Report of Meeting of the Regional Technical Advisory Group (RTAG) on Visceral Leishmaniasis and the National Visceral Leishmaniasis Programme Managers of endemic Member States

Virtual Meeting, 5–8 October 2020

World Health Organization
REGIONAL OFFICE FOR South-East Asia

SEA-CD-329

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Summary and recommendations

A virtual meeting of RTAG, with invitations extended to partners, was held over four days (5–8 October 2020) to review developments in the national visceral leishmaniasis programmes of the five VL-endemic Member States, scientific community, and WHO initiatives since the last RTAG meeting (held in Kathmandu, Nepal, 12–14 December, 2018). The main objective of the meeting was to determine how RTAG could support the regional elimination programme most effectively.

Following presentations of the recent evidences, and reports on progress, there were opportunities for extensive discussions leading to the following recommendations which were agreed for action with designated responsibilities:

(1) WHO SEARO to develop new elimination/validation/post-elimination plans for 2021–2030 *(WHO SEARO)*

- The current commitment under the NTD Roadmap expires in 2020 and a consensus is required to sustain programme successes. Despite the unprecedented success of elimination initiative, threat of resurgence persists, if complacency sets in: include post-kala azar dermal leishmaniasis (PKDL) in the roadmap, address cross-border issues, involve local leadership, prepare for the validation process and to develop disease integration frameworks to improve surveillance and sustain elimination efforts.
- Conduct a review of the existing evidence base, and consult Member States, to reconsider:
  - revising the threshold of elimination of VL as a public health problem based on different epidemiological scenarios from the present criteria of <1 VL case/10 000 populations, and
  - setting 'zero cases' and 'zero transmission' as aspirations goals, by 2027 and 2030, respectively provided additional tools to measure and achieve zero transmission are developed.

(2) Collate examples of innovation and good practices from Member States and share as best practices for intercountry learning *(WHO)*

(3) Align definitions of VL case, New Kala-azar (NKA), Relapse and KA Treatment failure, Death, Endemicity, Outbreak, PKDL with WHO terminologies *(All endemic countries)* At present, there are slight deviations between WHO-recommended definitions and those used by different KA-endemic Member States. A consensus to align these terminologies with those of WHO is necessary for intercountry comparison, effective cross-border collaboration, and *preparation of the new elimination plan*.

(4) Guidance on updating treatment regimens (as and when new evidences are available) and its continued availability with assistance of WHO. *(All endemic countries)*

VL elimination will require a continuous supply of safe, effective and quality assured drugs and diagnostics.

Appropriate guidance for the treatment regimens is needed for PKDL, VL and /HIV/TB coinfection, and relapse is expected beyond 2021.

Coordinated actions are needed by Member States and WHO for drug registrations (e.g. paromomycin is not registered in Bangladesh, and LAmB is not registered in Bhutan does not have access to miltefosine), pool procurement mechanisms, best practices and learnings from other regions (e.g. the Region of the Americas) should be examined for creation of strategic/revolving funds by Member States with WHO for procurements.

(5) Revisit the guidance on the process of validation of elimination of KA as a public health problem in SEAR (WHO HQ and SEARO)

(6) Provide advocacy and technical support guidance to continue and strengthen surveillance of VL and PKDL, VL/HIV and VL /HIV/TB coinfection (WHO)

- This should include SOPs for post-validation surveillance (active and passive), BCC (to improve treatment seeking behaviour of patients), and guidance on the most appropriate diagnostics and integration of actions across diseases (e.g. integrate with skin diseases for PKDL).
- Follow-up of VL patients for 3 years after case detection, and PKDL patients for 5 years should be performed, and a mechanism to achieve this should be developed by Member States.
- Follow up of VL and HIV/TB coinfection as these sub-groups of patients pose diagnostic challenges, clinical challenges in terms of limited therapeutic options, poor treatment outcomes with higher relapse and high mortality and public health challenges as they have high parasite load and are high reservoirs of infection.
- Where feasible, sero-surveillance should be considered as a control tool, and an SOP for its implementation be developed.
- Provide guidance on ascertaining endemicity status of non-endemic areas reporting new VL cases (Upazila in Bangladesh, Block in India and Districts in Nepal).
- Provide technical guidance and support for integration of skin and NTDs, including CL and initiate surveillance and reporting.

(7) Establish a VL sub-group in the WHO NTD diagnostic technical advisory group (WHO/NTD DTAG). (WHO)

(8) Establish cross-border collaboration between Member States (Bangladesh, Bhutan, India, Nepal and WHO)

Develop a cross-border coordination mechanism between Member States to share and information and learned experiences, similar to that experienced during polio campaigns or currently being used in malaria and EPI programmes. This may involve operational agreements as well as high level political commitment.

Explore the possibility of piggybacking the existing cross-border collaboration platforms.

(9) Continue vector control and surveillance

- Vector surveillance, including regular insecticide resistance monitoring, should be practiced routinely to support all vector control activities with due consideration on classes of insecticides to use to avoid further development/spread of insecticide resistance (particularly relevant when more than one intervention is used, e.g. IRS, larviciding and LLINs). Ensure a regular supply of WHO insecticide resistance test kits. *(All endemic countries)*

- IRS: the spray equipment should be checked regularly to ensure their proper functioning in spray operations, ensure supply of sprayers and spare parts and provide refresher training to spray teams and supervisory should be provided prior to each round of spraying. The determination of area sprayed around the household of each VL/PKDL case should consider evidence of local transmission scenarios (e.g. a 300 m radius use in Bangladesh). Where second cycle of IRS is not possible on time, insecticide of long effect should be used to scape second cycle. *(All endemic countries)*
- A review of evidence relating to alternative/supplementary vector control tools for sand fly control is required, with special attention given to evidence from research trials with insecticidal paints in Bangladesh and Nepal, and new generation LLINs that have gained momentum. *(WHO and partners)*
- Meanwhile, distribution of pyrethroid-LLINs to VL, PKDL and VL/HIV and confirmed cases is recommended; a strategic approach to supplement vector control focusing on preventing transmission of *Leishmania donovani* (from VL/PKDL patients to sandflies, or infected sandflies to people) is required rather than indiscriminate use of insecticides in households, which may lead to widespread resistance). *(All endemic countries)*

(10) Operational research (and funding) must continue to develop new tools to support the new plans for 2021-2030 for the elimination/validation/post-elimination plans. *(WHO and partners)*

The post-elimination era will require continuation of supplies and new tools with greater precision, e.g. the development of diagnostic tests for: VL cure, asymptomatic patients, PKDL (especially macular forms) and safe, new treatments for VL and PKDL patients. Strategies for appropriate vector control (e.g. when to stop IRS, use of alternative approaches, implementation of vector surveillance at sentinel sites to detect changes in vector infection, and a rapid response of targeted vector control) are required to supplement IVM. The integration of a vaccine programme with new, pipeline preventative and therapeutic candidate vaccines should be explored further. Operational research is required on innovation for newer tools as point of care tests.

(11) Conduct a COVID-19 Impact Assessment on VL programmes. *(WHO and partners)*

(12) Although great efforts have been made to continue with programme activities, such as IRS, the true impact of COVID-19 is unknown. Under reporting of cases may be an important issue which could result in resurgence and affect the precision of VL models. Furthermore, the impact on the health system including supplies and resources has not been fully appreciated. It is also likely that mass migration of non-immune people (e.g. from urban to rural environments) may become infected and contribute to further transmission. Health facilities in endemic and non-endemic areas should be sensitised to consider VL for patients presenting with a fever.

Country-specific recommendations

WHO to support Bhutan and Sri Lanka on capacity building, hot spot mapping and expansion of diagnostic and treatment services, surveillance and IVM.

Bhutan

- Harmonise case management protocols in line with WHO recommendations/other countries in WHO SEA Region.
- Conduct further research to better understand the epidemiology and transmission dynamics of VL.
- Make miltefosine available.

Thailand

- Harmonise case management protocols in line with WHO recommendations/other countries in SEAR.
- Conduct further research to better understand the epidemiology and transmission dynamics of VL, including regular species identification of parasites for CL and VL given their differences to the rest of the Region.

Sri Lanka

- Conduct further research to better understand the epidemiology and transmission dynamics of VL, including regular species identification of parasites for CL and VL given their differences to the rest of the region.
- Harmonise case management protocols in line with WHO recommendations/other countries in SEAR.

(1)

1. Proceedings of Day 1

1.1 Opening session

Due to COVID travel restrictions, the RTAG meeting was held virtually.

Dr Ahmed Jamsheed Mohamed (WHO SEARO) introduced Dr Sunil Bahl, the Acting Director of Department of Communicable Diseases in WHO Regional Office for South-East Asia (SEARO), who delivered the opening remarks confirming that work on neglected tropical diseases (NTDs) was a flagship focus of stakeholders and partners in SEA Region over the last 5 years resulting in sustained decline in VL. To maintain successes, it was appropriate to discuss clinical and programmatic matters to strengthen the program further. The objectives of the meeting were:

- Review the progress and challenges of the Member States on elimination of VL as a public health problem;
- Advise endemic Member States and WHO SEARO on measures to sustain the gain and further strengthen the programmes.

1.2 Participants

As the meeting was held virtually, we could invite more partners compared with previous RTAG meetings; a full list of participants provided at the end of this report.

1.3 Nomination of the Chairperson and Rapporteur

Professor Nirmal Kumar Ganguly was appointed chairperson and Prof Mary Cameron accepted her nomination to serve as the rapporteur. Professor Ganguly expressed how he looked forward to discussions regarding the need to improve diagnostics (for VL cure and PKDL confirmation) and vector control (based on vector bionomics). He welcomed all participants and emphasized the need to retain partnerships with continued investment through funders.

2. Presentations

2.1 Presentation: NTD Road map 2030 and its implication for VL elimination as Public Health Problem (PHP) – Dr Daniel Argaw Dagne (WHO, Geneva)

The NTD road map 2021—2030 was developed through an extensive consultation process and was released earlier in 2020 (see: https://www.who.int/neglected_diseases/Revised-Draft-NTD-Roadmap-23Apr2020.pdf?ua=1). The road map covers 20 NTDs and it is aligned to the UN Sustainable Development Goals and the WHO Thirteenth General Programme of Work (GPW13).

The road map has two purposes:

(1) Enable the national governments to take the lead delivering NTD programmes assist national programmes to take a leading role, and

(2) Encourage the global community and partners.

Of the 20 NTDs, two are targeted for eradication, ten for elimination and eight for control. Cross-cutting targets are presented.

For VL, several gaps were identified that required critical actions including improved diagnostics (VL and PKDL), effective interventions and advocacy to enable early detection and prompt treatment with more effective and user-friendly treatment and funding. This requires a shift from a silo approach to an integrated approach, with better coordination, collaboration and cooperation across sectors and across NTDs, particularly during and following the last mile of elimination. For example, VL/PKDL could be integrated with other similar skin NTDs (e.g. leprosy, cutaneous leishmiasis and scabies).

The key indicators for VL were presented, and it was predicted that WHO SEA Region should achieve elimination targets for VL in all Member States by 2023, and by 2030 for PKDL. A comprehensive strategy for VL elimination and post-elimination surveillance should be developed. Operational research is required for multiplex diagnostics and other similar diagnostic tools. Coordination with other sectors and programmes including vector control programmes should be improved.

2.2 Presentation: Global and Regional updates – Dr Saurabh Jain (WHO HQ) & Zaw Lin (WHO SEARO)

Global

According to the WHO Global Health Observatory (an interactive dashboard with distribution maps of VL cases using the DHIS2 platform), 78 countries are endemic for VL. Due to the success of VL elimination programme, the global burden of VL in our Region is at an unprecedented low of 27% (it was 70% in 2005); equal with AFR Region. The next highest burden is in the Region of Americas at 21% (mainly in Brazil).

Five new indicators for reporting VL were introduced since 2013—2018 data can be seen at: https://www.who.int/publications/i/item/who-wer9525):

- age-wise data (children and young adults continue to contribute to transmission),
- gender data (higher in males, better surveillance),
- PKDL (SEAR higher than AFR and EMR, but there has been a decline since 2017)
- VL case mortality (very high at 8% in Brazil, due to HIV/VL coinfections).

WHO has introduced an Integrated Medicine Supply System which allows forecasts of medicine requirements and tracks drugs that are available through WHO (those donated through WHO).

A Global Leishmaniasis Vector Surveillance Manual is under preparation and new WHO treatment guidelines for the treatment of visceral leishmaniasis in HIV coinfected patients are under development.

Regional

Significant progress has been made across the Region, and the number of reported cases has decreased significantly. The DHIS2 system is now fully used for VL surveillance in Nepal, and Bangladesh has strong political commitment and a comprehensive operation programme for VL elimination.

However, although Bangladesh and Nepal have reached their elimination targets, there are still some areas of concern, e.g. in Nepal, 5 new districts are now considered endemic bringing the total from 18 in 2019 to 23 in 2020.

The Region has reached its elimination target in 714/751 (95%) endemic Units by the end of 2019. In India, 37 blocks above target are in Bihar and Jharkhand and sporadic cases are reported from other States. Due to improved reporting, the number of cases of reported deaths due to VL has increased in India during the last 3 years.

2.3 Presentation: Country Presentation India – Dr Neeraj Dhingra (NVBDCP)

Definitions of case, relapse, deaths due to VL, and an outbreak according to three levels of VL endemicity, are provided in Table 1.

Progress

In 2019, 37 blocks (21 in Bihar and 16 in Jharkhand) had >1 VL case per 10,000 population. Up to August 2020, only 8 blocks were reported above this target in 2020. There is a 40% reduction in VL cases, and a 33% reduction in PKDL cases, in endemic districts till August 2020 compared with 2019. Bihar remains the State with the highest burden.

The programme has several challenges:

- There are 149 million people living in 4 endemic states (Bihar, Jharkhand, Uttar Pradesh and West Bengal)
- Sporadic reporting of VL has come from other States (e.g. Assam, Delhi, Kerala, Punjab, Sikkim, and Uttarakhand).

The response plan is:

- To treat sporadic cases according to guidelines (miltefosine supplied by NVBDCP)
- If local transmission is established, programme activities will be implemented according to guidelines e.g. capacity building, surveillance, IRS and logistic support.
- Nationwide guidance for surveillance and reporting to NVBDCP has been implemented (including training in Kerala and Sikkim)
- An outbreak management SOP has been prepared & disseminated to these States.

A summary of vector control and surveillance is provided in Table 2.

Response to independent assessment

The programme has made significant improvements in response to the recommendations made in the KA Independent assessment in Dec 2019 and its subsequent report (https://www.who.int/docs/default-source/searo/evaluation-reports/independent-

assessment-of-kala-azar-elimination-programme-in-india.pdf?sfvrsn=fa0d8baa_2). These include, but are not limited to:

- The role of partners reviewed periodically through coordination meetings.
- Clarity on operational definitions and dissemination of SOPs (case search, outbreak), with a uniform reporting system for surveillance in non-endemic areas, has been implemented.
- An adequate supply of quality assured drugs, diagnostics and insecticides has been made available
- KAMIS has been integrated on the Government portal.
- KA is a notifiable disease in all four KA endemic states.

An intensified village level, rather than block level, action plan is being considered and the government is building pukka houses in villages with high VL levels.

COVID-19 impact

The COVID-19 pandemic has added to the challenges (field visits hampered, IRS stopped temporarily after the first round, but second round is near to completion) but VL case search was integrated with COVID activities and identified cases were treated. The full impact of COVID-19 is not yet known.

Request for support and advice from RTAG

- Review of the validation requirement and pre-conditions to be met for declaring KA elimination as public health problem for India.
- Support and facilitate time-to-time evaluation of the programme.
- Sustenance of drug donation in the post elimination phase.
- Strengthening of border surveillance among Member States.
- A plan for the renewal of the MoU for the elimination goal among Member States in WHO SEA Region.
- Country guidance for the VL programme in line with NTDs roadmap 2021–2030.
- Guidance on rolling out the new KA-HIV treatment guideline.

The way forward

- Continued implementation of programme activities with necessary precautions amid COVID-19 pandemic to achieve KA elimination by 2021.
- Continue village-focused intensified plan for all programme components.
- Sustenance of the current momentum for the elimination drive on ground.
- Integrate VL programme activities with other VBDs and other programmes at grass root level.
- Prepare for the validation process for declaration of elimination.
- Shifting goal from incidence of less than one KA case per 10,000 population to zero case in future.

2.4 Presentation: National Kala-azar Elimination Programme (NKEP) in Bangladesh – Dr Abu Nayeem Mohammad Sobel

Definitions of a suspected and confirmed VL case are provided in Table 1.

Progress

The goal of the NKEP is zero KA transmission by 2030, and this will be achieved through:

- Early diagnosis and complete treatment
- Integrated vector management
- Effective disease surveillance
- Social/community mobilization and partnerships
- Operational research

In 2016, all of the 100 VL-endemic upazilas, where more than 37 million people are at risk, reached the elimination target and this has been sustained. Furthermore, there has been a marked decline in the number of VL and PKDL cases since the last RTAG meeting from 87 and 94 in 2019 to 28 and 36 in 2020, respectively. In 2020, there were no relapses.

However, 7.3% and 6.5% of confirmed cases were reported in non-endemic upazilas, in 2019 and 2020 respectively.

The response plan is to:

- Strengthen surveillance and outbreak management at all non-endemic upazilas
- Perform an outbreak investigation with endemicity assessment
- If upazilas constantly report cases, they should be considered as endemic

A summary of vector control and surveillance is provided in Table 2.

Vector control

In 2019, pre- and post-monsoon IRS with deltamethrin was performed in 41 and 49 upazilas, respectively. In 2020, pre-monsoon IRS was performed in 98 upazilas and coverage rates were very high with 614 291 out of the 614 446 households sprayed (99.97%).

Response to JMM

The programme has made significant improvements in response to the recommendations made in JMM in Dec 2017 and its subsequent report. These include, but are not limited to:

- Increasing the involvement of and delegation of all tiers in the health system (e.g. Civil Surgeon, CHCPs, UHCs)
- Developing and implementing a needs-based training plan for the health system
- Expanding diagnostic services, in particular availability of rk39 to all endemic UHCs to ensure universal access to diagnosis
- Using a standard population data for calculation of annual incidence rate of KA
- Improving the functionality of DHIS2 system

- Increasing local (upazila and community, community clinic and CHCP) involvement in active case detection to build sustainability

COVID-19 impact

The first COVID-19 case in Bangladesh was reported on 8 March 2020, and restrictions have been in place since 25 March 2020. The pandemic has brought several challenges: patient care, training sessions, pre-monsoon IRS and monitoring programme activities were interrupted but these have since been resumed.

Request for support and advice from RTAG

Technical support including:

- Strengthening surveillance in endemic and non-endemic area including
  - Post-elimination surveillance
  - Increase functionality of DHIS2 (incorporation of logistics, monitoring, IRD etc.)
- Dossier preparation and submission for certification of elimination as public health problem from WHO
- Establishment of cross border collaboration with India
- External programme review
- Quality assurance

Continuous support from WHO is needed for uninterrupted supply of logistics, vector control and active case search

Way forward

- Strengthen surveillance, including post-elimination surveillance, in endemic and non-endemic areas
- Extend programme activities (diagnosis, index case-based active case search, IRS, Zero reporting and outbreak management) at non-endemic upazilas
- Ensure Verbal Autopsy (VA) of all Kala-azar deaths
- Ensure uninterrupted supply of drugs, diagnostics and insecticides
- Adequate resource allocation for complete coverage of IRS and active case search
- Alternate drug for PKDL
- Cross-border collaboration

2.5 Presentation: Country Presentation Nepal – Dr Basudev Pandey (Director, EDCD, MoHP)

Definitions of a VL case, relapse, deaths due to VL, and an outbreak are provided in Table 1.

Progress

In 2019, there were 186 VL cases, 18 relapses and 1 case of PKDL in 50/77 districts in Nepal, the lowest ever recorded, and no endemic districts were above the elimination

target. However, one endemic doubtful district reported VL incidence above the target in 2017 and 2019.

In 2019, endemicity was classified as follows:

- Endemic districts* (18+5/77) 5 districts recently added to the endemic list
- Endemic doubtful districts* (46/77) 30/46 reported at least 1 VL case.
- Non-endemic districts (8/77)

*Endemic district- Full cycle of transmission has been demonstrated at any given time (maintained population of competent vector + parasite reservoir + locally acquired cases) AND at least one locally acquired case in the last 10 years.

Endemic doubtful district- Full cycle of transmission has never been demonstrated BUT at least one locally-acquired case in the last 10 years OR full cycle of transmission has been demonstrated at any given time, BUT no case has been reported in the last 10 years (0 case or no data)

Action taken and control plan

- Budget allocation for IRS in districts reporting VL cases.
- Active case detection (index case-based approach) for every reported VL cases to be conducted as per SOP.
- Training on IRS to district team and technical support for its implementation.
- Assess the endemicity status of doubtful districts so that appropriate interventions can be planned/taken.
- Capacity building of medical doctors/HWs for early case diagnosis and proper management as per the revised guideline.
- Strengthen VL surveillance through refresher trainings

COVID-19 impact

Although it was not possible to provide trainings on early case diagnosis, proper case management and disease surveillance as per the revised national guidelines, virtual training was conducted for strengthening VL surveillance and SOP for ACD was developed. Despite not being able to provide IRS training and on-site monitoring and supervision, it was possible to provide a regular supply of VL drugs and diagnostics, conduct insecticide susceptibility testing and analyse VL data to make informed decisions.

Request for support and advice from RTAG

Further clarification concerning confirmation of non-endemicity in non-endemic districts for validation purposes is sought.

The Way forward

- Transmission assessment of kala-azar and its vector in endemic doubtful districts
- Intensify active case detection to detect and treat cases early
- Intensify IRS training and implementation activities
- Capacity strengthening for case management and disease surveillance

- Ensure regular availability of drugs and diagnostics
- Continue good collaboration and partnerships

Discussion on the three country presentations – Led by Professor Ganguly

Speakers were congratulated on their commendable work and actions.

- Cross-border issues and impact of COVID-19 require further discussion.
- Since different programmes are close to elimination, the strategy needs to be revised with an integrated approach rather than a vertical approach. Further guidance is required on how this will be best achieved.
- The choice of diseases to integrate for post-elimination surveillance needs careful consideration and different Member States will have different needs (e.g. leprosy/PKDL, STH/VL/PKDL).
- Jharkhand introduced an integrated strategy for diseases targeted for elimination (KA/PKDL/TB/LF and malaria) at an implementation level in 2017.
- What will happen when the current commitment to supply AmBisome® runs out in 2021? Several manufacturers have expressed an interest in producing generic liposomal amphotericin and miltefosine and discussions have reached an advanced stage, but the timeline is not known yet.
- Quality control of generic drugs may be an issue and needs to be controlled.
- Eye problems in PKDL patients, resulting from 3 months of treatment with miltefosine, is an issue that needs further investigation.
- A procurement steering committee, consisting of key stakeholders from different regions, has been set up and ministries can transfer money to the local WHO country office rather than WHO headquarters to procure drugs.
- Bangladesh have opted for zero transmission goal, because of concerns related to drug supplies drying up. This will need to include PKDL to achieve success.
- India is aiming towards a zero-case goal.
- Intensified ACD is fundamental to achieve sustained elimination, but what type of ACD should be adopted in the post-elimination era? Different approaches are being investigated in Bangladesh through the ASCEND programme (following clusters, investigation of new cases, outbreak investigations and long-term follow up of previous cases/contacts).
- Although cases are coming down overall, new foci are important (e.g. Nepal-India border), and cross-border collaboration is essential to share experiences for control.
- If zero KA is a target, then a new road map is required. At the last RTAG (Dec 2017), a consensus was reached that zero KA was not achievable using the current tools, but zero transmission may be retained as an aspirational goal.
- Efforts are required to detect and treat more PKDL cases (including follow-up of VL cases up to 3 years post-treatment).
- Why is there only one roadmap for all NTDs? It lacks a post-elimination integrated surveillance plan.

- Has COVID-19 resulted in underreporting (which may threaten elimination and is a concern for prediction models)?
- It is important to examine the full impact of COVID-19 since it affects supplies and caused a huge migration of people. The economic downturn may also affect the health system.
- When diseases reduce, resources may be withdrawn, at a critical time when higher quality tools for diagnostics and surveillance may be required.
- Reporting of VL should include the screening population, as well as incidence, to provide evidence that surveillance is maintained at a high level.

3. Proceedings of Day 2

3.1 Presentation: Recap of Day 1 – Dr Usha Kiran

3.2 Presentation: Country wise presentation of Bhutan – Dr Tenzin Wangdi (NVBDCP)

Definitions of a suspected and confirmed VL case are provided in Table 1.

Progress

Only two VL cases were reported in 2019, and the mean number of cases over the last 5 years was 3.

Progress is being made since Bhutan joined the VL elimination initiative of SEA Region:

- An integrated Case Management Guideline for Neglected Tropical Disease is under development
- Serological (ELISA) and molecular diagnostic capacity has been established
- Vector studies are carried out in areas where cases are reported
- Since 2018, each reported case is epidemiologically and entomologically investigated and followed-up through a NIH supported project

However, there are several challenges:

- VL Surveillance and Control
  - Sporadic and very low incidence of the disease
  - Remoteness of cases
  - Limited capacity in the programme with multiple mandates
- Likely role of animal reservoir in VL transmission in Bhutan may hinder elimination status
- Emergence of PKDL cases and challenges in diagnosis and management (Pradhan A, 2020)

COVID-19 Impact

- Vector studies in sentinel sites have been hampered

- Training on serological and molecular diagnosis of leishmaniasis was deferred
- Leishmaniasis case investigation and follow-up has been impeded

Response to RTAG 2013 recommendations

- NIH Project-based reactive case finding for all positive cases ongoing (the results will inform a KA elimination strategy)
- Miltefosine is considered as the first line of treatment in the integrated guideline

Request for support and advice from RTAG

- A review of treatment guidelines
- Support in the development of a surveillance guideline and elimination strategy
- Advice and assistance in understanding the role of a possible animal reservoir and low sporadic nature of VL transmission in Bhutan

The Way forward

- Establish VL sentinel in at least 3 national referral hospitals
- Training workshop for clinicians and health workers in the districts and periphery for early detection of suspected cases and referral for diagnosis,
- Make rK39 test strips available in health facilities with endemic communities
- Follow-up of all VL cases for relapse and early detection of PKDL and subsequent elimination of human reservoir
- Delimitate endemicity of each districts or sub-districts

3.3 Presentation: Leishmaniasis – National Programme in Thailand – Ms. Susanee Rojanapanus

Definitions of a suspected and confirmed VL case, relapse, deaths due to VL and outbreak are provided in Table 1.

Progress

- 2018 1 CL, 1VL and 1 CL imported case (from Israel)
- 2019-2020 no reported cases

Control measures are as follows:

- Diagnosis: microscopic, PCR
- Treatment: VL-AMB, AMB plus Miltefosine
- Surveillance
- Monitor national diseases monthly report and other sources
- New reported case: case investigation, active case finding, vector/animal reservoir survey
- Vector control: IRS(Deltamethrin), environment improvement, LLIN

COVID-19 Impact

- It has had no impact.

Discussion following Bhutan & Thailand Presentations – Led by Professor Nirmal Kumar Ganguly

- Treatment of PKDL difficult as miltefosine is not available in Bhutan (but obtained through SEARO).
- Are the few, regular cases found in Bhutan and Thailand due to migrant workers from Nepal?
- Distribution of cases is in clusters. Difficult to prove that there is no local transmission or whether cases are imported.
- Thailand performs focal IRS and vector surveillance around a confirmed case.

3.4 Presentation: Validation for elimination of VL as PHP and its dossier preparation in brief - Saurabh Jain (WHO HQ)/Zaw Lin (WHO SEARO)

Please refer to the Generic framework for control, elimination and eradication of neglected tropical diseases (NTD-STAG) WHO/HTM/NTD/2016.6

For elimination as a public health problem, achievement of measurable global targets for both infection and disease; when reached, continued actions are required to maintain the targets and/or to advance the interruption of transmission.

The document "Process of validation of elimination of KA as a public health problem in SEA Region" published in 2016states that the expected impacts of the elimination initiative are:

(1) reduce KA in the vulnerable, poor and unreached populations in endemic areas;

(2) reduce case-fatality rates from KA to a negligible level,

(3) reduce PKDL by interrupting KA transmission and

(4) prevent the emergence of KA/HIV/TB coinfections in endemic areas.

The operational case definitions to be used for consistency are as follows:

Kala-azar case: A person from an endemic area suffering from fever of two weeks or more duration and splenomegaly that is confirmed by a rapid diagnostic test (RDT) or a biopsy.

Relapse case: A KA case that has an initial cure but has a recurrence of signs and symptoms and is parasitologically positive.

Probable PKDL: A patient from an area where VL is endemic – with or without a previous history of VL – who has a symmetrical macular, papular or nodular rash often starting on the face with further spread to other parts of the body without loss of sensation and positive rk39 RDT

Confirmed PKDL: A probable case as described above with parasite infection confirmed by PCR or a slit-skin smear or biopsy.

Population at risk: all inhabitants of endemic areas, i.e., an implementation unit (district, upazila, block) with local transmission.

Criteria for reaching elimination at the country level are:

(1) All the preconditions in the national elimination programme are present

(2) The country programme is in the consolidation phase

(3) Annual incidence of KA is below 1 case per 10,000 population, at upazila in Bangladesh, block in India and districts in Nepal for a minimum of three consecutive years

For validation, the MoH needs to submit a dossier to the WHO to validate the country's claim. WHO will convene an independent validation team (IVT) to visit the country to determine whether elimination has been achieved. If validated, elimination needs to be sustained (annual surveillance reports submitted) and a JMM conducted every 3 years.

A template for epidemiological surveillance has been developed and will be shared for peer review by Member States, and some points to note are:

- The endemic areas cannot change year by year (i.e. if there were 100 IUs at the beginning of the programme, all 100 IUs need to be retained).
- Active, as well as passive, case detection needs to be performed annually.
- All IUs need to report irrespective of the number of cases (nil reporting, if applicable).
- An underreporting ratio needs to be recorded

WHO is happy to assist countries prepare their dossiers and host a JMM every 3 years. The dossier needs to include the following:

(1) Documents supporting fulfilment of all preconditions.

(2) Detailed account of the historical perspective and epidemiology of kala-azar in the country.

(3) Description of the elimination programme strategy.

(4) Description of the surveillance system, including active case-finding strategies, collection of data from private health and facilities and information systems.

(5) Robust and representative estimates of the promotion of unreported cases according to the standard methodology.

(6) Diagnostic and treatment strategy for kala-azar.

(7) Quality control and monitoring system for activities within the programme.

(8) Report by year on the following:

- Number of endemic units, population at risk.
- Annual incidence rate of KA (new and relapse) in each unit.
- Annual incidence rate and prevalence of PKDL calculated in each unit,
- Report on number of active case findings conducted in each endemic unit.
- Proportion of targeted private health facilities reporting KA cases.
- Proportion of health facilities having adequate diagnostic facilities.
- Operation research conducted to detect proportion of unreported cases.

The visit by the IVT lasts 2 to 3 weeks, during which they:

- Review dossier for completeness and ascertain fulfilment of the elimination target
- Visits to endemic sites, health facilities and interview health personnel and others
- Potential areas to visit: (1) least satisfactory documentation, (2) as being at unusual risk of continuing transmission e.g. previous highly endemic areas, areas where the last cases occurred, and areas with a history of poor surveillance or increasing number of cases
- Examine records at both central and peripheral levels
- Finalize IVT report, presentation and feedback to National Programme and WHO

Discussion – Led by Professor Nirmal Kumar Ganguly

- The documentation is clear, and validation needs to include all areas reporting kala-azar cases, including sporadic cases.
- How will zero reporting be validated? [perhaps consider using DAT serology as part of elimination definition: https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(19)30536-4/fulltext]
- Can LF TAS methodology be developed for VL? [SPEAK India are looking to see whether we can develop a xenomonitoring strategy for VL (similar to LF). One problem is that, because VL cases are so low, it is difficult to establish a relationship between *Le. donovani* infection rates in sandflies and humans. Our work is ongoing].
- Is there a checklist of documents that need to be filed at each level? [a template has been developed]
- Active surveillance is very difficult in grey areas
- What type of data are required to prepare a dossier for validation? [A template is ready with standardized variables. Sporadic cases need to be reported in the dossier. It is not necessary to show that transmission has been interrupted since the target is elimination as a public health problem. However, this is not static and the guidance on validation can be revisited according to new issues raised by member states on experiences gained through validation of other diseases. What is an acceptable number of cases that can be tolerated without causing an escalation of outbreaks? Is there enough data to do the same for VL/PKDL?]

3.5 Presentation: Potential dynamics of VL 2020-22: targets and resurgence – Prof Graham Medley (LSHTM)

The SPEAK India consortium has recently published two models:

(1) A model for short-term block-level predictions of VL in India was presented (please refer to: https://pubmed.ncbi.nlm.nih.gov/32644989/). The model can provide an upper limit of expected cases per month according to previous incidence within a block and across its neighbours. It can be used to evaluate progress, highlighting blocks less likely to reach incidence targets. Smaller blocks have a higher risk of jumping over 1/10,000 and, because there are many such

blocks, the chance of them all being <1/10,000 for 3 years is very small. The district level is less subject to chance. In Bihar all but 4 districts have an incidence <1/20,000. In Jharkhand all districts have incidence >1/20,000.

- Predicting on the block level is useful for monitoring progress but cannot guide targeted control efforts within block.
- As incidence nears the target level, majority of cases likely come from small, highly localised clusters rather than uniformly across the block
- Diagnosis is both control and surveillance
- Lower diagnosis rate reduces the number diagnosed and allows more transmission

(2) Another model used data from Bangladesh 2002—2010 to predict the source of infections in transmission trees and the contributions of background transmission, asymptomatic individuals, pre-symptomatic individuals, VL cases, and PKDL cases to the total infection pressure on susceptible individuals (please refer to: https://pubmed.ncbi.nlm.nih.gov/32973088/).

- Transmission is highly focal: 85% of mean distances from inferred infectors to their secondary VL cases were <300 m
- Estimated average times from infector onset to secondary case infection were <4 mo for 88% of VL infectors, but up to 2.9 y for PKDL infectors
- Estimated that prevention of PKDL could have reduced overall VL incidence by up to 25%
- Supports direct assessment of infectiousness, that diagnosis and treatment of PKDL is essential for control and elimination of VL

The potential impact of COVID on the VL elimination programme was modelled by the NTD Modelling Consortium. The delay in reaching the elimination target is dependent on the endemic incidence but could be delayed by up 2 years (should PCD, ACD and IRS be interrupted for one year).

Village-level analysis could reveal an increased chance of large outbreaks depending on the level of PCD reduction.

3.6 Presentation: Final recommendations of Independent Assessment of KA Elimination Programme India, 2019 – Dr Dhruv Pandey (WHO, India)

The KA Independent assessment was conducted in Dec 2019 and a full report has been published (https://www.who.int/docs/default-source/searo/evaluation-reports/independent-assessment-of-kala-azar-elimination-programme-in-india.pdf?sfvrsn=fa0d8baa_2).

The general objectives of the assessment were to:

(1) identify any bottlenecks/hurdles/challenges in the last mile of elimination and recommend solution to overcome those challenges, and

(2) recommend measures for further strengthening of the programme towards elimination and sustain the elimination.

An extensive list of short-term, medium and long-term recommendations were made in the following areas:

(1) Surveillance and organization of preventive and curative services

- SoPs, standard uniform terminology and definitions
- Case search
- Information system
- Diagnosis, case management
- Relapse, Kala-azar and pregnancy, Follow up, Pharmacovigilance
- Post-kala-azar dermal leishmaniasis (PKDL), Kala-azar-HIV coinfection
- Transborder collaboration

(2) Vector control and entomological surveillance

(3) Research

(4) Health seeking behaviour, Community awareness and participation

(5) Stewardship and governance role of NVBDCP

(6) Collaboration with partners

(7) Budget and finance

(8) Supply chain and stock management

(9) Limitations of the mission

- Assessment exercise could not be done in West Bengal due to local administrative issues
- Methodology of assessment activity described and shared in the concept note was deviated to adapt the last-minute change of field visit plan.
- In the absence of systematic longitudinal data on sandflies and absence of complete epidemiological information of cases, the team could not establish the occurrence of local transmission.
- The pre-mission preparations like printing of guidelines, SoPs, displaying of banner and posters, filling of treatment card and even distribution of new treatment cards to the old patients, sensitizing frontline health workers etc. happened just before the arrival of the independent team.
- Two objectives of the mission – a) evidence-based policy formulation (operational research/research), contribution of research and regulation and b) to assess the national preparedness and readiness for validation of KA elimination as a public health problem, could not be discussed and illustrated in detail in the report.
- Concern about the lengthy appraisal tools which consumed longer time than expected, especially for those experts who had not experienced the implementation of the KA elimination programme closely.

The NVBDCP have already acted on around 75% of these recommendations (please refer to section 2.3).

It is important for VL cases to be followed up for 3 years, and PKDL for 5 years, in accordance with the NTD roadmap 2020–2030.

Discussion – Led by Professor Nirmal Kumar Ganguly

- Disadvantage of the smaller blocks is the greater concentration of residents being more in a small block as compared large blocks.

- We believe that the block size is important just because of the number. If the block is 50,000 people, then it only needs 5 cases to go above threshold - density of people is not a critical factor
- What about the role of HIV-VL cases in models which remain hidden (HIV status not known)? [we have not included specifically HIV cases, but this is an important issue and we will consider].
- The recommendations will help India in the country dossier in future IA; recommendations were to include LLIN in certain area with intense transmission. Further role of LLIN has to be evaluated.
- LLINs can play more of a role, particularly in preventing cases (VL and PKVL) from transmitting to sandflies. We recommended at the last RTAG in Nepal to investigate the role of LLINs further.
- Can we consider fogging for outer area? [We need to be strategic. If we are using insecticides outdoors and indoors, we need to be mindful if resistance developing. A targeted approach considering where transmission is occurring is best. We need to change our mindset from killing (uninfected) sandflies to preventing transmission (infected sandflies from transmitting and sandflies acquiring infections from infected people).]

4. Proceedings of Day 3

4.1 Presentation: Recap of Day 2 - Sabera Sultana (WHO, Bangladesh)

Dr Sabera Sultana from WHO Country Office for Bangladesh presented a recap of the proceedings of Day 2.

4.2 Presentation: Vaccines for Visceral Leishmaniasis – Professor Nirmal Kumar Ganguly

Vaccines are needed for the following reasons:

- They can reach the entire target population –a cost-effective health measure preventing the disease spread and necessary for eradication and elimination programmes
- They may prevent spread of infection from asymptomatic and PKDL patients
- They compensate for shortcomings or lack of Indoor residual spraying (IRS)
- They prevent reinfection in patients
- They may provide both prophylactic and therapeutic effects
- They may provide cross protection across several *Leishmania* parasites.
- Are a good alternative to VL drugs which can produce severe adverse reactions in some patients.

Desirable features of vaccines:

- Provide long term immunity
- Elicit immune response that favours protection over excess tissue damage,
- Produce strong memory and effect response upon subsequent challenge and is highly efficacious.

- **Should not** elicit an auto- immune response and be safe in immune-compromised persons including HIV patients as well as healthy asymptomatic infected persons.

The optimal vaccine would provide >95% protection against VL, result in no PKDL, last a lifetime and only a single dose required.

The minimal requirements are 70% protection, last for one year and two doses required.

There are several good candidate vaccines for VL in the pipeline at present. For example, Leish-F3 developed at IDRI, Mologen AG (LEISHDNAVAX) which offers preventative and therapeutic properties for VL in India and CL in Tunisia, and Paul Kaye's ChAd63-KH vaccine which is in Phase 2 in Sudan (see presentation 3.5 below).

It may also be appropriate to revisit live vaccines since safety concerns relating to visceralization can now be overcome using a dermotropic live attenuated *Leishmania* vaccine that does not visceralize since it has an antibiotic marker free parasite developed through CRISPR-CAS technology.

Advantages of live attenuated vaccines:

(1) They may mimic conditions of natural infection and recovery

(2) Some degree of persistence without causing disease

(3) Timed elimination from the host

(4) Less chance of reversion to virulent phenotype, unless it is not a complete geneKO parasites

(5) Produced in large quantities in well-defined conditions suitable for human vaccination

(6) Highly cost-effective.

The following Indian researchers are making good progress towards vaccine development against VL:

Poonam Salotra, National Institute of Pathology, New Delhi and A. Selvapandiyan, JHIMM, Jamia Hamdard, New Delhi are involved in development of live attenuated *Leishmania* vaccine against VL in collaboration with Hira Nakhasi, USFDA

Syamal Roy, IICB, Kolkata along with Christiane Juhls, Charles L. Jaffe, Pradeep Das, Hechmi Louzir, Simon L. Croft, Modabber, Peter Walden working for a Modular Multiantigen T- Cell Epitope– Enriched DNA Vaccine Against VL

Amitaba Mukhopathyaya and his colleagues from NII/ IIT, New Delhi, India recently found a vaccine candidate aimed at haemoglobin receptor which was able to protect mice and hamsters from the parasite.

4.3 Presentation: Updates on treatment regimen for VL and PKDL – Dr Saurabh Jain (WHO HQ) & Dr Fabiana Alves, DNDi

Dr Jain drew attention to Box 1 of the WHO Control of the Leishmaniasis document published in 2010 (https://www.who.int/publications/i/item/WHO-TRS-949) for recommended treatment regimens for anthroponotic VL and PKDL in SEAR.

The risk/benefit of treatment needs to be considered carefully, especially for PKDL which may benefit the community more than the individual, because long-term use of

pentavalent antimonials, SSG administered daily for 30-60 days in Sudan, and miltefosine for 12 weeks in SEAR, has high toxicity and can lead to eye complications.

DNDi are currently conducting a phase 2 clinical trial with KAMRC and RMRI in india and icddr,b in Bangladesh targeting Male/Female 6-60y, with confirmed PKDL by clinical presentation and demonstration of parasites by microscopy in a skin smear or by PCR.

The primary objective is to assess the safety and efficacy of two regimens for the treatment of PKDL: LAmB (AmBisome® monotherapy 5 x 4 mg/kg, total dose of 20 mg/kg) and combination LAmB+MF (AmBisome® as above plus miltefosine, allometric dosing, daily dose for 3 weeks) .

Secondary objectives

- To assess pharmacokinetics (in plasma and skin), parasitological (microscopy and qPCR) and immunological
- parameters before and after treatment
- To compare clinical, parasitological and immunological responses to identify markers for cure

All 126 patients were recruited by January 2019, currently in 24m follow-up period. Results expected by Q2 2021.

DNDi have long-term and short-term strategies with an objective to deliver:

- a safe, effective, short-course oral treatment for visceral leishmaniasis
- a new treatment for post-kala azar dermal leishmaniasis; and
- treatment options for HIV/VL co-infected patients.

The short-term strategy uses involves improving treatment with existing tools (e.g. the trial above), but the long-term strategy is to develop new field-adapted oral combination treatments with NCEs. Desirable features are: oral, well tolerated, improved efficacy, wide spectrum, integrated approach at PHC level and affordable.

Five NCEs are progressing well: Nitroimidazole DNDI-0690, Oxaborole DNDI-6148 Triazolopyrimidine LXE408, Pyrazolopyrimidine GSK-3186899 and Imidazopyridine GSK-3494245.

LXE408 is the most advanced project: Phase 1 study in the USA will be completed by Q1 2021, Phase 2 clinical trial to be submitted for approval in India in Q2 2021, Partners: KAMRC and RMRI.

4.4 Presentation: Advances and gaps in PKDL control and research – Dr Mitali Chatterjee

Macular PKDL patients serve as mobile reservoirs. Xenodiagnostic studies show that macular and polymorphic PKDL patients are infectious to sandflies, but macular PKDL patients have no reason to access treatment. PKDL should not be a neglected component of NTDs.

Minimally invasive tools are required to develop a test for cure since biopsies are required at different time points and 'cured' patients are reluctant to provide samples. Microbiopsies (depth up to 1.2mm) are less invasive and can be used to detect parasites (should any remain), so will be useful for the development of a test for cure such as qPCRs.

It was shown that there were no detectable parasites six months post miltefosine treatment, but parasite levels went up after AmBisome® treatment. In polymorphic PKDL cases, the number of parasites decreased following treatment but increased in macular cases 6 months post-treatment with LAmB. The reason why macular PKDL responds better with miltefosine treatment may be due to pharmacokinetic differences (Moulik et al., Indian J Dermatol Venereol Leprol 2020).

A prophylactic/therapeutic vaccine may be able to curb transmission. As mentioned earlier, the ChAd63-KH vaccine is currently in a Phase IIa trial to see whether it is effective in preventing PKDL in Sudan:

LEISH2a (NCT02894008) Phase IIa in Sudanese PKDL

- 24 participants: 16 adults, 8 adolescents
- Persistent PKDL > 6 months
- Vaccinated once with $1x10^{10}$ or $7.5x10^{10}$ vp ChAd63- KH i.m.
- Follow up: 42–90 days
- Whole blood transcriptomics and ELISpot.
- AmBisome® Rx at end of FU if <90% improvement

Conclusions:

(1) ChAd63-KH was safe and immunogenic in PKDL patients

(2) 30% of participants resolved their PKDL

(3) Clinical cure was associated with a blood transcriptomic signature

(4) linked to monocytes and endo-lysosomal proteins.

In summary, there are several directions for research to improve PKDL management:

- Improve PKDL case detection...Active surveillance
- Improve diagnosis.... Molecular tools
- Improve treatment.... Combinatorial t/t
- Prevention of PKDL....Vaccine

Discussion – Led by Professor Nirmal Kumar Ganguly

- Prof Sundar was invited to provide an update on the DNDi drug trial and reported that the results look promising.
- In MSF we used AmBisome® for PKDL in many hundreds of patients with excellent clinical response within 1-3 months after treatment. It is more patient-friendly than the other options. With the comprehensive DNDi study we will get more in depth and decisive insights about the possibilities.
- Liposomal Amphotericin B needs macrophages as the carrier. So, it could be proposed that as macular cases have less cell infiltration, they may have less drug reaching the lesions, accounting for parasite persistence.
- It will be very important to ensure a long follow up of PKDL patients. Relapses are seen after AmBisome® and sometimes after miltefosine treatment. Relapses could happen even after 12 months. In Africa PKDL is treated with SSG. It could be that relapses happen there also, but we have no way to track and follow the patients for 12 months or longer.

- Do we have a gold standard alternative for lab confirmation of PKDL cases recommended for the programme, that can be widely used in place of rk39, which is still the mainstay in the field? [For operational reasons for its availability, skin smear is currently the basis]
- There is an urgent need for validation of the PCR test for PKDL, especially for monitoring macular PKDL.
- Some concern was expressed regarding whether the research findings would be able to be implemented in time to contribute to the elimination target.
- Another concern raised was the difficulty of conducting clinical trials due the low number of patients available and it may be feasible to pool sites (although E. Africa has a very different epidemiology to WHO SEA Region).
- Different countries have used different approaches to treating relapse and PKDL, which will be discussed further in the meeting.

4.5 Presentation: Treatment for visceral leishmaniasis and HIV coinfection, current evidence from India – Dr Sakib Burza (MSF).

HIV/VL coinfected patients are very infectious, difficult to manage and treat, and difficult to diagnose. Furthermore, they were not a focus of the programme until recently.

In 2017, 593 PKDL and 181 VL/HIV cases were examined in Bihar. Having VL/HIV in the same year, and PKDL in the previous year, are strong predictors for VL incidence at the village level, since they infect others.

The collaborative research group studied whether there was a correlation between rK39 RDT results with qPCR, rk39 ELISA and urinary antigen detection in VL/HIV patients. In VL/HIV asymptomatics, 7.5% were positive using the rk39 ELISA but less were positive using the RDT.

They also examined different treatment options for VL/HIV patients: LAmB monotherapy versus LAmB+miltefosine with an endpoint of 6 months (75 patients in each arm; not sufficiently powered but informative).

On day 210, 85% of LAmB treated patients were alive and relapse free versus 96% of patients given combination therapy. The effect was even greater in patients with VL/HIV and TB. Around 20% of patients were co-infected with TB and they are 9 times more likely to die.

It is difficult to diagnose TB in HIV patients in a programme mode. However, combination therapy halves treatment duration. Therefore, it is recommended that all VL/HIV patients should be considered as having advanced HIV and given combination therapy. If LAmB fails, then miltefosine/paramomycin can be an alternative.

4.5 Presentation: Updates on new WHO guideline on the treatment for visceral leishmaniasis and HIV coinfection and related logistics – Dr Saurabh Jain (WHO HQ) and Dr Fabiana Alves (DNDi)

The WHO guideline development group met on 28 September 2020 to discuss provision of new treatment guidelines following new evidence from the Ethiopian trial (published in January 2019) and recent data from India.

The Global Leishmaniasis Surveillance update included HIV/Leishmaniasis co-infections for the first time and found that many VL cases were unaware of their HIV status (2016- 1.6% coinfected and 34% cases had unknown status; in 2017- 2.6% coinfected and 35% cases had unknown status; and in 2018, 3.8% were coinfected and 6% unaware of HIV status). VL/HIV coinfected patients have high parasite loads (super spreaders), high relapse rates and high mortality rates.

Following recent evidences of clinical trials of combination therapy of liposomal amphotericin B plus miltefosine, conducted in East Africa (Ethiopia) and South Asia (India), WHO constituted a Guideline Development Group (GDG). GDG has given its conditional recommendation of combination therapy. Draft guidelines are currently under review.

Factors affecting treatment success/compliance in VL/HIV coinfection include:

- Under-reporting of HIV/VL
- Need for early reporting/treatment
- Need to follow-up patients following treatment
- Limitation/continuation of drug supplies
- Limited information relating to quality of life of patients
- High out-of-pocket expenditure of patients prior to accessing programme treatments
- HIV stigma delays presentation

Discussions – led by Professor Nirmal Kumar Ganguly

- Adequate procurement of drugs is required by all Member States.
- Revisiting treatment guidelines was viewed as a welcome innovation.
- Drug supply chain and access needs to be given attention by RTAG and coordinated via SEARO.
- Member States need to register all necessary drugs for VL/PKDL/HIV treatment.
- Advocacy is required to continue innovations for VL to address the need for new tools to prevent new outbreaks.

4.7 Presentation: Update on the findings of the SPEAK India project including surveillance, vector monitoring, health systems and modelling. Prof Mary Cameron (LSHTM)

SPEAK India is an international, India-led consortium of researchers and stakeholders who developed ongoing research protocols designed specifically to address gaps in our understanding of transmission dynamics, surveillance and health systems for VL that threaten the sustainability of elimination. These challenges are addressed through four interconnecting research projects:

4.8 Project 1 - Surveillance: measurement of human experience of infection (BHU, KAMRC, ITM) Objectives:

- Develop a surveillance system integrated in the existing PHC system for:
- Monitoring of VL transmission
- Monitoring of PKDL incidence

- Monitoring of VL-HIV co-infection
- Develop and pilot a system of improved contact tracing and micro-planning
- Monitor the accuracy of the diagnostic algorithm as VL incidence decreases

(1) Monitoring transmission of *L.donovani* through serosurveys

Progress so far:

- 3,652 households visited in 5 clusters - 11,735 individuals
- Tested with rk39 RDT (0.00% seropositivity in non-endemic villages, 0.30% seropositivity in previously endemic villages, 0.42% seropositivity in currently endemic villages)
- Filter papers obtained for lab analysis

Preliminary results:

- Rk39 RDT shows a 100% specificity for endemicity at village level

To be finalized:

- 1 cluster yet to be surveyed (currently not possible due to covid pandemic)
- Laboratory analysis (direct agglutination test, rk39 ELISA)
- Historical comparison with sero survey 10 years ago (kalanet study)
- Formulate recommendations for the use of sero surveys for monitoring of VL elimination (including costing)

(2) Improving VL surveillance at PHC level

Progress so far:

- Validation of rK39 RDT based diagnosis by qPCR: 25/26 of VL patients (=96%, 95% CI 75-100%) diagnosed with current algorithm (rK39 RDT) were confirmed by qPCR
- Interviewing and mapping incident VL cases and former VL cases 975 former VL patients interviewed: Mean expenditure = 7305 INR (=100 USD
- Screening for VL, PKDL and leprosy of former VL cases and household contacts (last 5 years): 1,020 ex-VL participants successfully revisited in their homes + 4,282 household members present (3 new VL cases, 54 new PKDL cases & 1 new leprosy cases)

Preliminary results:

- Current algorithm (fever >2 weeks + rK39 RDT) seems still valid despite the low VL incidence (96% accuracy so far)
- PKDL prevalence of 1.26% among household members of ex-VL patients (last 5 years)

To be finalized:

- Final analyses
- Costing study

4.9 Project 2 – Defining endpoints of transmission through measuring *Le. donovani* infections in *Phlebotomus argentipes* sandflies (RMRI & LSHTM)

Objectives:

(1) Generate *Phlebotomus argentipes* sampling framework and standard operating procedures

(2) Collect and analyse *P. argentipes* from sites across blocks with no, low, and high VL transmission in Bihar

(3) Use data to develop transmission endpoint assessment guidelines for India's VL control program

(4) Utilize xenomonitoring and sero-surveillance data collected in the same place, at the same time, to improve transmission models

Preliminary Results:

- A field trial conducted in 2 VL endemic and 2 non endemic villages comparing different sandfly collection methods showed that CDC light traps collected significantly more P. argentipes (866 females) than either large mechanical aspirators (501) or prokopak aspirators (568).
- Therefore, CDC light traps were used in the main xenomonitoring study involving 144 households recruited in 12 villages, spanning three transmission strata: endemic, previously endemic and non-endemic.
- 60 households to overlap with the collection of human serum samples by the SPEAK India Surveillance project
- The estimated sample size to detect a difference in infection rate between the three strata is 3,750 P. argentipes females. So far, 3,173 Phlebotomus females have been collected of a total of 12, 456 sandflies (including 4,720 Phlebotomus males, 2964 Sergentomyia females and 1,599 Sergentomyia males).
- Surveys assessing household composition, building materials, and known risk factors for VL are being analysed.
- Two PCR protocols to detect *Leishmania* infection in sandflies compared (ssRNA primer qPCR versus customized primers probe mix, head versus abdomens, light versus heavy infections) – need field validation
- Xenomonitoring Toolkit Draft under review by team
- Xenomonitoring cost analysis underway

4.10 Project 3: Health Systems: finding and treating VL post-elimination (IPH, LSHTM, RMRI, PATH, UNION, CARE India)

Objectives:

- Document the best practices of states/countries that have achieved VL elimination
- Analyze the strengths and weaknesses of health systems in managing VL at a population level

- Based on these results, construct a possible model of a health system that will be responsive to the problem of VL in the elimination setting

Work completed:

Jharkhand – Union Team

- Completed analysis of facility survey data of 15 facilities (private plus public)
- Completed analysis of 23 interview transcripts and summaries prepared
- The Union team has started development of first draft of the report

Bihar – RMRI Team

- Completed analysis of 29 interview transcripts and summaries prepared
- Started development of first draft of state report
- Active case finding is not robust - delay in early diagnosis of VL

Early Findings:

- Referral process from peripheral facilities poor – especially fever / suspected case referral from periphery is poor
- Shortage of human resources for effective implementation of program activities
- Quality and frequency of IRS not adequate
- Fever care in public facilities not preferred by community - reliance on private providers
- PKDL early diagnosis efforts are poor at community and facility level – diagnostic services for PKDL not available at PHCs
- Challenging to complete PKDL treatment
- Poor availability of rk39 kits and medicines at facilities
- Delay in paying monetary incentives
- Poor awareness activities
- Availability of diagnostic facilities to confirm relapse / re-infection / co-infection poor

4.11 Project 4 - Mathematical modelling: understanding and controlling the patterns of VL and transmission (VCRC & LSHTM)

Aim is to develop mathematical models and software tools that can support the elimination of VL as a public health problem, and the maintenance of that elimination

Objectives

(1) Develop age-time-space based transmission dynamic models, using data from other SPEAK research programmes

(2) Use the models to consider the 'minimum surveillance set' of data required to understand VL transmission dynamics and predict epidemics

(3) Use the models to evaluate potential changes to interventions, e.g. focal IRS and active case finding

(4) Develop a framework for the short-term prediction of VL outbreaks and long terms changes in risk of lymphatic filariasis

(5) Support the development of quantitative capacity within NVBDCP to use these tools

Progress of this work was described in presentation 3.0. Also, note that a review on Modelling sandfly population dynamics and ecological modelling has also been drafted. VCRC have cleaned, collated and linked covariate data with VL case data for all 533 blocks in Bihar to further refine prediction models.

4.12 Presentation: IRS and alternatives vector control approaches – Dr Rajpal S. Yadav (WHO HQ)

IRS has been used in malaria control programmes and is expected to be effective for VL control by preventing house entry due to excito-repellency action and reducing longevity/survival and vector density.

However, in order for IRS to be effective, vectors need to be endophilic, dwellings/shelters must be suitable for IRS, the sleeping habits of occupants need to be considered (outdoor/indoor sleeping), a high coverage of targeted dwellings is required (usually ≥ 80%), an appropriate number of spray rounds to cover the entire VL transmission period is required, and communities need to be educated to minimize mutilation/plastering/painting of sprayed walls or surfaces.

Seasonality of sandflies needs to be considered – particularly in relation to parity rate and parasite infection rates as well as vector density. Parity rates are higher in Oct–Dec, and *L. donovani* infection rates are also higher in winter season.

Organochlorine DDT is neither prequalified by WHO nor recommended for use in IRS due to widespread resistance in sand fly vectors against it. The WHO prequalified insecticides include synthetic pyrethroids (alpha-cypermethrin, deltamethrin, lambda-cyhalothrin), organophosphates (malathion, pirimiphos-methyl), and a carbamate (bendiocarb). However, recent studies indicate appearance of some tolerance to pyrethroids due to involvement of *kdr* genes. Recently WHO has also prequalified clothianidin, a neonicotinoid compound in a new class group. Efficacy of pirimiphos-methyl and clothianidin has so far not been evaluated against field populations of sandflies. A WHO resistance test method is under development for monitoring changes in the susceptibility of the field populations of sandfly vectors against clothianidin when this product is introduced for IRS in the future for resistance management.

To increase performance of IRS and ensure human safety, WHO recommends the use of an effective, quality-assured, long-residual insecticide (2–3 months vs. 4–8 months efficacy), the pre- and post-shipment quality checks for all insecticide specifications parameters, to register and use alternative IRS products (i.e., organophosphates and neonicotinoids), procure insecticides packaged in sealed water soluble bags, maintain/repair/replace hand compression sprayers, and make provision for procurement of new sprayers, spare parts, Control Flow Valves, nozzles; personal protective equipment, other tools (e.g. measuring containers) and setting up repair teams at district level.

Alternative vector control methods to IRS include distribution of ITNs/LLINs considering the peak biting of sandflies around mid-night and some scientific evidence in favour of their use in the SEA Region. LLINs are not currently a core VL intervention in our Region but may be considered to be given to PKDL cases as a personal protective tool to prevent transmission of infection to other healthy persons.

A systematic review of the effectiveness of ITNs and IRS is under progress (by WHO HQ).

4.13 Discussion – Led by Professor Nirmal Kumar Ganguly

- Insecticides which have an active residual life of 6 months should be considered for IRS since they may cover both vector density peaks and negate the need to apply two rounds of spraying which are not always achievable.
- The hole size in malaria LLINs may be too large for sandflies to prevent biting, but sandflies can still pick up a lethal dose when they try to enter the nets to attempt biting on the sleepers, which prevents onwards transmission.
- RMRI evaluated efficacy of Actellic, malathion and deltamethrin against sandflies and found deltamethrin elicited the best results followed by actellic.

5. Proceedings of Day 4

5.1 Presentation: Recap of Day 3 – Dr Dhruv Pandey, (WHO India)

Dr Dhruv Pandey from the WHO Country Office for India presented a recapitulation of the proceedings of Day 3

5.2 Presentation: Innovation to achieve elimination as PHP and sustain the achievements – Dr Suman Rijal (DNDi).

Historically, the impact of IRS has waned since 2005 (see Fig 1 of a recent review: https://gatesopenresearch.org/articles/2-10/v1).

In 2007 when the elimination programmes were implemented, VL incidence was 30x higher in India and Bangladesh and 9x higher in Nepal than it is now, and a different epidemiological situation exists where 30% of KA is from new villages (previously endemic, but not in the last 3-5 years) in Bihar, India. Asymptomatic infections (diagnosed by a high DAT and/or rk39 +ve) outweigh clinical infections 9-fold in India and Nepal, and 4-fold in Bangladesh.

ACD needs a more integrated approach to be cost-effective, e.g. NTD diagnostic platforms, syndrome/fever approach and surveillance of NTDs with other skin diseases (e.g. leprosy and PKDL).

Median interval from VL treatment to PKDL onset was 3.9 years. Compared with VL, nodular PKDL was more likely and macular PKDL was less likely to result in positive xenodiagnoses. Asymptomatic VL in HIV was 7.5%.

There was a need for better diagnostic tools for PKDL, HIV-VLand relapse cases. FIND are working on new diagnostics, e.g. Leish Lamp, Looplamp and the KATex antigen test. Laboratory experimentation had demonstrated a risk of resistance towards AmB. Integration and inter-sectoral collaboration could be the way forward such as diagnostic platform for NTDs; syndromic approach; and surveillance of NTDs with skin manifestations e.g. PKDL and leprosy.

The NIDIAG study has enrolled 425 patients with persistent fever to develop a diagnostic algorithm for VL, rickettsiosis, leptospirosis, enteric fever and borreliosis.

Incidence of kala-azar dramatically reduced to almost elimination levels but expansion to new areas or previous endemic areas. There was gap for better understanding of transmission factors. Strategy for stratification and interventions should be tailored according to local epidemiology. There is a need to reinforce advocacy for continued political support and funding. With the cases coming down, interventions needed to be efficient as well as cost-effective. Member States have ambition to reach zero cases and zero transmission and WHO NTD Roadmap 2021–2030 has new targets. On these background, current WHO strategy document should be revisited to take into consideration these developments and address them.

5.3 Presentation: Skin NTDs – Drs Jose Ruiz Postigo & Saurabh Jain (WHO HQ)

The initiative is to integrate leprosy, yaws, PKDL, CL, Buruli ulcer, mycetoma, LF and podoconiosis since they are often co-endemic with the aim to strengthen the health system and reduce costs.

Guidelines to help frontline workers recognize skin diseases were published in 2018 (https://www.who.int/publications/i/item/9789241513531) and these have been supported with a **Skin NTD app:** https://www.who.int/news/item/16-07-2020-neglected-tropical-diseases-of-the-skin-who-launches-mobile-application-to-facilitate-diagnosis.

The app has a chatbot algorithm that uses data (signs/symptoms, location of body etc) to diagnose the most likely disease.

In the new NTD roadmap (2021–2030), CL is a global target and PKDL has a target in SEA Region. We need to review how RTAG/KAEP deals with CL, and which skin diseases it wishes to integrate.

5.4 Presentation: Lessons Learnt for cross border collaborations for VL elimination as PHP - Drs Risintha Gayan Premaratne & Sudhir Khanal (WHO SEARO)

VL may be able to learn from the malaria experience. Maldives and Sri Lanka are malaria free and Bhutan is close to elimination. Elimination is only possible if we deal with borders. Bhutan-India and Bhutan-Nepal borders were targeted since Bhutan is very close to elimination.

There was a regional action plan to make WHO SEA Region malaria free by 2030 (please refer to: https://apps.who.int/iris/bitstream/handle/10665/273938/sea-rc71-8.pdf?sequence=1&isAllowed=y).

A good example of cross-border collaboration was the RDSP project funded by the Global Fund artemesin initiative (RAI) 2E grant (2018-2020): https://www.theglobalfund.org/media/6509/publication_regionalartemisininresistanceinitiative_focuson_en.pdf

The regional action plan to prevent vaccine preventable diseases (2016—2020) identified improvements through better cross border collaboration. Issues encountered included:

- legal/illegal crossing points

- different religions, traditions, cultures and languages
- different health systems use different definitions/terminology
- poor coordination of data collection and data sharing.

The key lessons were:

- formalize relationships through signed MoUs (Indonesia, Timor-Leste, Myanmar & Thailand) and Bhutan/India and Nepal/India had informal relationships,
- need to establish sharing of information (informal by WhatsApp) but formal through high level political commitment facilitated by WHO.
- Make linkage Community event bases surveillance (CEBS) and border crossings beyond designated Point of Entry (PoE).

Discussion – Led by Professor Nirmal Kumar Ganguly

- PKDL and asymptomatics are not at the forefront of VL elimination but need to be considered as reservoirs that can threaten elimination. Asymptomatics are found close to VL and PKDL cases and can develop VL later (even if they do not transmit now, they should be followed up later).
- Integrated surveillance should consider the other causes of fever in addition to VL and use a multiplex system. Here, centres of excellence will be important since they may help with diagnosis of other causes of fever.
- Need more advice concerning integration [need to differentiate this advice between the medical diseases and the administration involved].
- VL could learn from the vaccine platform to improve cross border communication and tackle issues.
- There was a committee of State level disease control directors from Bangladesh and India which had regular meetings and could be reactivated.
- West Bengal and Bangladesh have strong cultural bonds and, although there are also partner agreements, central government approval is required.

5.5 Presentations: Updates from partners

ASCEND - Prof Dr Be-Nazir Ahmed (Bangladesh) Dr Sharad Bartakaki (Nepal)

The ASCEND programme in Bangladesh started in June 2019 and ends in March 2022. It is focused in 19 LF endemic districts and 26 VL endemic districts. For VL, a cluster search, case investigation, outbreak investigation and follow-up of previous patients' approach has been adopted for ACD.

Guidelines have been improved and staff given training in surveillance and use of a mobile app for patient follow-up (2514 in total). 9044 people were screened in the cluster investigation and 912 people were trained.

The aims of the programme in Nepal are to: provide HR support, support planning and implementation, improve advocacy and supply chains, strengthen data management, perform cluster assessments and an outbreak response and build private sector capacity at national and provincial levels.

BMGF – Dr Kayla Laserson (India)

The BMGF have supported the programme for over a decade by funding many different partners (e.g. SPEAK India, see 3.8 above, and CARE & PATH below) covering all aspects of elimination including advocacy, intensive disease management, vector control and surveillance, and operational research to inform a post-elimination strategy.

PATH - Dr Neeraj Jain (India)

Supporting VL/PKDL and LF elimination in Uttar Pradesh by strengthening IRS, Mobilization (health workers and ASHAS). They are also tracking TB (very important due to VL/TB co-infections).

CARE - Dr Sridhar Srikantiah

Provides support for the VL elimination programme in Bihar and Jharkhand and supports entomological surveillance in sentinel sites based in Bihar, Jharkhand and West Bengal. They helped set up the KAMIS system for surveillance, support IRS and are currently investigating a village level approach for case detection and follow-up.

COVID-19 has impacted care for fever cases. This could be a genuine reduction in incidence of fever from many causes, but it is definitely a fear to report. Thus, we should expect to see a resurgence of VL incidence and deaths from VL in the next few months.

5.6 RTAG Discussion, Recommendations and Closing – Led by Professor Nirmal Kumar Ganguly

The chair thanked all presenters and expressed the view that operational research is essential for innovation of new tools including oral drugs and point of care testing.

Prof Mary Cameron was invited to present the draft recommendations (please see the summary above) and a discussion followed. The draft recommendations were circulated to RTAG for further comment and revision.

The chair concluded that it has been an excellent, productive meeting and thanked the organisers and everyone involved.

Annex 1

Programme

Day 1: Monday 5 October 2020 (Times are Indian Standard Time – GMT +5.30 Hrs)		
11:30 – 11:40	Opening Remarks	*Dr Sunil Bahl/Acting CDS*
11:40 – 12:00	NTD Road map 2030 and its implication for VL elimination as Public Health Problem (PHP)	*Dr Daniel Argaw Dagne*
12:00 – 12:05	Appointment of the Rapporteur	*Dr Ahmed Jamsheed Mohamed*
12:05 – 12:25	Global and Regional Updates	*Dr Saurabh Jain/Dr Zaw Lin*
12:25 – 12:45	Country presentation: India	
12:45 – 13:05	Country presentation: Bangladesh	
13:05 – 13:25	Country presentation: Nepal	
13:25 – 14:00	Discussion on current achievement on elimination of VL as PHP in SEAR and its sustenance plan based on three country presentations	*Prof N.K.Ganguly/ Chair*
Day 2: Tuesday 6 October 2020 (Times are Indian Standard Time – GMT +5.30 Hrs)		
11:30 – 11:40	Recap of Day 1	*Dr Usha Kiran*
11:40 – 11:50	Country presentation: Bhutan	
11:50 – 12:00	Country presentation: Thailand	
12:00 – 12:15	Discussion	*Prof N.K.Ganguly/ Chair*
12:15 – 12:35	Validation for elimination of VL as PHP and its dossier preparation in brief	*Dr Zaw Lin/Dr Saurabh Jain*
12:35 – 13:05	Discussion	*Prof N.K.Ganguly/ Chair*
13:05 – 13:25	Potential dynamics of VL 2020-22: targets and resurgence	*Prof Medley*

13:25 – 13:45	Final recommendations of Independent Assessment of KA Elimination Programme India, 2019	*Dr Pandey Dhruv*
13:45 – 14:00	Discussion	*Prof N.K.Ganguly/ Chair*
Day 3: Wednesday 7 October 2020 (Times are Indian Standard Time – GMT +5.30 Hrs)		
11:30 – 11:40	Recap of Day 2	*Dr Sabera Sultana*
11:40 – 11:55	Vaccines for Visceral Leishmaniasis	*Prof. N.K.Ganguly*
11:55 – 12:10	Updates on treatment regimen for VL and PKDL	*Dr Saurabh Jain/ Dr. Fabiana Alves*
12:10 – 12:25	Advances and gaps in PKDL control and research	*Dr Mitali Chatterjee*
12:25 – 12:40	*Discussion*	*Prof N.K.Ganguly/ Chair*
12:40 – 12:55	Treatment for HIV-VL coinfection, current evidence FROM India	*Dr Sakib Burza*
12:55 – 13:10	Updates on Treatment for HIV-VL coinfection WHO guideline and related logistics	*Dr Saurabh Jain*
13:10 – 13:20	Discussion	*Prof N.K.Ganguly/ Chair*
13:20 – 13:35	Update on the findings of the SPEAK India project including surveillance, vector monitoring, health systems and modelling.	*Dr Mary Cameron*
13:35 – 13:50	IRS and alternatives of IRS	*Dr Rajpal Yadav/ Dr Bhupender Nagpal*
13:50 – 14:00	Discussion	*Prof N.K.Ganguly/ Chair*
Day 4: Thursday 8 October 2020 (Times are Indian Standard Time – GMT +5.30 Hrs)		
11:30 – 11:40	Recap of Day 3	*Dr Dhriv Pandey*
11:40 – 11:50	Innovation to achieve elimination as PHP and sustain the achievements	*Dr Suman Rijal*
11:50 – 12:05	Skin NTDs	*Dr Jose Ruiz Postigo/ Dr Saurabh Jain*
12:05 – 12:20	Lesson Learnt for cross border collaborations for VL elimination as PHP	*Dr Malaria and VPD colleagues FROM SEARO and ALL*

12:20 – 12:55	Updates FROM partners	*ASCEND, BMGF, CARE(India), CMMID, DnDi, MSF, PATH(India) & SPEAK(India)*
12:55 – 13:00	**Break**	
13:00 – 14:00	RTAG Discussion, Recommendations and Closing	*Prof N.K.Ganguly/ Chair*

Annex 2

List of participants

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Annex 3

Definitions relating to VL(=KA) epidemiology used by SEAR Member States

	India	Bangladesh	Nepal	Bhutan	Thailand
Case	A person from an endemic area with fever of more than 2 weeks duration and splenomegaly, who is confirmed by an RDT or biopsy.	New Kala azar (NKA): • Fever for >2 weeks AND Residing/traveling in Kala-azar endemic areas AND Splenomegaly AND rK39 RDT +ve • Additional symptoms: weight loss, anemia, enlarge liver, darkening of skin	**Probable**: A person living in or having travelled to kala-azar endemic areas showing clinical signs and symptoms of kala-azar (mainly irregular fever lasting more than two weeks and splenomegaly and/or weight loss), after ruling out malaria in endemic areas. **Confirmed**: • A probable VL case with laboratory confirmation, either serological (RDT, DAT, ELISA, IFAT) and/or parasitological (smear, culture) and/or positive by PCR or related techniques. OR • A probable VL case that has not been confirmed by any laboratory test (i.e. test(s) not done or negative) but is assessed by a clinician to be a confirmed VL case based on clinical grounds.	**Suspected:** A patient with fever of ≥2 weeks with any one of the following- splenomegaly, weight loss and anaemia **Confirmed**: A suspected case with rK39 positive result or demonstration of leishmania amastigote in aspirates of bone marrow, spleen or blood	**Suspect VL case**: A person living in or having traveled to endemic areas showing clinical signs of VL (irregular prolong fever, splenomegaly and/or weight loss etc.) **Confirmed VL case**: A clinical suspect person with laboratory confirmation of *Leishmania* parasites infection, either parasitological, serological and/or PCR.

	India	Bangladesh	Nepal	Bhutan	Thailand
Relapse	Any reappearance of KA signs and symptoms within a period of six months after the end of the treatment.	• Diagnosed as NKA and history of treatment for NKA AND • Reappearance of symptoms and sign of KA after 6 months of the end of treatment	• A kala-azar patient was successfully treated in the past but has presented again with clinical manifestations of kala-azar with parasitological confirmation at any point after cure.		A positive result of PCR sequence analysis showed 100% identity to spp. collect from the first episode.
VL-related death	Death of any person having been diagnosed of VL regardless of treatment status, whether the treatment was started or not, and the cause of death. Any death occurring between the moment the patient is diagnosed of VL and the final treatment outcome assessment at 6 months after the last drug was taken	Any death, whether related to Kala-azar or not, within 6 months after completion of treatment	Death of any person having been diagnosed of VL regardless of the treatment status and the cause of death within the standard post-treatment follow-up period. Death is notified as follows: • Death due to VL • Death due to HIV • Death due to other disease or medical condition(s) • Death due to SAE (iatrogenic) • Death due to non-medical condition (accident)		A confirmed leishmaniasis case that be recorded by physician showing major cause of death by VL.
Outbreak	**Criteria 1:** In high burden states i.e Bihar & Jharkhand, 10 or more laboratory confirmed cases reported in a given area (cluster/hamlet/village) or among a specific group of people within six	Occurrence of Kala-azar in a non-endemic area or in an endemic area beyond expected level (above average of three years cases)	**In kala-azar endemic districts** • Five or more (*) laboratory-confirmed local kala-azar cases reported in a given area such as cluster/hamlet/villages or among a specific group		Occurrence of more than 2 cases in the same community and the same period of time that be related epidemiologically

	India	Bangladesh	Nepal	Bhutan	Thailand
	months of occurrence of index case. **Criteria 2**: In low burden states i.e. Uttar Pradesh & West Bengal, occurrence of 5 or more laboratory confirmed cases warrants for an outbreak investigation. 5 or 10 cases "in a given area" may be scattered around the area without any geographical linking, or the clustering of cases on both sides of an administrative border may lead to a delay in recognizing an existing geographical linking **Criteria 3**: In non-endemic States or Non-endemic districts/blocks of an endemic state: Occurrence of even a single laboratory confirmed case reported in a cluster/hamlet/village and it amounts for KA outbreak. *SOP for Outbreak Investigation, NVBDCP, MoHFW, GoI. 2020.*		of people within six months of occurrence of index case. **In Grey districts** (there have been cases reported but it is not clear whether transmission occurs in that district or not) • Two or more (*) laboratory-confirmed local kala-azar cases reported in a given areas such as clusters/hamlet/ villages or among a specific group of people, within six months of occurrence of index case should be considered as an outbreak. (*) thresholds as proposed by the working group.		

	India	Bangladesh	Nepal	Bhutan	Thailand
Treatment Failure		Diagnosed as NKA and history of treatment for NKA AND No improvement after initial treatment within 1 month AND/OR reappearance of symptoms and sign of KA within 6 months			
PKDL Case		Residing/travelling in the endemic areas AND History of treatment for Kala-azar any time in the past AND Suggestive skin lesion without loss of sensation: macular, papular, nodular or mixed AND Exclusion of other causes of skin disease: leprosy, vitiligo, pityriasis, ring worm, arsenicosis AND rK39 (+ve)2 or slit skin smear positive or PCR positive.			

Annex 4

IRS and Entomological Surveillance

	India	Bangladesh	Nepal
Insecticide for IRS	Alphacypermethrin 5% WP – Synthetic Pyrethroid (SP)	Deltamethrin - SP	Lamda-cyhalothrin 10% WP - SP
No. of people protected by IRS & coverage rates	2019 - 49.7 M people protected in 2 rounds of IRS. 2020 - 28.1 M people protected in first round of IRS with 96.5% coverage against the target population in 4 states.	2019 - pre- and post-monsoon IRS performed in 41 and 49 upazilas, respectively. 2020 - pre-monsoon IRS performed in 98 upazilas with 614,291 of 614,446 households sprayed (99.97% coverage).	Information not provided.
LLINs usage	Not distributed for KA/PKDL under the KA programme, but JH and WB, co-endemic, for malaria are using them	No LLINs were distributed by the programme, but over 30,000 nets were distributed in a pilot study between 2013-2014.	Information not provided.
Susceptibility Testing	Entomological surveillance including susceptibility testing is being done by RMRIMS Patna, entomological units of CARE/LSTM and State entomological units. *Phlebotomus argentipes* is susceptible to the SPs Alphacypermethrin (0.05%) and Deltamethrin (0.05%), and the organophosphate Malathion (5%) and carbamate Bendiocarb (0.1%). However, it is resistant to DDT (<40% mortality).	Information not provided	Conducted in 10 selected villages of 5 districts: 5 intervention villages and 5 control villages Tests performed on Using malathion (5%), Bendiocarb (0.1%), Alphacypermethrin (0.05%), Deltamethrin (0.05%) And Lambda-cyhalothrin (0.05%) In intervention villages, *P. argentipes* showed some resistance to SPs but a mixed response in control villages. Malathion and bendiocarb were promising alternatives.


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