The epidemiology of visceral leishmaniasis in Bangladesh: prospects for improved control

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The parasitic disease kala-azar (visceral leishmaniasis, VL) was first described in 1824 in Jessore district, Bengal (now Bangladesh). Epidemic peaks were recorded in Bengal in the 1820s, 1860s, 1920s, and 1940s. After achieving good control of the disease during the intensive vector control efforts for malaria in the 1950s-1960s, Bangladesh experienced a VL resurgence that has lasted to the present. Surveillance data show an increasing trend in incidence since 1995. Research in recent years has demonstrated the utility of non-invasive diagnostic modalities such as the direct agglutination test and rapid tests based on the immune response to the rK39 antigen. In common with its neighbours India and Nepal, VL in Bangladesh is anthroponotic. Living in proximity to a kala-azar case is the strongest risk factor for disease, while consistent use of bed nets in the summer months and the presence of cattle are protective. Shortages of first-line antileishmanial drugs and insecticide for indoor spraying programmes have hindered VL treatment and vector control efforts. Effective control of VL will require activities to improve availability and access to diagnostic testing and antileishmanial drugs, enhanced surveillance for kala-azar, post-kala-azar dermal leishmaniasis and VL treatment failures, and increased coverage and efficacy of vector control programmes.

Key words Epidemiology - PKDL - vector control - visceral leishmaniasis

Historical perspective

The parasitic disease kala-azar (visceral leishmaniasis) was first described in 1824, in Jessore district, Bengal in what is now Bangladesh1,2. Historical records describe the classical picture of kala-azar - prolonged irregular fever, progressive emaciation, and enlargement of the liver and spleen1. The disease spread west to other parts of Bengal (1830s-1850s), Dhaka district (1862), Rangpur in northern Bengal (1872), northeast into the Garo Hills of Assam (1872), and west into Bihar (1872)1. Kala-azar appeared to have spread along the courses of the Ganges and Brahmaputra rivers, the major transport routes2. In these early outbreaks, the case-fatality rate was reported to be >95 per cent, with community-wide mortality rates of >25 per cent. The epidemic that occurred in Jessore from 1824 to 1827 reportedly killed 75,000 people. The first affected village in Dhaka district is said to have disappeared from the map1.
At the turn of the 20th century, kala-azar occurred as far south as Tamil Nadu, where Charles Donovan was a British military medical officer. Early in 1903, Donovan in Madras and Leishman in London independently demonstrated the causative parasite in splenic tissue in autopsies from kala-azar patients infected in India.3,4 Donovan performed a splenic aspirate in a young Indian patient in Madras later in 1903, demonstrating the parasite for the first time in a living patient.5 Within a few months, Ronald Ross proposed the name *Leishmania donovani* for the newly discovered parasite, although other classifications were used as late as the 1920s. Vector-borne transmission was hypothesized from early in the 20th century. Experimental transmission of *L. donovani* by phlebotomine sand flies to animals was demonstrated in 1931.7 In 1942, Swaminath et al demonstrated *L. donovani* transmission by *Phlebotomus argentipes* to human volunteers, establishing this species of sand fly as the vector in South Asia.

The first 40 yr of the 20th century also saw a series of key discoveries in the diagnosis, treatment and control of visceral leishmaniasis. The aldehyde test was developed in 1921 and a complement-fixation test in 1939. Splenic puncture was used from the early decades of the 20th century. Antimonials were first introduced for South American mucocutaneous leishmaniasis in 1913 and for kala-azar in 1915. Early trivalent antimonials caused severe toxicity, but the introduction of several pentavalent antimonials between 1915 and 1939 resulted in a 95 per cent cure rate, and treatment regimens not very different from those used today in Bangladesh. DDT and pyrethrum were known to be effective for sand fly control by the 1940s. Indeed, all of the major components of a kala-azar control programme were available by the 1940s.

Visceral leishmaniasis in Bengal before and during the malaria eradication era, and its subsequent resurgence

Kala-azar epidemic peaks were recorded in Bengal in the 1820s, 1860s, 1920s, and 1940s.1,2,9 In the 1920s, the All-Bengal Kala-azar Conference listed the districts most affected by kala-azar based on dispensary records as Tangail (in 1919), Rajshahi, Jessore, Mymensingh, and Noakhali.9 Sengupta reviewed surveillance data for >1,000,000 kala-azar cases reported in Bengal from 1931-1943.10 At that time, the most affected districts included Rajshahi, Dinajpur, Jessore, Noakhali and Chittagong (in East Bengal), as well as Murshidabad and Malda (in West Bengal). A large upsurge of kala-azar cases in the 1940s included urban transmission in some neighborhoods of Calcutta.

An intensive control programme aimed at the eradication of malaria was mounted in the 1950s and 1960s throughout the South Asian subcontinent. The effort was based in large part on indoor residual spraying with DDT. The simultaneous drop in kala-azar incidence was widely seen as a collateral benefit.9 However, within a few years after the end of the eradication effort, kala-azar returned to Bihar and to Bengal on both sides of the border.12,13 Investigators hypothesized that patients with post-kala-azar dermal leishmaniasis (PKDL) provided the infection reservoir that initiated foci of resurgence after intensive vector control ended, a hypothesis supported by the demonstration that PKDL patients infected a high proportion of laboratory-reared sand flies fed on them.13

In Bangladesh, sporadic kala-azar cases were reported in the 1970s, and an outbreak occurred in Pabna district in 1980.14 There has been kala-azar transmission in Bangladesh every year since then.14 Surveillance data are lacking from this period, but in a series of 59 kala-azar patients reported from 1968-1980, cases were reported from at least 7 districts in Bangladesh.15 The districts most affected in the early 1980s were reported to have been Sirajganj, Pabna, Mymensingh, Rajshahi and Tangail.

Recent kala-azar surveillance data

From 1994 through 2004, a total of 73,467 kala-azar cases were reported to the Malaria and Vector-
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Table I. The cumulative reported incidence of kala-azar by district from 1994-2004. The Table lists the 19 districts that reported 100 or more kala-azar cases over the 11-year period. Five additional districts reported 10 - 99 cases, 7 districts reported 2 - 10 cases; and the remaining districts reported no cases of kala-azar. Source of data: Directorate General of Health Services, Government of Bangladesh

<table>
<thead>
<tr>
<th>District</th>
<th>N</th>
<th>Total (%)</th>
<th>Cumulative (%)</th>
<th>Annual rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mymensingh</td>
<td>28607</td>
<td>38.9</td>
<td>38.9</td>
<td>5.8</td>
</tr>
<tr>
<td>Pabna</td>
<td>10400</td>
<td>14.2</td>
<td>53.1</td>
<td>4.3</td>
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<tr>
<td>Tangail</td>
<td>7940</td>
<td>10.8</td>
<td>63.9</td>
<td>2.1</td>
</tr>
<tr>
<td>Jamalpur</td>
<td>5734</td>
<td>7.8</td>
<td>71.7</td>
<td>2.4</td>
</tr>
<tr>
<td>Sirajganj</td>
<td>3256</td>
<td>4.4</td>
<td>76.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Gazipur</td>
<td>3179</td>
<td>4.3</td>
<td>80.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Natore</td>
<td>2715</td>
<td>3.7</td>
<td>84.2</td>
<td>1.6</td>
</tr>
<tr>
<td>Naogaon</td>
<td>2126</td>
<td>2.9</td>
<td>87.1</td>
<td>0.8</td>
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<tr>
<td>Manikganj</td>
<td>1445</td>
<td>2.0</td>
<td>89.0</td>
<td>1.0</td>
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<td>Rajshahi</td>
<td>1300</td>
<td>1.8</td>
<td>90.8</td>
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<td>Nawabganj</td>
<td>1224</td>
<td>1.7</td>
<td>92.5</td>
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<tr>
<td>Thakurgaon</td>
<td>820</td>
<td>1.1</td>
<td>93.6</td>
<td>0.6</td>
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<tr>
<td>Panchagarh</td>
<td>796</td>
<td>1.1</td>
<td>94.7</td>
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<tr>
<td>Patuakhali</td>
<td>753</td>
<td>1.0</td>
<td>95.7</td>
<td>0.5</td>
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<tr>
<td>Dinajpur</td>
<td>730</td>
<td>1.0</td>
<td>96.7</td>
<td>0.3</td>
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<tr>
<td>Rajbari</td>
<td>618</td>
<td>0.8</td>
<td>97.5</td>
<td>0.6</td>
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<tr>
<td>Jhenaidaha</td>
<td>541</td>
<td>0.7</td>
<td>98.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Dhaka</td>
<td>491</td>
<td>0.7</td>
<td>98.9</td>
<td>0.06</td>
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<tr>
<td>Gaibandha</td>
<td>224</td>
<td>0.3</td>
<td>99.2</td>
<td>0.09</td>
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<tr>
<td>Narayanganj</td>
<td>131</td>
<td>0.2</td>
<td>99.4</td>
<td>0.06</td>
</tr>
<tr>
<td>Joypurhat</td>
<td>122</td>
<td>0.2</td>
<td>99.6</td>
<td>0.1</td>
</tr>
<tr>
<td>Bogra</td>
<td>118</td>
<td>0.2</td>
<td>99.7</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Mean number of kala-azar cases reported per 10,000 per year, based on estimated district population in 1998.

Although kala-azar cases were reported from 34 of Bangladesh’s 64 districts, more than 90 per cent of cases were reported from just 10 districts (Table I). Eleven districts reported >1,000 cumulative cases over the 11 yr period 1994-2004 (Fig. 2), while 6 reported 100-999, 5 reported 10-99, and 7 districts reported 2-9 kala-azar cases. From 1994 to 1996, Pabna district reported the highest annual number of kala-azar cases. From 1994 to 1996, Pabna district reported the highest annual number of kala-azar cases. From 1994 to 1996, Pabna district reported the highest annual number of kala-azar cases.

Fig. 1. Kala-azar cases reported by year in national surveillance data. (Source: Malaria and Vector-Borne Disease Control Unit, Directorate General of Health Services, Government of Bangladesh, Dhaka).
kala-azar cases. After 1996, the incidence in Mymensingh overtook that in Pabna, and has continued to rise since that time (Fig. 3). Every year from 2000 to 2004, Mymensingh accounted for more than 50 per cent of the total kala-azar cases reported in Bangladesh, and disease transmission in the district appears to be the major focus fueling a sustained epidemic.

Annual kala-azar incidence rates calculated using total district population as the denominator (Table I) are misleading, since not all thanas in an affected district report cases. In Mymensingh district, only 5 of 12 thanas reported kala-azar cases in recent years (Fig. 4). Using the population of the respective thana as the denominator, the incidence of kala-azar in Fulbaria thana ranged from 30 to 33/10,000/year since 2000, while that in Trishal, the next most affected thana, ranged from 21 to 26/10,000/year. Over the same period of time, the incidence in the other 3 endemic thanas, Bhaluka, Muktagacha, and Goforgaon, ranged from 5 to 15 cases/10,000/year. For the 5 endemic thanas of Mymensingh district, the mean annual reported incidence since 2000 was 17/10,000/year, compared to 8.3/10,000 when the total district population was used (Table I).

One international expert in the field estimates that the number of cases reported in surveillance data is likely to be at least a 5-fold underestimate (personal communication, P. Desjeux). Based on currently available information, it is not possible to assess the degree of underreporting with precision, nor the extent to which this varies from one district to
Fig. 3. Kala-azar cases reported by year from the 3 highest incidence districts. (*Source*: Malaria and Vector-Borne Disease Control Unit, Directorate General of Health Services, Government of Bangladesh, Dhaka).

Fig. 4. Cumulative kala-azar cases reported from 2000 to 2004 from 5 thanas of Mymensingh district. (*Source*: Office of the Civil Surgeon, Mymensingh District).
another. The estimate of 5-fold underreporting would imply that the true incidence of kala-azar in Bangladesh is closer to 40,000 to 45,000 per year. The area most affected by kala-azar in Bangladesh since 1994 has generally encompassed the center and the northwestern quarter of the country, with endemic districts reaching to the border with West Bengal; the estimated population at risk is said to be 20 million people. Nevertheless, both the recent surveillance data and the historical record clearly indicate that the area of potential risk for visceral leishmaniasis is much larger, stretching from Noakhali and Patuakhali on the Bay of Bengal to Chittagong in the southeast and the border with Assam in the north.

Research on visceral leishmaniasis in Bangladesh since 1990

Since 1990, more than 20 research articles on visceral leishmaniasis in Bangladesh have been published. More than half of the articles focus on applied laboratory issues, such as the development and implementation of better non-invasive diagnostic tests (Table II). The next most numerous set of articles describe case series of patients and address key clinical issues. Only a handful of studies addressed the epidemiology of the disease, and many key epidemiologic questions remain (Table III).

In the late 1980s and early 1990s, several large surveys were conducted in VL-endemic districts16,17. The later survey also included a comparison site in an area not considered endemic for VL. These studies, as well as several related laboratory-based evaluations22,24 established the utility of the direct agglutination test (DAT) as a diagnostic and epidemiologic tool in Bangladesh. Using some combination of clinical screening, parasitologic diagnosis and DAT, the 1987-1989 survey in Mymensingh district ascertained 1,273 prevalent kala-azar patients in a total population of 476,000, corresponding to an approximate prevalence of 26/10,000 population16. The 1991-1992 study included serologic screening of 17,826 residents of endemic areas. The prevalence of positive DAT was 423 of 9,619 (4.4%) residents of Trishal thana (Mymensingh district) and 495 of 7,328 (6.75%) residents of Shahjadpur thana (Sirajganj district)17. The 125 participants suspected to have kala-azar based on clinical findings and positive DAT underwent bone marrow aspiration; only 29 were found to have parasites on aspirate. Nevertheless, all 125 were reported to have recovered clinically in response to antileishmanial treatment. The ratio of asymptomatic DAT-positive participants to those considered to have kala-azar was 739 to 125 (approximately 6 to 1).

Laboratory-based studies have demonstrated that the predominant parasite strain causing visceral leishmaniasis and PKDL in Bangladesh is *Leishmania donovani* (sensu stricto) MHOM/IN/80/DD826,27, identical to the predominant strain in Bihar, India18. DAT and the rK39 immunochromatographic strip test perform with excellent sensitivity and good specificity in Bangladesh16, as in India39-41 and Nepal42-44. Newer diagnostic tests, especially the urine-based tests28,31, show great promise as another non-invasive diagnostic modality.

Clinical case series document a 5 per cent case-fatality rate for kala-azar patients in the hospital, and demonstrate jaundice, bleeding, tuberculosis and ascites as complications of the disease34. Bangladeshi investigators report bleeding and cardiac arrhythmias as adverse effects of antimonial drug treatment35,37. In clinical case series, male kala-azar patients generally outnumber females; however, because females often have poorer access to hospital care than males, these data cannot be generalized to the community.

One major community study of kala-azar was published in recent years. The study was conducted in a highly endemic village in Fulbaria thana, Mymensingh district, where the average kala-azar incidence from 2000 to 2002 was 2 per cent per year18. Of 492 houses surveyed, 99 (20%) had at least one member with kala-azar during the 3-year period, and 29 (6%) had more than one member with kala-azar. The median time from onset of illness to
Table II. Visceral leishmaniasis research studies published from Bangladesh, 1990-present

<table>
<thead>
<tr>
<th>Design</th>
<th>Location</th>
<th>Major findings</th>
<th>Reference</th>
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<tbody>
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<td><strong>Community-based studies</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Serosurvey</td>
<td>Mymensingh</td>
<td>DAT &gt;99 per cent sensitive for kala-azar 93 per cent specificity in endemic controls</td>
<td>16</td>
</tr>
<tr>
<td>Serosurvey</td>
<td>Mymensingh, Sirajganj</td>
<td>4.4 and 6.75 per cent prevalence of DAT+, ratio of kala-azar to subclinical infection –6 to 1</td>
<td>17</td>
</tr>
<tr>
<td>Epidemiologic and qualitative study</td>
<td>Mymensingh</td>
<td>2 per cent incidence of kala-azar in community; kala-azar identified as a major health problem; kala-azar diagnosis and treatment represent major economic burden; delay before kala-azar treatment longer in women, case-fatality rate higher than in men; kala-azar clustered within village. High risk of kala-azar associated with living in same household or within 50 m of previous case, lower risk for presence of cattle, use of bed nets.</td>
<td>18, 19, 20</td>
</tr>
<tr>
<td><strong>Laboratory based studies</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Diagnostics</td>
<td>Dhaka</td>
<td>IFAT 100 per cent sensitive in 125 parasitologically confirmed kala-azar patients, 100 per cent specific in 100 healthy controls, 50 controls with other diseases, 81 per cent positive in 100 suspect kala-azar</td>
<td>21</td>
</tr>
<tr>
<td>Diagnostics</td>
<td>Mymensingh, Dhaka</td>
<td>DAT antigen production in Dhaka and implementation in endemic district are feasible, autochthonous strain gives higher DAT titres</td>
<td>22</td>
</tr>
<tr>
<td>Strain typing</td>
<td>Dhaka</td>
<td>Isoenzyme profiles from 11 kala-azar and 4 PKDL patients all identical to reference strain <em>Leishmania donovani</em> (<em>sensu stricto</em>) MHOM/IN/80/DD8 (LON41)</td>
<td>23</td>
</tr>
<tr>
<td>Diagnostics</td>
<td>Dhaka</td>
<td>DAT 100 per cent sensitive in 38 parasitologically confirmed kala-azar patients; 75 per cent of 15 suspect patients positive on bone marrow aspirate were also DAT positive</td>
<td>24</td>
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<tr>
<td>Diagnostics</td>
<td>Chittagong, Dhaka</td>
<td>High concordance among IFAT, ELISA and DAT in 81 parasitologically confirmed kala-azar, 74 suspect kala-azar, 250 healthy and 80 ill controls; DAT most practical</td>
<td>25</td>
</tr>
<tr>
<td>Strain typing</td>
<td>Bangladeshi specimens</td>
<td>6-phosphogluconate dehydrogenase enzyme most useful for electrophoresis; all 5 Bangladeshi isolates identified as <em>L. donovani</em> MHOM/IN/80/DD8</td>
<td>26, 27</td>
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<tr>
<td>Diagnostics</td>
<td>Bangladeshi specimens</td>
<td>Development of urine ELISA tested in Bangladeshi specimens; sensitivity 95 per cent, specificity 95 per cent using acetone-treated promastigotes</td>
<td>28</td>
</tr>
<tr>
<td>Private laboratory case series</td>
<td>Mymensingh</td>
<td>Suspect kala-azar referred for rK39 strip test. 66 per cent male, 60 per cent from 2 most affected subdistricts, but 40 per cent from 13 other subdistricts</td>
<td>29</td>
</tr>
<tr>
<td>Diagnostics</td>
<td>Mymensingh</td>
<td>Compared to bone marrow/splenic aspirate culture in 38 cases and 13 ill controls, sensitivity/specificity of rK39 strip test 100/92 per cent, aldehyde test 92/46 per cent</td>
<td>30</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Design</th>
<th>Location</th>
<th>Major findings</th>
<th>Reference</th>
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</thead>
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<tr>
<td>Diagnostics</td>
<td>Bangladeshi</td>
<td>Development of urine DAT (sensitivity 91%, specificity 86% in negative controls, 71-100% in ill control groups) and ELISA (sensitivity 93%) tested in Bangladeshi specimens</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Mymensingh</td>
<td>Splenic aspirate 90 per cent sensitivity, bone marrow aspirate 72 per cent sensitive</td>
<td>32</td>
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<td>Hospital-based</td>
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<tr>
<td>Clinical case series</td>
<td>Dhaka</td>
<td>20/134 (9.4%) patients with febrile illness lasting &gt;3 wk had kala-azar, 3rd most common diagnosis after TB and enteric fever</td>
<td>33</td>
</tr>
<tr>
<td>Clinical case series</td>
<td>Rajshahi</td>
<td>Of 553 kala-azar patients, 27 (5%) died during treatment from haemorrhage (12), sudden death (7), varied causes (5), pulmonary TB (3)</td>
<td>34</td>
</tr>
<tr>
<td>Clinical case series</td>
<td>Mymensingh</td>
<td>81 adult kala-azar patients, 58 per cent male: 100 per cent fever, splenomegaly, 91 per cent hepatomegaly, 17 per cent jaundice, 5 per cent bleeding, 5 per cent ascites; 7 per cent urinary tract infection, 4 per cent TB, 4 per cent heart failure.</td>
<td>35</td>
</tr>
<tr>
<td>Hospital-based</td>
<td>Mymensingh</td>
<td>60 parasitologically confirmed kala-azar patients, 60 ill and rK39 strip test sensitivity 96.6 per cent, specificity 98.3 per cent</td>
<td>36</td>
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<td>diagnostics study</td>
<td></td>
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<tr>
<td>Case report</td>
<td>Rajshahi</td>
<td>Report of one kala-azar patient with arrhythmia and syncope apparently due to antimonial</td>
<td>37</td>
</tr>
</tbody>
</table>

DAT, direct agglutination test; IFAT, immunofluorescent antibody test; PKDL, post-kala-azar dermal leishmaniasis

initiation of antileishmanial treatment was 4 months; females were ill significantly longer than males (5 versus 3 months, P=0.03). Although the incidence of disease did not differ significantly between sexes, females with kala-azar were nearly 3 times more likely to die (P=0.06)\(^\text{18}\). In focus group interviews, community members expressed the desire to learn more about kala-azar and the willingness to take collective action.

The same community study included a risk factor analysis, whose objective was to guide development of prevention strategies\(^\text{20}\). In age-adjusted multivariable models, 4 factors that altered kala-azar risk were identified: age between 3 and 45, and proximity to a previous case [OR 25.4 (95% CL 15,44) in the same household; OR 3.2 (1.7,6.1) living within 50 meters] were associated with increased risk, while higher numbers of cattle per 1,000 m\(^2\) [for each additional cow per 1000 m\(^2\), OR 0.8 (0.70,0.94)] and consistent use of a bed net in summer [OR 0.7 (0.53,0.93)] were associated with protection. A total of 86 per cent of the population reported sleeping under a bed net at least some of the time, and 91 per cent lived in a house that owned at least one net. These analyses suggest that bed nets are already acceptable in Bangladeshi communities and that insecticide-treated nets could be a highly effective preventive intervention. Data from this study suggested that rates of treatment failure and of PKDL were relatively low: only 3 treatment failures and 6 cases of PKDL were detected, out of 155 kala-azar cases that occurred in the 4 yr before the analysis\(^\text{20}\). However, caution must be used in interpreting these data; follow up was not complete for the more recent cases, and the population under surveillance was relatively small. These data cannot be taken to represent the incidence of PKDL and treatment failure in the wider population.
Data collected in connection with the Fulbaria study examined the economic impact of kala-azar on affected households (D.A. Sharma, unpublished data). To obtain health care for one kala-azar patient, the median direct expenditure and the median income lost were equivalent to 80 and 40 per cent of the yearly per capita income, respectively. The total costs of 120 per cent of the yearly per capita income in the study population represent a catastrophic burden for affected households. Families were forced to sell livestock and land, and to take loans to pay for treatment.

Challenges for visceral leishmaniasis control efforts in Bangladesh

A Memorandum of Understanding was signed by the Ministers of Health of India, Bangladesh and Nepal, and the Southeast Asian Regional Office of the World Health Organization during the 2005 World Health Assembly. This document calls for aggressive action to decrease kala-azar incidence below 1 case per 10,000 inhabitants in VL-endemic areas by 2015. Anthroponotic visceral leishmaniasis meets the technical criteria for a disease potentially capable of elimination, and the experience of the malaria eradication era demonstrated that control measures available in the 1950s and 1960s were able to decrease the incidence of kala-azar below detectable levels. However, formidable tasks lie ahead for those working to control visceral leishmaniasis in Bangladesh (Table IV).

Untreated kala-azar and PKDL patients constitute the major reservoir for ongoing transmission of anthroponotic visceral leishmaniasis. Therefore, timely, effective diagnosis and drug treatment are essential not only to cure the individual patient, but also to decrease the leishmaniasis infection reservoir. The first step in this process is to decrease the time from onset of illness to diagnosis. The median delay from onset of fever to treatment in South Asia is 4 months; this period almost certainly represents 4 months of a kala-azar patient being highly infective to sand flies and increased disease risk to family members and near neighbours. Currently, the costs of accessing diagnostic services contribute to this delay; these costs include both the substantial direct cost of some tests, and the loss of income incurred by household wage earners to take family members for care. Availability of sensitive, specific non-invasive tests, such as the rK39 immunochromatographic strip test, through a public sector visceral leishmaniasis control programme could dramatically decrease the delay in diagnosis, especially if coupled with health education campaigns to raise awareness.

The most urgent challenge facing the VL control programme in Bangladesh today is to achieve affordable, reliable access to antileishmanial drug treatment in all endemic thanas (Table IV).
<table>
<thead>
<tr>
<th>Table IV. Major challenges facing the visceral leishmaniasis control programme in Bangladesh and potential solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Challenge</strong></td>
</tr>
</tbody>
</table>
| Improve antileishmanial drug access | Government registration of SAG from several sources  
Ensure supply of second-line antileishmanial drugs to affected thanas  
Accelerate licensure of newer antileishmanials  
Implement sustainable drug supply mechanisms  
Link drug distribution to thanas most affected in recent surveillance data |
| Shorten time from onset of illness to diagnosis | Explore ways to provide rK39 rapid tests at the thana health complex  
Improve referral system for patients needing bone marrow or splenic aspirate  
Develop an algorithm for diagnosis based on cost-effectiveness model  
Identify barriers to timely diagnosis  
Community health education campaigns to raise awareness and improve understanding  
Explore methods to institute active case finding in highly affected areas |
| Improve and update surveillance system | Evaluate current surveillance system to identify methods for improvement  
Perform an explicit assessment of accuracy of reporting in several thanas  
Establish indicators for adequacy of surveillance  
Establish sentinel thanas to institute surveillance for treatment failures and PKDL  
Implement timely reporting mechanism |
| Enhance vector control activities in preparation for VL elimination programme | Conduct thorough programme evaluation to identify needs  
Ensure reliable supply of insecticide  
Improve supervisory staffing, protocol and implementation  
Establish direct link between vector control programme and epidemiologic surveillance, to implement rapid targeting of activities  
Evaluate potential for community-based vector control activities, including insecticide-impregnated nets, environmental control |
| Ensure rapid response to surveillance findings and evaluation of impact | Improve data reporting and sharing between surveillance system and vector control programme  
Joint epidemiology-entomology task force to establish surveillance thresholds and guidelines for vector control action  
Incorporate annual evaluation of vector control actions triggered and implemented, including assessment of impact on disease incidence |
| Establish an effective national VL control program | Establish national task force with expertise and political authority to guide the VL control programme  
Establish interactive network of treatment centers that share guidelines and conduct clinical trials  
Ensure continuity of personnel at national, district and thana levels  
Create reference laboratory for conventional and molecular diagnosis, and molecular epidemiology  
Build and sustain political commitment at national regional levels |

SAG, sodium antimony gluconate; PKDL, post-kala-azar dermal leishmaniasis
guidelines recommend sodium antimony gluconate (SAG), 20 mg/kg intramuscularly for 20 days, as first-line treatment of kala-azar. For PKDL, the national guidelines recommend SAG 20 mg/kg for 20 days per month for 6 months, totaling 120 injections. Since 2000, endemic districts of Bangladesh have experienced severe shortages of SAG, both in the THC and the private sector. Second-line antileishmanial drugs are rarely available. The only licensed manufacturer of SAG in Bangladesh ceased production of the drug in 2003, and its stockpiles are said to be nearly exhausted. The supply scarcity in combination with rising kala-azar incidence has led to high prices for SAG sold in private pharmacies. Surveys of pharmacies in Mymensingh in 2004 showed prices up to 4 times the official market price (D.A. Sharma, unpublished data). The antileishmanial drug shortage is likely to lead to many preventable deaths, suboptimal treatment courses, and more rapid development of SAG resistance. An additional issue is whether 20 days is still adequate for the treatment of kala-azar in Bangladesh. In Nepal and in parts of India where SAG still has acceptable efficacy, the standard SAG treatment regimen consists of 20 mg/kg per day for 30 to 40 days.

Ascertainment and treatment of PKDL patients will become a key issue for the control programme, especially when kala-azar incidence rates fall. Epidemiologic analyses suggest that under current circumstances in highly endemic areas, kala-azar patients are the predominant reservoir fueling ongoing transmission. However, experience in the VL resurgence of the 1970s suggests that a small number of untreated PKDL patients could initiate renewed transmission in an area, and that PKDL patients may become proportionately more important as a reservoir if kala-azar incidence falls. Given the shortage of SAG, it is doubtful that most PKDL patients in Bangladesh are able to receive the current recommendation of 120 days of treatment, and there have been few clinical trials to establish the best regimen. Alternative, more practical treatment regimens for PKDL are urgently needed. Efforts are also needed to develop active surveillance methods to ascertain PKDL patients and institute appropriate referral for treatment.

In preparation for the upcoming elimination effort, it would be extremely useful to review and update the Bangladesh national visceral leishmaniasis diagnosis and treatment guidelines. In addition, improvement of the drug licensure, procurement and distribution system for SAG in the public sector will be necessary to ensure timely treatment of kala-azar and PKDL. Predominant reliance on the private sector to provide diagnosis and treatment may jeopardize the control effort. The time required for an impoverished family to gather the resources to pay for diagnostic tests and drug purchase leads to more treatment delays and increased disease transmission. A useful model may be that used for tuberculosis, another disease for which ill humans are the reservoir for transmission. The DOTS model, implemented through a partnership between non-governmental organizations and the government sector, has already proved highly successful for tuberculosis control in some of the thanas most affected by visceral leishmaniasis. In India, a different model of public-private partnership was also successful in promoting cooperation in provision of treatment for tuberculosis.

Vector control is the other major component of the effort to eliminate visceral leishmaniasis. The current vector control programme is much smaller than the programme that was so successful in the 1950s and 1960s, and has struggled recently with shortages of insecticide. Increasing the capacity of the vector control programme will be essential, as will activities that promote co-ordination between epidemiologic surveillance and the vector control programme. Epidemiologic data suggest that when transmission in a community is high, the susceptible population becomes saturated within a few years. Thus, the window of opportunity for vector control measures to interrupt transmission is relatively
short. Careful evaluation, expert recommendations for specific strategies, reliable insecticide supplies, and effective, ongoing supervision of field teams will be key to the success of the vector control programme.

Finally, an effective national VL control programme will have the essential role of oversight and integration of the diverse components outlined above, and will require a national steering committee with the expertise and political authority to ensure its success. The programme will have the task of coordinating diagnostic, treatment and vector control activities in order to maximize their impact, as well as ensuring adequate surveillance to monitor progress toward the goal outlined by the Memorandum of Understanding. Indicators to monitor the adequacy of surveillance will need to be developed. Treatment centers will need to be linked by shared guidelines and timely feedback of surveillance data. Such a linkage could form the basis for a collaborative network for multicenter clinical treatment trials, and surveillance for treatment failures and development of drug resistance. A national reference laboratory is needed to ensure and monitor quality of diagnosis at the peripheral level, and to be the center for molecular diagnosis and epidemiology. The Memorandum of Understanding for the elimination of VL in South Asia has the potential to represent a turning point in the long history of visceral leishmaniasis. Whether this potential can be fulfilled depends on the scientific expertise and political commitment that Bangladesh can bring to this challenging enterprise.

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