sup>13,14</sup> The slightly higher incidence in males is similar to that found by Ramaiah and others,<sup>13</sup> in contrast to the much higher incidence in females found by Gyapong and others.<sup>14</sup> As far as we are aware, this study is the first to provide controlled estimates of the risks for acute disease associated with chronic disease. The two major previous studies measured chronic disease only in those with acute disease. In our study, chronic disease is clearly a strong risk factor in all four anatomic locations considered. In contrast with the results of Gyapong,<sup>15</sup> we also found microfilaremia to be a risk factor. The explanation for this difference may lie in the tendency for acute disease to peak at younger ages in microfilaremic people. This means that the overall relationship between microfilaremia and acute disease could depend on the breakdown of the population by age and microfilarial density. On the other hand, the relative importance of bacterial etiology may differ between populations and between anatomic locations.

Among those people with acute disease, the number of episodes followed an approximately similar distribution in this study to that of Ramaiah and others.<sup>13</sup> Here, the number of such people with only one episode in the leg in a year's surveillance was 60%, as opposed to 64%. Gyapong and others<sup>14</sup> also found a generally similar pattern: although their data are presented slightly differently, the average number of episodes among affected individuals was 1.5. Thus, the greater morbidity burden in our study area is largely due to a greater prevalence of acute disease, rather than a greater number of episodes in those with the condition, and that in turn is presumably related to the greater prevalence of patent infection as measured by microfilaremia.

This work is part of a randomized trial of diethylcarbamazine (DEC) alone versus a combination of DEC and ivermectin.<sup>10</sup> We have already shown that the combination is superior in terms of one-year reduction in microfilarial density, and analysis of the post-treatment acute disease data should provide information on another important aspect of



the relative merits of the two regimens, and further indications of disease mechanisms. In addition, more intensive studies on changes in microfilaremia, antigenemia, immune responses, and clinical and bacteriologic aspects of secondary infections over the course of acute attacks are warranted. These would help quantify how much adenolymphangitis is of purely filarial etiology, and how much has other causes for which lymphatic damage may be a predisposing factor. More work is also needed to help establish the relative importance of immune responses, both reactive and tolerizing, inherited susceptibility, transmission intensity, and other postulated mechanisms such as parturition of adult worms.

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**Authors' addresses:** Neal D. E. Alexander, Infectious Disease Epidemiology Unit, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, Keppel Street, London, WC1E 7HT, United Kingdom. Robert T. Perry, Makerere University-Johns Hopkins University Research Collaboration, PO Box 23491, Kampala, Uganda. Zachary B. Dimber, Papua New Guinea Institute of Medical Research, PO Box 400, Maprik, East Sepik Province 533, Papua New Guinea. Phillip J. Hyun, 670 Alvarado, San Francisco, CA 94114. Michael P. Alpers, Papua New Guinea Institute of Medical Research, PO Box 60, Goroka, Eastern Highlands Province 441, Papua New Guinea. James W. Kazura, Division of Geographic Medicine, Case Western Reserve University School of Medicine, Room W137, 2109 Adelbert Road, Cleveland, OH 44106-4983.

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