

Regional Technical Advisory Group on Kala-azar Elimination

*Report of the First Meeting
Manesar, Haryana, 20-23 December 2004*

WHO Project: IND CDR 714



**World Health
Organization**

*Regional Office for South-East Asia
New Delhi, October 2005*

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EXECUTIVE SUMMARY

Kala-azar is a disease of immense public health importance in Bangladesh, India and Nepal affecting largely the poorest population groups among marginalized communities living primarily in rural areas. About 150 million population is at risk of kala-azar in approximately 94 districts in the three endemic countries. Elimination of kala-azar in South-East Asian countries is feasible because of its unique epidemiological features: (a) human beings are the only reservoir in the countries; (b) there is only one vector species, which is amenable to control and (c) the limited geographical distribution of the disease. With the availability of new diagnostic tools and effective medicines, political commitment at the highest level in the endemic countries and the encouraging past experience of collateral benefits of the malaria control programme, elimination of kala-azar in the Region has become achievable. Elimination of kala-azar will promote equity and poverty reduction, and lead to socioeconomic development of targeted areas and strengthen the capacity of the health system.

Since more than 50% of cases are from the border districts in the three endemic countries, intercountry cooperation and collaboration with the support of WHO are crucial for successful elimination of the disease. There is a strong political and administrative commitment in the three affected countries to eliminate kala-azar, as mentioned at the Eighteenth Meeting of Health Ministers in 2000 and reiterated as the Twenty Second Meeting of Health Ministers in 2004.

In order to accelerate efforts towards the elimination of kala-azar, a Regional Technical Advisory Group (RTAG) was established in the Regional Office with the following terms of reference:

- (1) To advise the Regional Director, on policies, strategies and activities that are crucial for accelerating the elimination of kala-azar;
- (2) To provide strategic directions for implementing the WHO regional strategy for elimination of kala-azar in endemic countries;
- (3) To identify the strengths and weaknesses of kala-azar elimination strategy and to make recommendations;
- (4) To advise on the use of an appropriate and new technology for effective elimination of kala-azar, and
- (5) To advise the Regional Director on various aspects of research on kala-azar including operational research.

The first meeting of the Regional Technical Advisory Group (RTAG) on kala-azar was held at Manesar, Haryana, India, from 20-23 December 2004. The meeting reviewed the situation in the endemic countries, the draft regional strategic plan and the progress made. To achieve kala-azar elimination in the three countries of the Region, RTAG made the following recommendations:

- (1) Kala-azar should be eliminated from the three endemic countries by the year 2015
- (2) WHO should assist the programme by increasing access to population at risk
- (3) Country-specific plans for elimination should be developed within the framework of the regional strategic plan by using the regional guidelines for preparing national plans. WHO should provide technical support in the preparation of national plans for elimination of kala-azar.
- (4) The elimination programme should be directed:
 - (a) to ensure early diagnosis and complete treatment that is operationally feasible to ensure outreach to the poorest like appropriate dipstick diagnosis and safe and effective oral medicine;
 - (b) to strengthening disease and vector surveillance through an efficient, in-built management information system for networking of all reporting facilities;
 - (c) to vector control through Integrated Vector Management (IVM) with the focus on IRS, ITN and environmental management;
 - (d) to social mobilization directed towards behavioural change through effective communication strategies, and
 - (e) to clinical and operational research to support the elimination programme.
- (5) With particular attention to the poor and marginalized groups, of health care. The approach should include urging Member States to review and establish policies and strengthen programme.
- (6) In order to achieve elimination of kala-azar, community participation, appropriate communication strategies on community actions with the focus on the poor to improve their living conditions and their participation in the elimination of kala-azar should be an integral part of the programme;

- (7) WHO should initiate appropriate actions to establish sustainable partnerships through the regional alliance/partnership forum for resource mobilization and for enhancing technical support through networking and intercountry cooperation. WHO should coordinate the partnership for implementation of the elimination programme.
- (8) WHO should work with countries to finalize a MOU to affirm commitment of the three countries to eliminate the disease through regional collaboration and cooperation. WHO should initiate appropriate preparatory actions for the signing of MOU, preferably during the forthcoming World Health Assembly in May 2005.
- (9) An appropriate advocacy document/kit should be prepared to mobilize resources required for elimination of kala-azar. Potential partners and donors should be invited to participate in the ceremony for the signing of MOU.
- (10) WHO should continue to provide necessary support to Member States for effective implementation of the programme to achieve the goal of elimination by 2015.

1. BACKGROUND OF THE MEETING

The Regional Director, WHO, South-East Asia Region, established a Regional Technical Advisory Group to accelerate efforts towards the elimination of kala-azar, with the following terms of reference:

- (1) To advise the Regional Director, on policies, strategies and activities that are crucial for accelerating elimination of kala-azar;
- (2) To provide strategic directions in implementing the WHO Regional Strategy for elimination of kala-azar in endemic countries;
- (3) To identify the strengths and weaknesses of the elimination strategy and to make recommendations;
- (4) To advise on the use of an appropriate and new technology for effective elimination of kala-azar; and
- (5) To advise the Regional Director on various aspects of research on kala-azar including operational research.

The first meeting of the Regional Technical Advisory Group (RTAG) on kala-azar was held in Manesar, Haryana, India, from 20-23 December 2004. The participants included members of RTAG, 2 temporary advisers and WHO staff from TDR/HQ, the Regional Office and country offices. The list of the participants is at Annex 1 and the Programme at Annex 2.

2. OPENING CEREMONY

Dr Chusak Regional Adviser, WHO, welcomed the members of RTAG and the other participants. Dr N Kumara Rai, WHO/SEARO, and Dr N.K. Ganguli, Director-General of Indian Council of Medical Research (ICMR), India, lighted the lamp before starting the proceedings.

Dr Kumara Rai, Director, CDS, WHO/SEARO readout, the Regional Director's inaugural address. In the SEA Region, kala-azar is reported from Bangladesh, India and Nepal. As a collateral benefit of malaria eradication, kala-azar was virtually eliminated from the region, but there was a slow build-up of the vector again leading to a resurgence of kala-azar. It is mainly a disease of the poor and diagnosis and treatment is often incomplete. A

problem to contend with is the problem of post kala-azar dermal lesions (PKDL) which leads to continued transmission. Elimination of kala-azar is now feasible since a reliable test is available for screening cases suspected to be suffering from kala-azar. Miltefosine, an oral drug, is very effective and safe. Surveillance of cases and vectors is necessary for elimination of kala-azar. Now Geographical Information System (GIS) mapping can be done to focus indoor residual spray (IRS) operations. The vector continues to be sensitive to available insecticides. Political commitment is high for disease elimination, as expressed repeatedly by the health ministers of the endemic countries. Continued research is important in the diagnosis, treatment and other operational issues to support elimination efforts. Sustained intercountry cooperation and networking will be crucial for elimination of the disease, which is a priority for WHO. A draft regional strategic plan has been prepared. It should be discussed and finalized to take the next steps.

Dr Juntra, TDR/HQ readout the remarks of Director TDR who recognized the importance of the RTAG meeting. He said that the existing political commitment of the health ministers should be sustained. New tools for field diagnosis are available and the oral drug, Miltefosine, has been registered in India and in Germany. Other drugs like Paromomycin are under trial and are promising. The progress made in kala-azar illustrates the value of collaboration between TDR, research institutions and the private industry to develop suitable tools.

Dr N.K. Ganguly, Director-General Indian Council of Medical Research (ICMR), India, was nominated Chairperson and Dr Manas Bannerjee, Senior Public Health Officer, Nepal, as Co-chairperson of the meeting. Dr N.B.L. Saxena, Joint Director of National Vector Borne Disease Programme, India, as Rapporteur. The Programme of the meeting is at Annexure 2.

Chairman's remarks

Leishmaniasis is a global problem; there is no animal reservoir in Asia but it could survive in humans as PKDL and this can maintain the chain of transmission. It affects the poorest of people amongst the poor and they get poorer if they suffer from kala-azar since they sell their assets for treatment of the disease. Treatment is expensive since a large proportion of patients seek treatment from private doctors and quacks. Treatment in the private sector is often inappropriate and incomplete. Public-private mix is necessary to improve the situation. The basket of drugs currently available does not have

many choices. Research should be continued to explore options of new drugs and drug combinations. Funding is the main constraint and additional funding is needed for elimination of the disease. Coinfection with HIV/AIDS and TB is a real threat; therefore it is important to factor in the problem of HIV/AIDS in the programme. The success of the elimination programme will depend on partnerships. Bill and Melinda Gates Foundation may be interested in supporting kala-azar elimination efforts. There are many operational problems in elimination. These include access, utilization of services and treatment adherence. The insecticides have to be used judiciously so as not to lead to environmental degradation. Safeguards against environmental degradation can be increased through personal protection. A vaccine trial is in the pipeline but its use on a large scale for elimination of kala-azar will take time. However, elimination is possible even with the tools available at present.

3. OBJECTIVES

The objectives of the meeting were:

- (1) To finalize the draft Regional Strategic Plan for the elimination of kala-azar from SEA Region;
- (2) To evaluate the available technical inputs in the countries of the Region, discuss country strategies, vision, goals and objectives for elimination of kala-azar;
- (3) To identify areas for capacity building and operational research on kala-azar, and
- (4) To prepare plans for resource mobilization, including a roadmap for prevention, control and elimination of kala-azar by 2015.

4. KALA-AZAR SITUATION

Dr Chusak Prasittisuk, Regional Adviser, WHO/SEARO, summarized the situation in the Region. Only three countries viz. Bangladesh, India and Nepal, are endemic for visceral leishmaniasis (kala-azar). An estimated 150 million people are at risk. About 94 districts are endemic. In India the disease is endemic in Bihar, Jharkhand, UP and West Bengal in 56 districts. There are 25 000-30 000 cases and 200-300 deaths are reported every year. These are gross underestimates and there is a need to determine the true burden of the disease. Effective interventions are available e.g. rapid diagnostic tests, oral effective and safe drug, Miltefosine, and indoor residual spray (IRS). There is

no animal reservoir for kala-azar and therefore disease transmission can be interrupted in the countries of the Region. There is high political commitment that is sustained, and elimination of kala-azar has been endorsed by health ministers of the endemic countries. India has provided a separate budget for elimination of the disease. The goal is to eliminate disease incidence to less than 1/10 000 population at district level or subdistrict level by the year 2015. The main strategies are disease and vector surveillance, access to early diagnosis and complete treatment, vector control with community participation, social mobilization and partnership building, strengthening managerial and technical support and environmental management. DDT is effective and can be used in India but not in Bangladesh or Nepal. Communication strategies like Communication for Behaviour Impact (COMBI) that are promising should be considered. There is also a need to develop partnerships and networking amongst institutions and with the programme. Implementation should be done within the available infrastructure. All the endemic countries have agreed to develop an elimination programme. Miltefosine has already been registered in India and Germany. Phase IV trials are in progress in Bangladesh and Nepal, and preliminary results are available. A draft regional strategic plan and guidelines for preparing national plans have been developed. Cross-border collaboration is important in elimination since more than 50% of the affected districts are across international borders. Technical issues have been enlisted from the programme for discussions in RTAG.

Dr A.T.M. Mostafa Kamal, Programme Manager, Bangladesh presented the kala-azar situation in Bangladesh. About 40 million population in 34 districts is at risk. The prevalence of the disease is estimated at around 40 000 cases and the incidence at about 10 000 cases every year. Facilities for early diagnosis and prompt treatment are inadequate. Sodium Antimony Gluconate (SAG) is the main drug used. The country reports about 6 000 cases and 25-50 deaths every year. Cases are reported only from hospitals and thus there is gross under reporting. The country has a draft operational plan which is similar to the regional strategic plan. Case definitions for kala-azar, PKDL and treatment failure have been developed though these are not uniformly applied. The practices in the public health sector at the community, upazila and district level were described. For prevention of the disease DDT is used on a limited scale even though it has been banned since 1994 and stocks in the country have run out. Periodic vector surveys are done. Sylhet district was selected for cross-border collaboration but not much progress has been made.

DAT and ICT are available in some areas but not used widely. The programme and funding constraints were identified. There is a need to strengthen linkages, intensification of vector control measures, surveillance and community participation.

Dr N.B.L. Saxena, Joint Director – National Vector-borne Disease Control Programme, speaking on behalf of Programme Manager, India, summarized the progress of kala-azar control programme in India. The disease is reported from 56 districts in four states. The kala-azar control programme was initiated in 1990 as a centrally-sponsored programme; this was intensified in 1991. The national policy supports the elimination of kala-azar. The strategy for indoor residual spray (IRS) was to use DDT, to be sprayed upto a height of about 6 feet above ground level. The programme stresses on diagnosis and treatment, information education and communication (IEC) and capacity development, besides IRS. The programme was reviewed twice during the past decade. The achievements were impressive during the first five years but progress was slow during the next five-year period. When the resources are adequate, there is improvement but reverses occur as soon as the measures are relaxed and funding is reduced. The constraints are underreporting, increase in PKDL cases and indiscriminate use of drugs, especially by private doctors and quacks. Besides the above-mentioned factors, SAG resistance is a problem in about 60% of cases in some districts in Bihar. The focus of the programme now is on surveillance, diagnosis and treatment, networking, and community participation. Kala-azar is a notifiable disease with active and passive case detection. Surveillance is maintained in non-endemic areas too. Diagnosis is done by syndromic approach with a positive serological test. No standardized test is done uniformly. At secondary and tertiary levels, a parasite demonstration is necessary. There is a national drug policy and this has been reviewed twice during the past decade. The emphasis of the programme is on compliance to help in monitoring completion of treatment. Vector control comprises DDT, entomological monitoring, sanitation and personal protection, and IRS for three consecutive years. IEC has had limited success. Capacity building has been emphasized at all levels. NGOs and the private sector have not been fully involved. Milestones have been developed for monitoring, an expert committee has been established and 100% central assistance is provided. The programme will be implemented in collaboration with HIV/AIDS and leprosy programmes.

Dr G.D. Thakur, Programme Manager, Nepal, summarized the progress of kala-azar control in Nepal. The country has political commitment to

eliminate the disease by 2015 and to eliminate PKDL by 2018. The objectives and strategies have been identified. One weakness of the programme is the very low level of community awareness. This is to be supported by reliable diagnosis and appropriate treatment at hospital level. The other strategies are selective IRS, capacity building, cross-border collaboration, regular supply of drugs and logistics, and identification and mapping of at-risk population. The programme will provide drugs free of cost. The number of cases has been around 2000 and these have been increasing since 2001. The number of reported deaths have varied between 12 and 65. Case-fatality rates have been declining. There are 11 districts that are kala-azar endemic (10 are border districts). The first-line drug is SAG and the second line is amphotericin B. Miltefosine has been under trial in the country. The strategy is to try the directly observed treatment.

Chairman's summary

- All the countries have a static situation although there may have been some declining trend in recent years.
- There is paucity of epidemiological information with a large gap between reported and estimated cases.
- The diagnostic test has not been introduced systematically and widely.
- Private sector may not be interested because of the low profits involved since kala-azar patients are poor and cannot afford to pay.
- Although GIS exists, it is not being used.
- Personal protection and social marketing are important strategies.
- There are major policy and regulation constraints.

5. STRATEGIC FRAMEWORK FOR ELIMINATION OF KALA-AZAR

Dr Jai P. Narain, Coordinator, CDS/SEARO, introduced the subject of elimination of kala-azar. There is a sense of urgency amongst decision-makers to eliminate the disease. Political commitment is high although resources are inadequate. Countries have to some extent started to implement the programme. WHO has identified kala-azar elimination as a priority for the endemic countries in the SEA Region. TDR endorses this commitment.

Appropriate diagnostics and treatment are available and the vector is responsive to IRS. A clear and coherent strategy, a mechanism to track progress, and adequate resources can help to eliminate the disease. It will be important to arrive at a consensus on the time-frame, the criteria for elimination and the targets. Technical guidelines and tools have to be standardized and operational research will need to complement implementation. A choice has to be made of effective interventions and a plan implemented for their scaling up. It is also important to agree on the key indicators required to measure the progress.

Dr V. Kumar, Temporary adviser WHO/SEARO, summarized the progress in preparing the strategic framework and the road map for the elimination of kala-azar. The Regional Strategic Plan was drafted in 2003 and reviewed at an intercountry consultation held in Varanasi in November 2003. The plan was further revised according to the recommendations of the consultation. The present document is supported by the guidelines for preparing national plans for elimination of kala-azar. Advocacy plans to sustain political commitment and for mobilizing additional resources are required. National plans should be developed and consolidated into a project document. This should be followed by development of guidelines and tools for diagnosis, treatment, surveillance, and Behavioural Change Communication (BCC) based on standards and standard operating procedures.

Discussion points

- National plans and the regional plan should reflect the costs involved and identify funding gaps. Costing should be detailed to include all aspects including improved housing, outsourcing, transportation, diagnostics, and treatment supervision. National plans should be comprehensive.
- The major constraint in the elimination of kala-azar is the lack of resources. The programme should prepare advocacy plans to mobilize resources on a sustainable basis. Economic argument is important to convince donors and partners. Kala-azar is a disease of the poor and its treatment makes them poorer. There is a need to showcase the adverse socioeconomic impact of the disease and benefits of elimination programme for socioeconomic development. The information on DALYs is useful. One DALY lost is equal to one year's loss of productivity. This can give an estimate

of the economic losses. The close connection of kala-azar with TB and HIV/AIDS is an important advocacy issue.

- The presentation from Bangladesh emphasized the relevance of including gender issues. Some of the drugs recommended are not suitable for pregnant women and children. Ethics and equity have to be looked at very closely.
- The role of the private sector is extremely important even though at present, it is a programme constraint. Public-private mix is an important consideration. A situational analysis in a metropolitan city in India showed that doctors were using 80 different regimens in the treatment of TB. This was corrected after publication of the national guidelines. Development of national treatment guidelines and tools should be a priority for ensuring standard practices.
- In planning for public-private mix, make use of the lessons learnt from the TB programme. More than 60% of patients go to the private sector for treatment. In the TB control programme, boxes are provided to private providers who take responsibility for treatment and have an ongoing communication and information exchange with the government programme. An example each was provided of NGO and private and public mix.
- It is crucial to know the disease burden to estimate the extent of the problem. There has to be a mechanism for knowing the real burden of the disease. Periodic household and health facility surveys are important.
- The programmes in the endemic countries have listed the gaps well. It is important to undertake a situational analysis and identify existing gaps which can be considered while preparing national plans.

6. DISEASE SURVEILLANCE

Dr N.B.L. Saxena covered disease surveillance, reporting and validation. Surveillance is mostly passive. At present the private sector is not covered by the surveillance system; this is a gap in the programme. In the peripheral areas, diagnosis is made on clinical grounds and only sometimes the diagnosis is supported by serological tests which are not frequently validated. Parasite demonstration is not done in the periphery but does take place in some

secondary and many tertiary hospitals. Active case detection in India is done once a year. If done well, it has great potential. Nearly 30% of the case detection is done through kala-azar fortnight. Besides case detection, it helps to increase awareness and enhances the knowledge of health care providers and health volunteers. As prevalence goes down, the frequency of active case detection has to be increased. A standard case definition is included. In some situations, splenomegaly is taken into account while in others this is not done. The inclusion of spleen enlargement increases specificity but its limitation is that health workers and health volunteers may have difficulty in recognizing splenic enlargement. Splenic aspiration, which is considered as gold standard, is not done because of the risks involved in the procedure. Bone marrow is less invasive but it is not very sensitive. Serological tests are available but have variability in sensitivity and specificity with variations from batch to batch. False positive is common. One serious limitation of the system at present is that the existing surveillance does not provide information on disease burden. Disease surveillance can be improved through improved access to diagnosis and treatment supported by partnership with the private sector. Surveillance has to be an integral part of the programme. It should also cover non-endemic areas since new foci may develop. Kala-azar should be made a notifiable disease in the affected areas to improve reporting. The main channel is the primary health care system into which serology should be introduced. Hospitals should add an element of confirmatory diagnosis. At least serology should be promoted with the private sector. Detection of cases of PKDL is important since they are responsible for continued transmission of the disease. Networking with dermatologists is necessary for confirmation of PKDL cases since variable presentation of these cases requires expertise on diagnosis. Dr Saxena suggested classification of cases into suspected, clinical and confirmed categories based on case definition, serology or parasitological diagnosis. Amongst the different antigens available, the best candidate at present is rk 39 because of its high sensitivity and specificity. Serological tests can also help to pick up sub-clinical infection. It is likely that rk39 and DAT become positive even before the appearance of symptoms of the disease. In one study, 77.7% were positive prior to patients showing any signs of the disease. The Health system has to be organized to streamline the flow of information. The programme should aim for monthly reporting and feedback. The information should be kept as record of individual cases. This would facilitate the provision of feedback which is essential for maintaining the quality of the programme. Districts should be the coordinating institutions for programme management. Endemic states and the centre can be involved appropriately.

Reporting to WHO should be done annually on a standardized and agreed format. In the beginning, sentinel centres can be used for examining the trends and for comparing the data coming from the field. The databases can be exchanged between the endemic countries with the help of WHO if required. Appropriate surveys should be conducted prior to the country programme review.

Discussion points

- Programme managers from Bangladesh and Nepal summarised surveillance for kala-azar. In Bangladesh, the programme has a unified system of reporting and surveillance. For priority programmes, programme managers get reports directly from districts. In Nepal, there is routine HMIS. For kala-azar, the reports come through EWARS for which there is a weekly system of reporting. The kala-azar-affected districts in the country serve as sentinel sites.
- Integrated disease surveillance is being introduced in the endemic countries and could be used but it might take many years to become operational. HMIS can be useful but the information is often delayed, and this limits the scope of feedback at local level for taking corrective programmatic interventions. In the existing system, reporting is often delayed for more than one year and the programme cannot wait that long for initiating corrective measures (replanning and reprogramming). Even though there are limitations in endemic countries in working with HMIS, there should be a system of regular exchange of information between HMIS and the programme.
- The importance of active surveillance was discussed. In active case search, community-based detection is important. Community-based health workers do house-to-house search of cases. This helps to substantially increase the number of cases reported. However, this is resource intensive and cannot be done often. In the beginning, at least one active search should be carried out per year. The main responsibility for case detection is that of health workers and health volunteers who live closer to people than hospitals. Campaigns should be avoided early in the programme until there is readiness to be able to diagnose and treat cases adequately.

- One institution in Bihar is doing hospital-based surveillance. This by itself provides a lot of information. It also helps to locate cases in the catchment area where further investigation can be carried out. This hospital is also monitoring drug efficacy and drug resistance.

7. VECTOR SURVEILLANCE AND CONTROL

Mr N.L. Kalra, Temporary Adviser, SEARO, summarized vector surveillance and vector control. The vector of kala-azar likes alluvial soil, capillary-bound moisture, congenial temperature and high humidity. It has a habitat that contributes to clustering of cases. At present kala-azar is reported from the Indo-gangetic plains affecting Bangladesh, India and Nepal. The distribution of the disease has been changing due to ecological changes and migration patterns. Flooding in Bihar washes down the anopheles but sandflies survive. This reduces density but prolongs longevity. Very high density occurs in February and March of the year. This is the time when people should be maximally protected. Gujarat and Sri Lanka have reported occurrence of the disease in cutaneous form. In Tamil Nadu, the disease could be eliminated because the foci were unstable and there was a very effective control programme. For an understanding of vector bio-ecology, it is important to understand the breeding habits and the life-cycle of the vector. For elimination, the epidemiologically dangerous period needs to be identified including biting habits of the sandfly. Longevity and infectivity are important considerations. The strategy of spraying operations has to be guided by the local scenario. Spraying should be done around water bodies to be focused for maximal impact and economy. This approach is also environment friendly. Water bodies can be identified through RS and GIS. Resting habits of the vector are indoor – in the cracks and crevices of mud houses. They survive up to 2 meters and can hop for about one meter. Sandflies have also been detected in rat burrows. The vector is anthropophilic and is an opportunistic feeder. The population build-up is slow because of the lengthy life-cycle. Following control measures, the build-up of the sandfly will be slow after the decline in the effect of the insecticide. DDT is quite effective for about one year. it not only kills, but also repels the sandfly population and there is poor survival when it is exposed to inhospitable terrain. Pyrethroids are also effective but they are expensive. The spraying has to be done in two rounds and there is a risk of development of resistance to pyrethroids. Because of the local and focal nature of the disease, the integrated vector management (IVM)

strategy is more likely to be successful than IRS strategy applied in isolation. Insecticide-treated nets (ITNs) work by acting as a man-mosquito barrier. The requirements for IVM were identified.

Dr Chusak Prasittisuk, Regional Adviser, WHO/SEARO, considered kala-azar as a disease that occurs in conditions of high humidity. It is related to environmental sanitation. India has depended a lot on IRS, Bangladesh on IRS and ITNs, and Nepal has used control measures on a limited scale. Dr Chusak recommended increased adoption and endorsement of IVM. The IVM policy will not only be useful in kala-azar elimination but will also help in the control of other vector-borne diseases. IVM includes IRS, ITNs and environmental management organized and managed according to programme needs. The environmental programme should adopt the COMBI strategy through a healthy public policy and IVM should be implemented within the framework of this policy. He reaffirmed the need to enhance the capacity of the health system by using the Geographical Information System (GIS).

Discussion points

- There should be integration of disease surveillance and vector surveillance in the elimination of kala-azar. These surveillance systems should be action-oriented so that there is prompt response that contributes to reduction of disease burden.
- In contrast to malaria, the vector has remained stable and has not changed its characters. Humidity, vegetation, habitat, crop and temperature requirements of the vector are known. Meteorological data are available for more than 50 years. This would be useful for GIS. There is a need to use GIS in the stratification for kala-azar elimination efforts. The use of GIS and RS will help to undertake focused IRS to economise on the use of insecticides and reduce environmental degradation,
- The quality of ITNs and IRS should be assessed and built in-to the programme.
- There are information gaps which need to be identified and rectified. Capacity has to be increased for implementing IVM. If there are difficulties encountered in IRS, outsourcing should be considered as an alternative. This should be coordinated with COMBI. Entomologists in each country should be able to carry out

entomological studies. WHO should help in capacity development. Bihar has a poor capacity at the moment. At this time it is not practical to place an entomologist in each district. Programme difficulties should be taken into account while making recommendations about staffing.

- Cleaning up of the environment and improving the living standards of poor people is an integral part of IVM. This will also help in poverty reduction. The focus of the elimination programme is to encourage cleaner homes and peridomestic environment. Low-cost methods should be a part of BCC like regular plastering of floors and walls with mud mixed in lime. This should be scientifically tested for efficacy.
- For ITNs, the size of hole of nets is important since sandfly is much smaller than anopheles mosquito. A unified insecticide policy for endemic countries is necessary for effective elimination of the disease.

8. DIAGNOSIS OF KALA-AZAR

Dr Abdullah El Masum (Bangladesh) stated that the diagnosis of kala-azar is not easy or cheap. Immunodiagnosis is widely used since it is simple. However, conclusive evidence comes from bone marrow aspiration which can help in diagnosis. However, the sensitivity is low. Splenic puncture is the gold standard but it has risks and therefore not widely used. Skin smear is useful in the diagnosis of PKDL. Serological tests include aldehyde test, and antimony test. Aldehyde test is quite popular; it becomes positive three months after infection. Most doctors start treatment if this is positive. Immunofluorescent Agglutination Test (IFAT) is also quite a popular test. It has a high sensitivity and specificity but this is not done in Bangladesh. DAT is simple and reliable but it is expensive. Bangladesh has established five sites where this test can be done. Of these, only one centre in Dhaka is functioning. The sensitivity and specificity of the available serological tests were reviewed. ICT can be done even in remote areas of the country. In Bangladesh, diagnosis is very difficult in the early stages of the disease. Therefore, the patient gets treated with antibiotics and steroids by quacks. Then the patient is taken to a GP who tries different treatments and following failure, the patient is referred to the upazila health complex where an aldehyde test is done. ICT is available in

the district hospital and in the private centers. This is expensive and unaffordable. Results from the laboratories should be reliable and there should be quality assurance and quality control. TDR is helping in this effort. The effort in Bangladesh has included training in good laboratory practices in 14 centres. The sensitivity and specificity of rk39 are well above 90%.

Discussion points

- In one endemic district in Nepal, rk39 was done in a door-to-door campaign. The rk 39 positivity rate was very high. The test was used only in cases who were suspected to be suffering from kala-azar. The test was provided with support from USAID. Training was given to the staff and monitoring was done. Confirmation was done with bone marrow. There are four reference laboratories that helped in quality assurance. In a study comprising more than 900 individuals, the sensitivity exceeded 95% for rk39 dipstick test. Now the programme is being supported by the World Bank.
- In India the sensitivity of rk 39 is 98%. This study was done in more than 1 000 patients. This was a part of phase IV trials of miltefosine.
- The rk 39 is not produced in the endemic countries. It has limitations in cases of kala-azar HIV coinfection. The price for ICT is US\$1.5, and the test is available for widespread use. The recombinant rk 39 is a patented product. This test needs to be validated under field conditions.
- DAT is produced in India by research laboratories. There are efforts to decentralize the production of DAT in India and Sudan. DAT can be a cottage industry product but it will have to be backed up by a quality control system for the test to be reliable. DAT requires cold chain and it would be strategic to establish links with cold chain which is already functional and is monitored by the EPI programme. DAT remains positive for about three years. Therefore there is a risk of retreatment when the patient has been cured already. Currently, the cost of DAT is about US\$ 3. If there is a global market for these tests, the cost is likely to come down. Therefore, an estimate should be made of the requirements so that WHO can undertake negotiations for a price reduction for the test.

- Diagnostic systems are available for detecting PKDL. These are important issues to be discussed in RTAG.
- Programme issues relating to laboratory diagnosis include recommendations regarding the choice of tests at different levels of the health system, standardization of blood to be tested, humidity and temperature, training of staff responsible for doing the tests and monitoring of quality.

9. DRUGS AND TREATMENT

Dr S.K. Bhattacharya, Director, Regional Medical Research Centre (RMRC), Patna, India, reviewed the treatment of kala-azar and summarized the new developments and problems in currently-used treatment. The currently-used drugs are becoming ineffective since there is about 50-60% drug resistance (SAG) in some districts in Bihar. Cardiac toxicity is a major limitation of the drug. Pentamidine was tried but this is associated with irreversible diabetes mellitus. Amphotericin B is useful but it requires hospitalization and has to be given by injections. Liposomal amphotericin is good but very expensive. Miltefosine was originally developed as a drug for the treatment of breast cancer. Following successful experience in experimental animals, miltefosine was tried by Dr C.P. Thakur, Dr TK Jha and Dr Shyam Sunder in India. It showed 94% efficacy as compared to 97% for amphotericin group of drugs. The fever comes down in about seven days after starting the treatment. Miltefosine is given as a 28-day course. The side-effects include vomiting, diarrhoea and rigors. These occur during the first week and are self-limiting. Miltefosine is not advised in pregnancy during the first three months because of the risk of teratogenicity of the drug. Women of reproductive age given miltefosine should be asked to use contraceptives to ensure that they do not become pregnant while on miltefosine. Pregnancy should not occur for at least six weeks after discontinuation of miltefosine. Contraception is advised during this period. The side-effects of miltefosine were less common than amphotericin. The efficacy was also established in children in more than 95% cases. The cure rates are above 90% in previously-treated cases. Phase III trials were followed by phase IV trials in 1 000 patients. This phase was carried out on out-patients. In this phase there was a six-month follow-up and one and a half years, follow up for adverse effect on male reproductive system. Phase IV studies were conducted in 15 centres. This was jointly done in collaboration

between TDR, ICMR and coordinated by RMRC. There were 369 females in this trial. There were 5 deaths. Out of 1 000 patients enrolled, only 50 dropped out and there were less than 30 treatment failures. Rescue treatment was needed only in 12 patients. Of the 1 000 patients, 92% were parasite positive. There was 94% initial cure and 84% final cure. Side-effects were reported in 8% patients in the first week and only 0.8% at the time of final follow-up. The drug is now registered in India and in Germany. Paromomycin is a new drug under trial in Phase III. The results are not yet available. Drug trial for PKDL is proposed.

Dr C.P. Thakur, Chairman, Balaji Uthan Sansthan, India, stated that there may be under-reporting of cases by 5-6 times. The first peak of kala-azar was in 1977, the second peak was in 1992 and currently the disease, which is third peak, has spread from Bihar to Bangladesh and Nepal. In Nepal, it first appeared in the border districts but it is now spreading northwards. The occurrence of the peaks was followed by intensification of efforts and enhanced resources for diagnosis, prevention and treatment which led to a decline in the number of cases reported. Once the cases decline, control measures are relaxed, and funding is reduced, which leads to a build-up of the disease. Due to favourable temperature and humid conditions, the spread of the disease has been more to the east than to the west. Since the early 1970s, cases of PKDL have steadily increased. Cases of PKDL will be a major bottleneck in disease elimination. The only oral drug is miltefosine; paromomycin is given IM while amphotericin is given IV. SAG is still an effective drug in Nepal and Bangladesh. Amphotericin B is very effective but has a toxic effect. It can only be given IV and therefore can be used only in hospitals. Liposome is not toxic. It can be used as a rescue drug. Due to the risks associated with injectable drugs, auto-disabled syringes have to be used. There is a need to consider both paromomycin and miltefosine as the first-line drug. While miltefosine has been registered, paromomycin is going through Phase III trials. For treatment with paromomycin, a 21-injection course is recommended. The risk of these drugs is enhanced if the patient is severely anaemic. Therefore prevention and treatment of anaemia in kala-azar-endemic areas is of paramount importance. Linkages should be developed with programmes for anaemia control. The drug of choice in kala-azar and HIV/AIDS coinfection is to use amphotericin B. For vector control, DDT can be used and ITNs treated or untreated can also be useful. Pyrethroids can be used but they are four times more expensive and resistance is likely to develop within two years of starting pyrethroids. Sanitation and hygiene

should be stressed. Housing and ecological conditions need to be improved. The roles of centre, state and districts was defined. The national government holds the key for defining the policy, funding, mobilization of resources from international agencies and for supervision of the programme. The state government has got a huge infrastructure and which can be galvanized for the programme. For elimination, funding is crucial. Lack of funds is responsible for failure of the elimination programme. There is a need to involve private doctors since they are approached first for diagnosis and treatment. Non-allopathic practitioners need to be involved too. Efforts to involve NGOs were not very successful because of the lack of control and regulation. Training and capacity development and monitoring and evaluation are crucial for success. The four centres contributing to research in India should be fully utilized and networking of institutions is important. In addition, medical colleges can be involved. Involvement of the people in kala-azar elimination is necessary and improvement of the home environment is the key to success.

Discussion points

- Since miltefosine can be given orally, it can be administered on an ambulatory basis. This helps to increase access to treatment. Miltefosine has not been registered in Bangladesh and Nepal yet. This may be a constraint in expansion of the programme. A regulatory and testing framework is important and this needs to be strengthened. Miltefosine may have a teratogenic effect if used during pregnancy. Therefore it is to be avoided during early pregnancy. Pregnancy should not occur until six weeks after discontinuation of the drug. The cost of pregnancy test should be included in the programme. Birth control has to be advised to avoid pregnancy. Pregnancy is not common in patients having kala-azar and, if present, the cases for some reasons abort.
- Paromomycin can be a good first-line drug but is awaiting registration. It is undergoing Phase III trials. Patients who do not respond to miltefosine should be put on paromomycin. The cost of paromomycin is less than miltefosine but the added cost of auto-disable syringes and the cost of injections neutralize this advantage. Doctors have to be aware of the toxic effects. More information on paromomycin is needed before it can be recommended as the first-line drug for the treatment of kala-azar.

Table. Comparison between miltefosine and paromomycin

Parameter	Miltefosine	Paromomycin
Stage of development	Phase III and IV completed in India. Phase IV in progress in other countries.	Phase III in progress
Registration	India, Germany	Not done
Route of administration	Oral	IM
Duration of treatment	28 days	21 days
Cost	Expensive - about US\$ 50 per treatment	About US\$ 10 for adult and US\$ 5 for child. Add the cost of auto-disable syringes and the cost of injection to this cost for 21 days treatment.
Toxicity	Gastro-intestinal	Ototoxicity
Dangers of administration	None	HIV,HCV,HBV, other infections due to poor hygiene during injection
Training	Yes	Requires staff trained in giving injections
Acceptance	Likely since the drug is given orally	Low compliance since patient must come regularly for injections
Storage	Easy	Requires cold storage
Experience with treatment	Yes	None
Pregnancy	Contraindicated in early pregnancy	No safety data but side-effects unlikely

- In Bangladesh, the only drug that is available is SAG. This drug can produce abortion. In Nepal, paromomycin is still under Phase III trials. This drug is likely to be available in India with the possibility

of local production. Initial cure means cure at one month i.e. parasite negative and final cure means no parasites at the end of six months.

- Amphotericin B and liposomes should be used in cases of hospitalization and reserved as rescue drugs.

10. SOCIAL MOBILIZATION THROUGH COMMUNICATION FOR BEHAVIORAL IMPACT IN KALA-AZAR ELIMINATION

Dr Ashok Sharma, NPO, WHO/Nepal, presented the experience with IEC for kala-azar. It was carried out in two districts, Dhanusha and Mohatari. High risk communities for kala-azar were identified. There is a large cadre of female community health volunteers (FCHV). One FCHV is available for about 400 population. Many of these FCHVs are illiterate. The task was to help identify cases of kala-azar through FCHVs. Their diagnosis was backed up by health centres, health posts and primary health care centres. Rapid diagnostic test rk 39 was provided in primary health care Centre (PHCC) with a population of about 10 000. SAG was made available in PHCCs. The programme was backed up by a referral system. This system ensures the provision of back-up facilities for patients of kala-azar. A treatment card was devised as a tool to ensure treatment adherence. The process comprised analysis of community awareness and existing behaviour, which was followed by a key message development workshop. Relevant material was developed followed by testing and then production of key behavioural messages. The nine tools developed for BCC comprised umbrella logo, wall posters, consumer leaflets, flip charts, comic wall posters, wall paintings, street dramas, haat bazaar mikings, and songs. This was done to empower people. The materials developed were presented. The Nepal group demonstrated to RTAG a drama on kala-azar lasting about 25 minutes. A local NGO could cover about 600 people at a cost of about Rs 2 000. Another strategy was to package a two-minute message. A video was developed to educate the community at district level. The expected outcomes were defined.

Dr Joshi, Tribhuvan University, Nepal, stressed the importance of social diagnosis of the disease before launching interventions. A model was presented to improve the quality of life through behavioural change brought about by health promotion. The combination of behavioural change and environmental support comprising improved housing and environment is an important component of behavioural change.

Dr N.B.L. Saxena, summarized the experience in India. In the first phase of the programme, the focus was to target diagnosis and inform the public that diagnosis and treatment are accessible. The intention was to focus on the bad effects of wrong treatment. This increased awareness but did not bring about behavioural change. Now the focus is on bringing behavioural change along with impact assessment. The programme recognizes the importance of sanitation and hygiene as an integral part of kala-azar elimination. The other emphasis will be on seeking early diagnosis and treatment. A public-private mix should be considered.

Discussion points

- Since kala-azar is a disease predominantly of the poor, community mobilization is extremely important but this aspect often gets ignored in the programme. The access at present is poor and linkage with the community is not adequate. IEC has been disappointing. However, investments in IEC activities have been low. BCC and COMBI should be considered in enlisting community involvement. Criteria to identify the poor to target interventions is a gap that has to be addressed.
- A lot of success in social marketing has been achieved in some countries. Since BCC may be expensive, it may be useful to pilot the strategies in selected districts in the country before committing large resources. This would be useful in modifying plans and in refining them before scaling up.
- The BCC approach brings in a wealth of information to learn about people's behaviour and living conditions. For the elimination of the disease, political commitment is very important and it needs somebody to champion and sustain it. Investments on BCC should be substantially increased and inputs from social sciences discipline involvement should help in developing a behavioural change strategy and provide guidance and support during programme implementation.
- For behavioural change to occur, there is a need to fit the programme into the lifestyles of the people in a seamless manner. Efforts made in Nepal seem to have worked even in areas the literacy levels are very low and the socioeconomic status is poor. The success of the programme has depended on the woman

volunteer who lives in the community. Village-based women volunteers in all the three countries are potentially powerful change agents who can involve people in bringing about behavioural change but there has to be a link between health facilities and volunteers for the programme to succeed.

- Home care of patients suffering from kala-azar is important. Training material can be prepared for home treatment of the disease. There are experiences that demonstrate the role of female health volunteers in helping to reduce infant mortality rate through application of simple interventions in the control of ARI and diarrhoeal disease. There is also a successful home care programme for mental health. Home care guidelines will help in meaningful participation of families and health volunteers. They will help to empower people to be able to take care of themselves, adhere to treatment, and provide guidance on the food that they eat, the clothes that they wear and on the housing conditions and cleanliness around their home.
- For BCC to succeed it is important to know the main behavioural objectives that are to be identified by the people. At the same time, people should be aware of the programme and know that treatment is provided free of cost. Instructions should be clear so that they can be followed. BCC should also involve decision-makers and advocacy should be sustained. WHO should be involved in this advocacy. The social class affected by kala-azar is changing. IEC and BCC should be so designed as to fit very low literacy levels of the population. To take the programme to the poorest people BCC should be simplified.
- Considering the ecology of the disease and the issues related to poverty, sanitation of household and peridomestic environment is an important part of environmental management. Cheaper housing for the poorest segments in the areas is important and this may be taken up with poverty mitigation programmes.
- Housing conditions need to be changed along with bringing about a social change. It is important to know what contributed to the success and to review the lessons learnt. The success in Nepal was due to a commitment and decentralized planning of the control programme. Resources were reasonable and this contributed to the success of the programme. A single factor which led to failure was

the lack of sustenance of funding and resources. However, at that time, the drugs used were toxic and cumbersome to administer.

- In Nepal, specific communities (*Moosahars*) are affected. They are landless and work as contract labourers. They eat rats and live in one corner of the village. The disease is changing its target from the well to do to the poor and now the poorest. The *Moosahars* are amongst the poorest amongst the poor. Their housing conditions are very poor. Collaboration is needed with poverty elimination/mitigation programmes and those that focus on environmental improvements. Message development has to be targeted to the poorest of the poor in the community – one that catches the imagination of the people.

11. ECONOMIC IMPLICATIONS OF KALA-AZAR

Dr S.R. Howlader, Dhaka University, Bangladesh, described the economic implications of kala-azar. In Bangladesh, at least 30% of the people are poor with earnings of less than 1 US Dollar per day and the national per capita income is about US\$ 350 per year. There are more than 1 000 NGOs but the government health sector and NGOs do not have access to remote and poor people living in low-lying areas of the country where kala-azar is endemic. Besides the goals and targets, an important challenge is to address the problem of inequity and tackle financial gaps. The government is addressing the problems through a Poverty Reduction Strategy Paper (PRSP). Kala-azar is mentioned in the national policy and plans. Kala-azar affects the poorest amongst the poor and therefore there is a need for its elimination to provide for equity and for promoting SE development. DALYs are widely used but they do not take into consideration economic losses as a result of illness of individuals in the family. Economic burden should be estimated on the basis of loss of future income, expenses incurred by the family on the illness, funds expended by the government or others, non-medical expenditures and losses as a result of loss of work. To this should be added the value of income lost. The loss of income is higher when the poor get sick as compared to the rich. Elasticity in the poor is limited since the expenditure on medical expenses has an impact on food and other essential expenditure. In case of death, the loss has to be calculated on the number of years of loss of productive life.

Discussion points

- A study supported by USAID in Nepal showed that the proportion of household expenditure on medical care is higher amongst the poor than the well-to-do. Poor people usually go to private doctors who charge about Rs 8 000 on an average. In a sample population, some people were spending even more than Rs 50 000. For treatment of the disease, they ended up selling their house, their cattle and other possessions. This drove them further into poverty and led to a complete breakdown of family finances.
- There is an adverse impact of kala-azar on the health system too. In a small hospital in a district in Nepal, 12 out of 15 beds were occupied by patients with the disease. Clearly, other patients deserving of care are marginalized and excluded from treatment.
- Kala-azar is not only a disease of poverty but also a source of poverty. In another study, outreach programmes were responsible for the diagnosis and treatment of kala-azar adopted as a strategy. There was a six-fold saving in using the outreach detection and treatment system as compared to hospital-based diagnosis and treatment.
- Economic implications are very important for advocacy and this should be done first on the basis of the available knowledge and, at the same time, develop a partnership with health economists. This partnership would be important in providing evidence to planners and key decision-makers in the country to make a strong case for resource commitment from them.

12. MONITORING AND EVALUATION

Dr Manas Bannerjee, Senior Public Health Specialist, Nepal reviewed the key issues relating to M&E. Case-based data would help to sharpen programme management through a system of prompt feedback. He recommended the use of input and process indicators. This should be complemented by output and outcome indicators. Special household and health facility surveys are needed to assess the impact to complement routine information but should be performed once every 2-3 years since they are expensive and resource intensive.

Input indicators

Policy, strategy and guidelines, advocacy plans, identification of funding gaps, and efforts made to mobilize additional funds should be monitored on a quarterly basis. A national coordination committee for kala-azar, a functioning task force, as well as regular meetings of the task force are important input indicators to monitor.

Process indicators

Include the preparation of guidelines for training doctors and health workers, spray team members and supervisors, and use of a supervisory checklist. Other important process indicators are procurement of supplies, establishment of a system of supplies, quality of drugs and diagnostics, proportion of health facilities where quality check is done, proportion of cases detected through search, recommendations on the use of insecticides, national guidelines for the use of insecticides, timeliness of supplies, and stock-outs of medicines, diagnostics and insecticides.

Output indicators

The proportion of population with access to diagnosis and treatment may be reflected as the number of health centres and hospitals that provide standard diagnosis and treatment. The outcome indicators include knowledge and practices of the target population, their knowledge about the existence of the facilities, number of cases detected by active search, and cases of PKDL. Information can also be obtained from implementation research supported by TDR in India.

Impact indicators

Include response to treatment, proportion of cases cured of kala-azar, participation in IRS, sanitation and personal protection measures, decline in the number of reported cases, deaths, PKDL etc. These can be measured once every 2-3 years by household and health facility surveys.

Discussion points

- Besides surveillance, the programme should consider process indicators as intermediate to case detection. The use of process indicators can be covered under monitoring and evaluation of the programme.

- It is important to explain the indicators and define the criteria to determine the outcome. Indicators should be finalized after reaching a consensus. Then, how to measure the indicators that are agreed upon should be defined. Validation of findings is an integral part of monitoring and evaluation. M&E is an essential part of the programme but does not receive as much attention as it deserves. Funds allocated for M&E are a serious limitation. M&E can serve as an advocacy tool to demonstrate the performance. The results help in sustaining the interest of the partners as well as in sustaining resource mobilization. An important issue is to ensure the “doability” of M&E while maintaining the quality. It should be reviewed to identify and adopt the indicators relevant to measure programme performance. From an operational perspective, M&E should not be put off. The staff should be trained on M&E right from the beginning. In the plan to eliminate kala-azar, there should be 3-4 indicators in each area to assess the progress made in the elimination of the disease.

13. NETWORKING OF INSTITUTIONS

The technical support to be provided through institutional networks for capacity development was reviewed by Dr Ravi Kumar, NPO, WHO/India. District is the basic unit for health care delivery in the three endemic countries. District-level management guidelines should be available so that kala-azar elimination is possible through the adoption of a decentralized integrated approach. Capacity development comprises diagnosis and treatment, vector control through IVM and disease surveillance. The main management issue is the management of logistics and supplies. The target for training are trainers, researchers, laboratory personnel, treatment providers and spraying staff. The staff for training has to be targeted to include public and private health care providers. The network should include health department and universities, funding agencies, WHO, UNICEF, CDC, private sector including manufacturers, private doctors and NGOs. The action points include coordination of activities through intercountry consultations, in-country reviews and external evaluations and coordination of activities through RTAG. The issues and challenges include funding support on a sustainable basis, coordinating epidemiological and entomological studies, international partnerships that are sustainable, cross-border collaboration,

synergies with related programmes, microstratification using tools like RS and GIS, development of COMBI, and new tools for ongoing programmes.

Dr Mannan Bangali NPO, WHO/Bangladesh, commented that capacity is required for diagnosis and treatment, disease and vector surveillance, IEC and BCC, and operational research. Capacity development is required at all levels and involvement of other sectors in this is important for successful elimination. He emphasized the need for socioeconomic impact studies. The institutions should provide evidence for policy development and refinement.

Discussion points

- Tools and guidelines for training of health care providers is a priority. There should be national treatment guidelines to make the practices uniform. The training package should comprise guidelines for hospitals, health centres and homes. The training guidelines should be developed based on standard operating procedures, and include vector control.
- Capacity development is the key to success in the elimination of kala-azar. Networking and partnerships would be crucial in capacity building through development and adaptation of training material and by training of staff at different levels of the health system. Behavioural change communication should be included as an integral part of capacity development. Networks would also be useful in involving the private sector and NGOs. It is important for the success of intercountry and cross-border collaboration. Research capacity development and research coordination can be streamlined through networking. Its value in facilitating information exchange for action cannot be underestimated.
- There are a number of institutions that are contributing to research relating to kala-azar. Medical colleges in the affected states and districts should also be involved to enlarge the scientific and research base for kala-azar elimination.
- Quality assessment and assurance are going to be important and monitoring of drug resistance, drug and diagnostic quality and insecticide resistance and treatment completion are to be monitored closely as an integral part of elimination efforts. This can be facilitated through networking.

14. RESEARCH PRIORITIES IN KALA-AZAR

Dr S.K. Bhattacharya, RMRC, India, identified the research priorities in kala-azar. Aldehyde test is non-specific and should be discontinued. He recommended research on the usefulness of rk39 under field conditions, especially how the test performs under high humidity and temperature conditions in the field. The validity of DAT as compared to rk 39 should be evaluated. DAT has been produced by three laboratories in India. There is a need to standardize the DAT test for quality. There is a latex urine test which needs to be evaluated further. Urine test is unlikely to be helpful in diagnosing of kala-azar. Further research on paromomycin and trial of combination of miltefosine and paromomycin can enlarge the basket of treatment and increase preparedness of the programme to deal with the problem of drug resistance. The PKDL problem needs to be better defined, its diagnosis made more reliable and its treatment evaluated for 8-12 weeks of treatment by miltefosine. Phase IV trials of paromomycin are recommended. The issue of research on new drugs and monitoring of drug resistance is important. For this, implementation research supported by TDR is in progress. The success in kala-azar programme will be determined by the success in treatment adherence. This is critical since treatment of kala-azar is prolonged and there may be gaps in continuity.

Dr Axel Kroger, TDR/HQ, stated that implementation research is important to decide effective delivery strategies. To start implementation research in India, a workshop was organized by TDR in Varanasi in 2003 to identify research questions, methodology and define interventions. Time-lines were established, protocols prepared and capacity developed. The focus of research is on treatment adherence. The various factors that are included are the health system, health facilities and patient-related factors. A household screening survey will be done by two centres to cover about 80 000 population to determine disease prevalence and incidence. This will be followed by an in-depth interview of households where cases are detected and behaviour and the attitudes of families assessed. Social scientists will do a policy and behavioural analysis. Another group will focus on cost aspects. Results are likely to be available in about one year. It is hoped that contextual factors, people's behaviour and providers practices, skills and resources will be determined. This package will contribute to the first phase of the elimination programme. There will be a review meeting in which recommendations and guidelines as well as behavioural change interventions will be validated. This research may be extended to Bangladesh and Nepal if

there is national interest. In the vector control area, we know that even untreated nets provide some protection when the biting habits of the vector are indoor and ITNs are adapted to the biting habits of the vectors. It has a great potential if there is community empowerment. An insecticide for treatment of nets was demonstrated. Insecticide-treated material such as a curtain, used in Mexico, was shown. The issues to be addressed for research are to know when and where people are exposed to the vector, development of resistance to pyrethroids and cost comparison of ITN with IRS (DDT or pyrethroids).

Discussion points

- Latex agglutination test is under evaluation. In this test, leprosy and other diseases may be confounding the results. ELISA can be considered to make the task of surveillance more user-friendly. However, this needs to be researched before it can be recommended for the programme. For monitoring of the programme, a sero surveillance tool might be very useful. This can be used for the early warning system once it is proven to be useful.
- Operational research issues need to be defined. Operational research should help identify constraints in implementation and it should complement elimination efforts. The establishment of diagnosis at community level is going to be a colossal task. A lot of research is already going on. This needs to be reviewed, collated and used in preparing country profiles that reflect the special features relating to programme management in each country.
- Research on PKDL. Validation of tests in the community, how serological tests behave after implementation is started are important programme issues. It would be useful to know if the parasite load can be recognized through PCR techniques. PKDL cases can be treated but the duration is 120 days. It is advisable to use short courses with a gap of about 10 days. The efficacy of this treatment should be determined. Miltefosine is likely to be useful since it was originally used for skin metastasis of breast cancer. PKDL cases are confirmed by skin biopsy.
- ITNs are likely to work if there is community back-up for buying and for retreatment of the nets. Research on equitable distribution of ITNs and their social marketing is relevant.

- Operational research to validate surveillance will be important to support the programme. A study of the indicators and how they are working is a priority. Research on outcome and output indicators will be very useful for the programme.
- Besides efficacy, feasibility is very important; what models can be developed that patients adhere to treatment and how best adherence can be ensured; what is the role of public-private mix and what should be the practices of private doctors. It is important to determine the economic impact of the programme. Piloting of the elimination strategy might be useful to help refine it.
- Estimation of economic burden of disease is needed to enlist commitment of the government. What are the cost projections when a switch-over to new diagnostics and treatment is undertaken?
- Avoiding research that is repetitive is important. Partnerships should be evaluated and factors identified which facilitate or constrain partnership sustenance. There can be partnerships in capacity building. It is necessary to identify who will be trained. Data sharing should be expanded. These partnerships can be useful in identifying support organizations.
- Behavioural research should be prioritized e.g. household and peridomestic environment and bringing about the change, mainstreaming of the poorest, ITNs and treatment-seeking behaviour. There is a need to promote economic arguments for elimination of the disease.
- Research on issues which are impeding the implementation of key interventions and research on management of the programme and those issues which relate to measurement of the progress are important. Access to the poorest of the poor is the most important challenge. Researchable issues in relation to vector control should be identified. How we take policy decisions based on evidence is important. A lot of research has taken place during the past 10 years but implementation has been less than 5%. This imbalance needs to be corrected.

15. GROUP WORK

The participants were divided in two groups. Each group was given separate terms of reference: Group 1 was chaired by Dr S.K. Bhattacharya and Group 2 under Dr P.L. Joshi.

Discussion points

The core issues identified were prioritised and discussed during the group work.

- Elimination of kala-azar would require mobilization of additional resources. Advocacy plans for mobilization of resources from the other partners should be developed.
- Success of the elimination efforts would depend on effective mobilization of the community. District plans for community mobilization need to be drawn up and implemented through involvement of the community through village committees.
- Monitoring the quality of drugs, their uninterrupted supply, insecticide and drug resistance is necessary to ensure the quality of treatment and its impact. To monitor the quality of diagnosis and treatment, linkages will be required with laboratories and research institutions.
- Treatment adherence is important. Treatment should be provided free of cost in the public and private sectors for the elimination to succeed. Other measures include the provision of free treatment to patient's attendants during hospitalization. The use of treatment cards is likely to increase treatment compliance. In the case of very poor patients, expenses may have to be borne also for covering the cost of travel to the treatment centre.
- Treatment of PKDL should be part of the guidelines. Treatment of PKDL is a priority. This is difficult and drugs should be given for several months in the form of 4-6 courses of treatment for curing the disease. Interruption of drugs may be required for a period of 10 days to reduce the risk of toxicity. The programme should place priority on recognition of cases of PKDL. If this is not done, then transmission of the disease cannot be stopped.
- Miltefosine cannot be given during early pregnancy; therefore recommendations are needed on treatment of kala-azar during this period.
- The adverse socioeconomic effects should be estimated. This should be the subject for operational research. The findings of this research may help in sustaining efforts towards mobilization of additional resources.

- The link between kala-azar and HIV/AIDS may be an important issue in elimination. Patients with HIV/AIDS who also have kala-azar should be treated with ARV drugs irrespective of CD4 counts.
- Determining donor profiling is important since it may be possible to match the profile with what component each donor would like to support.
- An expert committee should be constituted by WHO to finalize the monitoring and evaluation strategy.
- Multi-centric research should be supported. Research related to implementation, initiated in India, should be extended to other countries. The issues should be based on needs. Research priorities should be provided to TDR for consideration. There should be TDR profiling. The studies should be on efficacy and operational feasibility of use of the drug and of using it in the programme.
- There should be an understanding among Member States that a drug which has been approved for registration in one country it should not require similar procedure in other countries.
- Validation of guidelines for IVM.

16. RECOMMENDATIONS

- (1) RTAG noted with concern under-reporting of patients receiving treatment outside government health facilities. To pursue the goal of kala-azar elimination, an effective surveillance system on kala-azar and PKDL with uniformity in reporting criteria is essential. To ensure timely access to information for decision-making it is necessary that appropriate data are compiled and managed as an in-built and integral component of the Kala-azar Elimination Programme.
- (2) Institution-based passive surveillance should follow standard case definitions as follows:

Suspect: A case of fever of >2 weeks not responding to antimalarials and antibiotics

Clinical: A suspect case with serology (DAT/rk39) positive

Confirmed: A clinical case with evidence of parasite demonstration

- (3) Criteria for case reporting at different levels of the health system
 - Union (Bangladesh), PHC (India) and Health Post (Nepal) to report Kala-azar suspect cases as per case definition
 - Upazila (Bangladesh), CHC (India) and PHC (Nepal) to provide access to serology test (rk39) and report clinical kala-azar based on serology evidence.
 - District (Bangladesh/India) Zonal/District (Nepal) to provide access to confirmatory diagnosis for reporting confirmed kala-azar cases.
- (4) Monthly reporting should list suspect, clinical and confirmed cases for analysis and prompt response with intervention.
- (5) Since PKDL cases are important reservoirs of infection, surveillance systems should include reporting of PKDL.
- (6) Active surveillance should complement passive surveillance. A well-planned campaign with appropriate service back-up should be organized at least once a year.
- (7) Behavioural change communication should be introduced through appropriate health promotion activity encouraging community to seek health care at the appropriate facility.
- (8) Research Institutions should develop and validate sero-surveillance system that could be integrated in the Kala-azar Elimination Programme.
- (9) Keeping in view the operational feasibility of miltefosine being an oral drug, it should be the first-line drug for clinical and confirmed kala-azar cases. The recommended line of treatment is:
 - Male patient with clinical or confirmed kala-azar should be treated with miltefosine in recommended doses. Non-pregnant female patients accepting birth control measures could be treated with miltefosine. Pregnant females and females not accepting birth control measures should not be provided miltefosine treatment and must be referred for alternative treatment.
 - Patients not responding to miltefosine should be referred for alternative treatment.
 - Efficient systems should monitor patient compliance for complete treatment and ensure that drug is not administered

to high-risk groups, viz. pregnant women and women of reproductive age not accepting birth control.

- (10) Entomological database at local level needs to be generated for efficient kala-azar transmission control through IVM. To facilitate this, a district entomology unit should be operational. The entomological team, besides raising technical data, should develop intersectoral linkages and partnerships as per requirement of IVM strategy.
- (11) IRS, which remains the most effective available tool for vector control, needs to be sustained for a minimum of 3-5 years. In India, DDT is the potent insecticide for this purpose. However, Bangladesh and Nepal have to use synthetic pyrethroids in view of the ban on DDT use.
- (12) In view of ecological sensitivity of the kala-azar vector, environmental sanitation is an effective long-term sustainable approach for source reduction. It needs to be promoted through appropriate behavioural change communication strategies.
- (13) In low-risk areas, personal protection methods should gradually replace IRS.

17. CONCLUDING REMARKS

The participants expressed the hope that the goal of elimination kala-azar will come true. Dr Chusak thanked every one for sparing their time to come and participate in the meeting and for their invaluable contributions. This may be the beginning of making of history in the elimination of this scourge. Thanks were expressed to the Chair and the Rapporteur and all the people who worked hard to make the meeting a success. The technical contributions of RTAG were appreciated.

The Chairman thanked RTAG members for their contributions and for assisting in the conduct of the meeting, and the temporary advisers for their contributions. The Chairman thanked WHO/HQs for its technical support. The sustained interest of TDR was appreciated. Thanks were expressed to Dr Chusak for his painstaking efforts in organizing the meeting.

Annex 1

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Annex 2 PROGRAMME

Day 1 (Monday 20, December 2004)

0800–0900	Registration	
	Session I – Opening Ceremony	
0900–0930	Inaugural Address by the Regional Director, WHO	To be read out by <i>Dr N. Kumara Rai</i> , Director, CDS, WHO/SEARO
	Remarks by TDR/CDS/WHO/HQ	<i>Dr R. Ridley</i> , Director, TDR/CDS/HQ
	Briefing on RTAG Advisory Group Terms of reference and meeting objectives	<i>Dr N. Kumara Rai</i> , Director, CDS, WHO-SEARO
	Introduction of participants	<i>Dr Chusak Prasittisuk</i> , WHO-SEARO
	Nomination of Chairperson, Co-chairpersons, and Rapporteur	<i>Dr Kumara Rai</i> , Director, CDS, WHO-SEARO
	Administrative announcements	<i>Dr Chusak Prasittisuk</i> , WHO-SEARO
	Session II – Kala-azar situation	
10.00–10.30	Review of kala-azar situation in the South-East Asia Region	<i>Dr Chusak Prasittisuk</i> , WHO-SEARO
10.30–10.50	Kala-azar in Bangladesh	Prog. Manager, Bangladesh
10.50–11.10	Kala-azar in India	Prog. Manager, India
11.10–11.30	Kala-azar in Nepal	Prog. Manager, Nepal
	Session III – Discussion on Kala-azar elimination	
1130–1230	Vision, goals, objectives and targets for Kala-azar elimination	<i>Dr J.P. Narain/ Dr Vijay Kumar/ Dr N.B.L. Saxena</i>

1330–1430	Regional strategic framework and road-map for prevention, control and elimination of kala-azar by 2015	<i>Dr Vijay Kumar</i>
1430–1530	Disease surveillance (Reporting and validation of report)	<i>Dr N.B.L. Saxena</i>
1600–1730	Vector surveillance and control with special emphasis on IVM	<i>Mr N.L. Kalra Dr Chusak Prasittisuk</i>

Day 2 (Tuesday 21, December 2004)

0830–1000	Diagnosis	<i>Dr Abdullah El Masum Dr Kesara Na-Bangchang</i>
1030–1200	Drugs and treatment	<i>Dr C.P. Thakur Dr S.K. Bhattacharya Programme Managers (Bangladesh, India and Nepal)</i>
1200–1300	IEC and community mobilization	<i>Dr Jotna Sokhey Dr Anand B. Joshi Dr Ashok Sharma</i>
1400–1500	Economic Aspects including Disease Burden	<i>Dr Sushil Ranjan Howlader</i>
1530–1700	Monitoring and evaluation	<i>Dr M.K. Banerjee</i>

Day 3 (Wednesday 22, December 2004)

0830–1000	Research priorities	<i>Dr Juntra Loathavorn Dr S.K. Bhattacharya Dr Axel Kroeger</i>
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**Session IV – Inter-country collaboration,
partnership and advocacy**

1030–1230	Inter-country collaboration and partnerships to strengthen advocacy efforts	<i>Dr N.K. Ganguly Dr Vijay Kumar</i>
1330–1500	Technical support through institutional networks for capacity development both at the national and regional levels, followed by discussions	<i>Dr M. Bangali Dr Ravi Kumar</i>

Session V – Working Groups

1530–1730	Group work (2 groups) Development of national work plans for Advocacy for Kala-azar Elimination, and development of a draft National Strategic Framework	Programme Managers and RTAG Members
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Day 4 (Thursday 23, December 2004)

0830–1030	Group work (2 groups) (continued...)	
1100–1230	Group work presentations, followed by discussions	Chairman and Rapporteur of each group

Session VI

1330–1415	Conclusions and Recommendations, followed by general discussions	
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Session VII – Closing Session

1415–1515	Vote of thanks and closing remarks	<i>Dr N. Kumara Rai,</i> Director, CDS/SEARO
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