Increasing Incidence of Post–Kala-Azar Dermal Leishmaniasis in a Population-Based Study in Bangladesh

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Post–kala-azar dermal leishmaniasis (PKDL) occurs after kala-azar treatment and acts as a durable infection reservoir. On the basis of active case finding among 22,699 respondents, 813 (3.6%) had had kala-azar since 2002, of whom 79 (9.7%) developed PKDL. Eight additional patients with PKDL had no history of kala-azar. Annual kala-azar incidence peaked at 85 cases per 10,000 person-years in 2004 and fell to 46 cases per 10,000 person-years in 2007, but PKDL incidence rose from 1 case per 10,000 person-years in 2002–2004 to 21 cases per 10,000 person-years in 2007. The rising PKDL incidence threatens the regional visceral leishmaniasis elimination initiative and underscores the urgent need for more effective PKDL diagnosis and treatment.

In South Asia, visceral leishmaniasis (VL; also called *kala-azar*) is caused by the protozoan parasite *Leishmania donovani* and is transmitted by female *Phlebotomus argentipes* sand flies; humans with VL form the only known infection reservoir [1]. The governments of Bangladesh, India, and Nepal are committed to an ambitious initiative to eliminate VL by 2015 [2]. However, no project to demonstrate proof of principle has been undertaken. Instead, the initiative assumes feasibility [2] based on the near elimination that occurred as a collateral benefit of indoor residual insecticide application during the Global Malaria Eradication Program in the 1950s and 1960s [3, 4]. The explosive VL resurgence that began in 1970 and that continues today calls into question the validity of this experience to support the feasibility of elimination [4, 5].

Patients with post–kala-azar dermal leishmaniasis (PKDL) are thought to have provided the durable infection reservoir that allowed the parasite to survive the malaria eradication era [3]. PKDL is a chronic maculopapular or nodular rash that occurs months to years after apparently successful kala-azar treatment [6]. Laboratory diagnosis of PKDL is challenging, and most cases are diagnosed on clinical grounds. Systematic incidence data are lacking in South Asia, but PKDL is reported to occur in 5%–10% of patients treated for kala-azar and occasionally in individuals with no history of kala-azar [7]. A study of 4 patients with nodular PKDL confirmed their ability to transmit infection to 53% of laboratory-reared sand flies [3]. Unlike kala-azar, which is ultimately fatal without treatment, PKDL is not usually associated with systemic illness, and patients can remain infectious for years or even decades [3, 6].

In Bangladesh, 20 million people (18% of the population) are considered to be at risk for VL, with 4000–9000 patients identified annually in facility-based surveillance [8]. Official figures are thought by most informed observers to be substantial underestimates [9]. We conducted a population-based survey to estimate kala-azar and PKDL incidence and identify risk factors for the development of PKDL after kala-azar treatment. To our knowledge, these data are the first population-based PKDL incidence data based on active ascertainment in the South Asia region and have important implications for the regional elimination program.

Methods. We conducted the survey in the Fulbaria subdistrict of the Mymensingh district in north-central Bangladesh. In recent years, this subdistrict has consistently reported the highest national kala-azar incidence [10]. From July 2007 to March 2008, we conducted a survey of all consenting households in 8 communities chosen on the basis of a high reported kala-azar incidence. The protocol was approved by the ethical review committees of the International Centre for Diarrhoeal Disease Research, Bangladesh, and the Centers for Disease Control and Prevention. After obtaining informed consent, we collected demographic data and used a structured questionnaire to ascertain past and current cases of kala-azar and PKDL with symptom onset since 2002. Data included month and year of kala-azar and PKDL symptom onset and treatment.

Study physicians examined persons with suspected kala-azar

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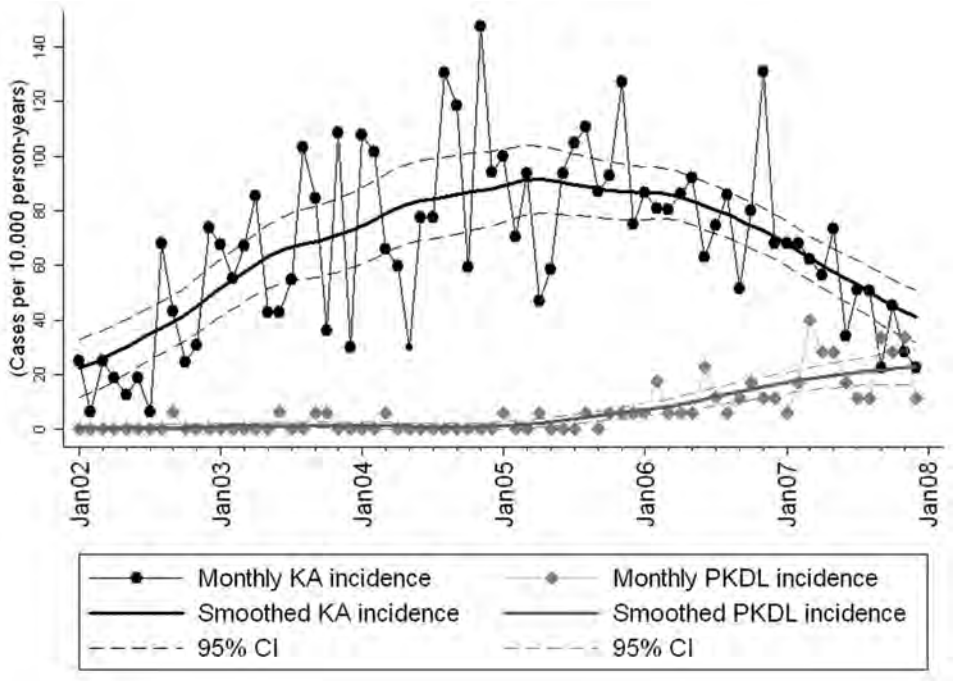

Figure 1. Scatterplot, smoothed curves, and 95% confidence intervals (CIs) for monthly kala-azar (KA) and post-KA dermal leishmaniasis (PKDL) incidence from 2002 through 2007 in a population of 22,699 residents of the Fulbaria subdistrict in Mymensingh, Bangladesh.

and PKDL who were symptomatic at the time of the survey and applied an rK39 rapid test (Kalazar Detect; InBios International), which was reported to have 97% sensitivity and 95% specificity for kala-azar in South Asia [11]. We defined past kala-azar as a febrile illness with weight loss and/or abdominal swelling, diagnosed by a physician and treated with an antileishmanial drug with resolution of symptoms. We defined current kala-azar as an illness with at least 2 weeks of fever plus skin darkening, weight loss, splenomegaly, and/or hepatomegaly as well as a positive rK39 result [12]. Past PKDL was defined as a macular, papular, or nodular rash lasting at least 1 month, diagnosed by a physician, and treated with sodium stibogluconate with resolution. Current Bangladesh national PKDL treatment guidelines call for 120 intramuscular injections of 20 mg/kg sodium stibogluconate daily in 20-day cycles with 10-day rest periods. Patients with a current rash lasting at least 1 month were examined by the study physician. For patients with findings consistent with PKDL, a slit skin specimen was collected from the most prominent lesion and placed in phosphate-buffered saline, and a 3-mL peripheral blood specimen was collected in ethylenediaminetetraacetic acid (EDTA). Because of logistical difficulties, specimens were collected only from a subset of patients. Polymerase chain reaction (PCR) was performed on slit skin and blood specimens. DNA was extracted from blood by means of a QIAamp DNA Mini kit (Qiagen), used in accordance with the manufacturer's instructions. Slit skin specimens underwent proteinase K digestion at 50°C for 60 min, followed by the same extraction method. DNA was amplified using a nested PCR targeting the small subunit ribosomal RNA of the *L. donovani* complex, following published methods [13].

Questionnaire data were double-entered, cross-checked for data entry errors, and cleaned by running logical cross-tabs and checking against questionnaires. We calculated monthly kala-azar and PKDL incidence with new cases in each month as the numerator and study population members present in that month as the denominator. Two-way scatterplots were used to show incidence over time. Local polynomial regression was used to obtain smoothed incidence curves and 95% confidence interval (CI) bands [14]. Risk factors were analyzed using the χ^2 and Wilcoxon rank sum tests. Analysis was performed using Stata statistical software, version 10.0 (StataCorp).

Results and discussion. The survey population totaled 22,699 members of 4553 households; 11,226 (49%) were male, and the median age was 20 years. A total of 813 study participants (3.6%) had kala-azar with symptom onset between 2002 and 2007; 783 (96.3%) were treated with sodium stibogluconate, whereas 30 (3.7%) were treated with miltefosine in a clinical trial in 2006–2007. Seventy-eight sodium stibogluconate–treated patients (9.9%) developed PKDL, with a median time from kala-azar onset to PKDL onset of 21 months (95% CI, 16.4–25.6 months). Eight additional patients with PKDL had no history of kala-azar. Slit skin and blood specimens were obtained from 10 patients with PKDL; 4 (40%) had positive

PCR results for *L. donovani*, 3 in both blood and slit skin specimens and 1 in blood only.

The median patient age at kala-azar onset was 13 years (95% CI, 11.6–14.4 years), compared with a median age of 20 years (95% CI, 19.7–20.3 years) for study participants without kala-azar ($P < .001$). Among patients who subsequently developed PKDL, the median age at the time of kala-azar onset was 11 years (95% CI, 7.3–14.7 years), compared with 14 years (95% CI, 12.5–15.5 years) for patients who did not develop PKDL ($P = .028$). Patients with kala-azar were more likely to be male than participants without kala-azar (60% vs 49%; $P < .001$), but there was no difference in sex between patients with kala-azar who did and did not develop PKDL ($P = .73$). No miltefosine-treated patient developed PKDL by the time of analysis; however, we lacked the statistical power to detect a difference by drug because of the small number of miltefosine-treated patients and their short follow-up time (mean, 9 months). The annual kala-azar incidence rose from 28 cases per 10,000 person-years in 2002 to a peak of 85 cases per 10,000 person-years in 2004 and then fell to 46 cases per 10,000 person-years in 2007 (Figure 1). By contrast, PKDL incidence increased steadily from 1 case per 10,000 person-years in 2002–2004 to 21 cases per 10,000 person-years in 2007.

From 2001 to 2006, a kala-azar epidemic occurred in this part of Bangladesh, fueled by antileishmanial drug scarcity, delayed treatment, and an almost complete absence of vector control [15, 16]. In our study population, the annual kala-azar incidence remained >80 cases per 10,000 person-years from 2004 to 2006, >80 times the elimination target of 1 case per 10,000 person-years. Earlier data from one of the current study communities demonstrated an evolution from a highly clustered epidemiology in 2001 to saturation of the community by kala-azar cases and subclinical leishmanial infections by 2004 [12, 17], suggesting that the fall to 46 cases per 10,000 person-years in 2007 reflects a natural cycle resulting from exhaustion of the susceptible population rather than the effect of deliberate interventions [18].

Of even greater concern is the recent sharp rise in PKDL incidence, because this condition, although not life-threatening to the individual, is far more difficult to diagnose and treat than kala-azar and represents a sustained infection reservoir. The difficulty of confirmatory diagnosis, especially in macular PKDL, limits the potential for sorely needed clinical treatment trials. Without new tools, PKDL may pose an insurmountable challenge to the elimination effort. The steep increase in PKDL occurrence can be considered an echo of the kala-azar epidemic; consistent with previous reports [7], 90% of PKDL cases occurred in patients treated for kala-azar. The median 21-month delay between kala-azar and PKDL is also consistent with earlier findings [6, 7] and suggests that the PKDL echo epidemic will continue for several more years. Indian investigators report lower numbers of patients with PKDL seen in hospitals since the early years of this decade as resistance to antimonial drugs has shifted treatment patterns to other antileishmanials. However, the information supporting this opinion consists of passive facility-based data and ecological comparisons, precluding firm conclusions about the role played by antimonial drugs in the pathogenesis of PKDL [19]. In our data, the 10% of patients with PKDL who did not have antecedent kala-azar demonstrates that antimonial exposure is not a necessary precondition. Unfortunately, our limited follow-up data for miltefosine-treated patients do not allow us to draw firm conclusions regarding risk. Nevertheless, the current regimen recommended by the Bangladesh national guidelines of 120 painful injections of sodium stibogluconate (a drug well known in VL-endemic communities for its toxicity) is neither practical nor acceptable to patients with PKDL. More effective, shorter-course treatment regimens and sensitive, point-of-care PKDL diagnostic testing adaptable to community-based active case finding are urgently needed to enable the regional VL elimination initiative to succeed.

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