The challenge of sustaining elimination, role of asymptomatics and PKDL

Consortium: Setting the Post Elimination Agenda for Kala-Azar in India (SPEAK India)
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Epidemiological triad in visceral leishmaniasis

Susceptible host

Agent: *L. donovani*
Reservoirs: VL, HIV-VL, PKDL, asymptomatic, relapsed case

Environment
Breeding sites, poor housing and sanitation, migration, climate change, new settlements,

Vector
Asymptomatic leishmanial infection (ALI)

• Currently there is no reference standard or appropriate biomarker
  o Serological test: rk39 ICT, rk39 Elisa, DAT
  o PCR, qPCR
  o LST
• Increase proportion of ALI to VL:
  o Bangladesh: 4 :1. (Bern 2007)
  o India/Nepal: 8.9: 1 (Ostyn 2014)
• Risk factors associated with VL also associated with ALI
• Progression of ALI to VL:
  o Proportion progressing to symptomatic disease within one year ranged 1.5–23%
  o strongly associated with initial sero status (high titers) and with seroconversion;
  o high titer DAT convertors, the hazard ratio as high as 97.4 (compared to non-convertors)
Comparative results of PCR, DAT and rK39 ELISA from India and Nepal (Srivastava 2013)

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<tr>
<th>Groups</th>
<th>% Positive AI</th>
<th>% Negative AI</th>
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<tbody>
<tr>
<td>HNK</td>
<td>17.9 (5.5–30.2)</td>
<td>36.0 (27.1–44.8)</td>
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<tr>
<td>HHC</td>
<td>20.9 (5.5–36.2)</td>
<td>25.0 (17.3–32.6)</td>
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<tr>
<td>HPK</td>
<td>15.8 (2.0–29.5)</td>
<td>27.6 (19.6–35.5)</td>
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Agreement indices (AI) between PCR, Direct Agglutination Test
Asymptomatic leishmanial infection (ALI) II

- Are ALI infectious:
  - Mathematical modelling suggests that they constitute a reservoir of parasites driving the epidemic (Staunch 2011)
  - Asymptomatic infected persons in early stages of HIV infection were able to infect sand fly (Molina 1994)
- Do we have the drugs to treat asymptomatic otherwise healthy individuals?
- What is needed?
  - Standardized definition, validated biomarkers/ diagnostic tests.
Post Kala-azar Dermal Leishmaniasis (PKDL)

- Incriminated in the resurgence of VL in India in the 1970s following discontinuation of insecticide spraying
- Case definition:
  - Probable: Skin lesion+ (Person living in endemic area + rk39+ve)
  - Confirmed: Probable + parasitology+ve.
- Prevalence of PKDL: few prospective cohort studies conducted
  - Bihar: Probable, 7.8/10,000 and Confirmed, 4.4/10,000 population (Singh 2012)
  - Bengal: 1% point prevalence (Ganguly 2015)
  - Bangladesh: 3.8-7.3 /1000 population (Rahman 2010)
- Interval between treatment of VL and onset of PKDL: 6 months -3 years or longer (14 yrs).
- Up to 27.5% of KA cases developed PKDL in Bengal. (Ganguly 2015)
Case finding: No standardized validated active strategy. Delay in diagnosis even with active approach.

Diagnostics: limitations in the field
- SSS: Macular very low; Papulo-Nodular – 20 to 40% (Ramesh 2015; Singh 2015)
- Biopsy: Macular Macular 40%; PN 91% (Verma 2015)
- qPCR: 96-100% (Kumar 2009)

Treatment PKDL: prolonged and difficult
- Miltefosine for 12 weeks
- Amphotericin B 60-80 inj
- LAMB 3 weeks.
PKDL and transmission

• 1933 Napier: Parasites demonstrated in sand flies feeding on 2 patients with nodular.
• 53% of sand flies that fed on 4 PKDL patients with nodular or nodulo-ulcerative lesions developed infection (Addy 1992).
• VL outbreak in southern West Bengal in the 1980s implicated on PKDL (Addy 1992)
• PKDL and increasing drug resistance:
  o Increasing resistance to antimony in the 1990’s was thought to be contributed by even more resistant strains in PKDL patients (Singh 2006)
  o Decline in Clinical Efficacy of Miltefosine in PKDL in India (Ramesh 2015)
  o In vitro susceptibility towards miltefosine of parasites isolated after relapse was significantly lower (>2 fold) in comparison with the pre-treatment isolates (P<0.005).
Conclusion

• Elimination of kala-azar as a public health problem target is not only to be achieved but sustained as almost all of the variables in the transmission triangle will continue to exist.
• Better understanding on the role of the ALI and PKDL needs to be defined
• Development of tools for diagnosis and appropriate safe treatments would be required if these entities are proven to play a significant role in the transmission..
Thank you