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Retrospective Quarterly Cohort Monitoring for patients with Visceral Leishmaniasis in the Indian subcontinent: outcomes of a pilot project

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Abstract

OBJECTIVE To evaluate a new tool for the monitoring of Visceral Leishmaniasis (VL) treatment outcomes in primary healthcare (PHC) settings, adapted from the standardised Retrospective Quarterly Cohort Monitoring done in tuberculosis control.

METHODS We developed standard case definitions for early and late VL treatment outcomes, a single register allowing for one-line entry per patient as registration tool, and quarterly reporting formats for the clinical outcomes. We pilot-tested these tools in three Indian Primary Health Centres and two Nepalese district hospitals, as well as in a charity VL treatment centre and a university hospital.

RESULTS Data collection for early treatment outcome was easily implemented but information on late treatment outcome was hard to obtain. Effectiveness of Miltefosine under routine care conditions was about 87% at end of treatment, and 76% at 6 months post-treatment related to the high number of patients lost to follow up at the latter end point.

CONCLUSION A retrospective cohort monitoring methodology is conceptually a good framework for monitoring clinical outcomes for chronic conditions as VL. The monitoring of early outcomes of VL treatment is perfectly feasible in Primary Care settings. The completeness of information on late outcomes can be improved by a number of strategies that remain to be field tested. Generally, clinical outcome monitoring should be strengthened in the VL control programmes.

keywords Leishmaniasis, Visceral, treatment outcome, retrospective cohort monitoring, resistance, treatment failure, intention-to-treat analysis, Miltefosine, Amphotericin B, efficacy, Visceral Leishmaniasis elimination

Introduction

Visceral Leishmaniasis (VL) casts a heavy burden upon the Indian subcontinent (ISC), more specifically in the Gangetic plains of Bangladesh, India and Nepal. The annual VL incidence in this focus is estimated at 160 000 –315 000 cases, that is, 80% of the world's VL burden (Alvar *et al.* 2012). VL generally touches the poorest of the poor (Boelaert *et al.* 2009) and is fatal if left untreated. In the last decade, the development of a rapid diagnostic test (rK39) and new treatment options such as Miltefosine oral treatment have allowed diagnosis and treatment of VL to shift from specialised centres to the primary healthcare (PHC) level (Bhattacharya *et al.* 2006). An ambitious regional elimination programme was launched in 2005 focusing on early diagnosis and Miltefosine-based treatment as one of its main control strategies (WHO 2005; Mondal *et al.* 2009). Very soon, concerns were raised that large-scale and unsupervised Miltefosine use might fuel drug resistance (Croft *et al.* 2006).

Unfortunately, VL control programmes give little attention to monitoring of patient adherence and clinical outcomes (Hasker *et al.* 2010; Malaviya *et al.* 2011). Current VL registers capture treatment initiation, but treatment completion or final outcome is rarely recorded. Monitoring of clinical outcomes is crucial for the patient though, as Miltefosine treatment needs to be maintained for 28 days to be effective, and has considerable, mainly gastrointestinal side effects (vomiting, diarrhoea), jeopardising correct intake and adherence. Treatment generally results in rapid clinical improvement with resolution of fever and improvement of appetite after a few days, also contributing to the risk of poorer adherence. But as VL is

a chronic condition, the verdict 'cure' can only be pronounced some months after treatment, currently empirically set at 6 months. Secondly, monitoring of clinical outcomes on any VL drug is also crucial at programme level. Tertiary-level hospitals and specialised centres have long been the only source of research data on VL treatment and treatment efficacy, with the inherent risk of bias in two ways: possibly better outcomes because of dedicated staff and resources on the one hand, but a selected population of referred or more severe cases on the other. Data on treatment outcomes at primary health-care level are essential to appreciate the quality and effectiveness of the control programme and the efficacy of a non-supervised, ambulatory treatment such as Miltefosine. Such data, if reliable, would be instrumental in the formulation of drug policy for the VL elimination programme.

Declining efficacy of a given treatment in VL is difficult to detect. Failure to treatment may appear through relapse after initial cure, rather than through immediate non-response to therapy during the drug course. Patients who relapse furthermore may not choose to return to the health-care provider or site where they were initially treated so the problem may be missed by the prescribing doctor (Hasker *et al.* 2010).

The gold standard for ascertaining cure in VL is a negative smear in direct microscopy on post-treatment bone marrow or spleen aspirate taken 6 months after last drug was taken, which is not feasible in the PHC setting. Diagnostic antibody tests such as DAT or rK39 RDT that have replaced direct microscopy as a diagnostic tool, remain positive for several years after treatment and thus cannot be used as a test of cure. Therefore, in practice, a patient is declared as definitively cured from VL when no clinical signs (fever or increase in spleen size since last visit) of VL have reappeared 6 months after completion of therapy (TDR 2010). In case of failure of treatment, presenting either as persistence of VL symptoms or return of symptoms of VL during or within 6 months after treatment, patients should thus be referred to a referral hospital for bone marrow of spleen aspiration and second-line treatment.

In most efficacy studies, outcome at 6 months is taken as end point (Sundar *et al.* 2002), but a recent cohort study in Nepal (Rijal *et al.* 2013) and surveys in India (S. Bursa, MSF, personal communication) indicate that relapses in the period 6–12 months post-treatment may be as frequent as before 6 months. A 6-month end point might therefore overestimate the true efficacy of certain drug regimens (Rijal *et al.* 2013).

In summary, the protracted nature of VL and the need for final outcome evaluation long after the end of the drug course pose a challenge to the primary health-care system, a situation very similar to other chronic infectious diseases as tuberculosis or HIV: In the directly observed treatment (DOTS) Strategy for control of tuberculosis, where treatment is given for 6 or 8 months, patients are registered systematically in a register that keeps track of periodic evaluations (sputum smears) and final treatment outcome in one single line. Treatment outcome is noted using well-defined, mutually exclusive categories (cure, treatment completed, treatment failure, death, default or transfer) (WHO 2001, 2006). Analysis of the treatment results is made through Retrospective Quarterly Cohort Analysis, calculating the proportions of the different treatment outcomes with as denominator the total number of patients reported for the quarter concerned one year earlier. In antiretroviral treatment (ART) care, there are three types of cohort analysis: (i) a quarterly analysis of new patients started on ART in the latest three-month period, (ii) a cumulative analysis of all patients ever started on ART and (iii) a group cohort treatment outcome analysis related to set time periods (WHO 2001, 2003; Ormerod *et al.* 2002; Chemtob *et al.* 2001; Veen *et al.* 1998). We thus adapted the retrospective cohort monitoring methodology to the specific case of VL treatment. The objective of this study was to field test this method in a few selected health facilities in VL endemic zones in India and Nepal.

Methods

Study setting

Three PHCs in Muzaffarpur district, Bihar, India and two district hospitals in Nepal were purposefully selected. Clinics were chosen on the following criteria: case load of VL patients, distance from the research centre, and preparedness of the medical staff to participate. In India we selected the PHCs of Kanti, Kudhani and Motipur. In Nepal, where PHC centres are rarely staffed with medical doctors, the lowest level of health-care provision for VL is not the PHC centre but the district hospital. We selected the hospitals of two endemic districts, that is, the Jaleswor district hospital in Mahottari district and the Siraha district hospital located in Lahan. The method was also tested in the coordinating VL research centres in each country. The Kala-azar Medical Research Center (KAMRC) in Muzaffarpur, Bihar is a private, non-profit treatment and research centre working exclusively on VL. B.P.Koirala Institute of Health Sciences, Ghopa, Dharan, Nepal, is a university hospital with a tropical disease unit specialised in VL care.

Inclusion criteria

Patient enrolment period started on different dates in the course of 2009 and ran up to 31st May 2011, with an additional 12 months for data collection on follow-up. All patients diagnosed with VL in the health structures during the above period were enrolled in the cohorts, regardless of age, address, way of diagnosis, past treatment for VL or not and treatment chosen.

VL diagnosis and treatment are provided free of charge in all settings. To monitor for side effects, patients in the PHCs receive tablets for the first three days to take at home and are asked to report back, while in Nepal, they are usually hospitalised during the first day of treatment. When no adverse events are reported, the required number of tablets is given to last up to the date of the next appointment, that is, 14 days after start of treatment. At that time, the remaining tablets are given to complete 28 days of therapy, and an appointment is made for a follow-up visit. This scenario was applied in all participating settings, except for KAMRC, where patients were hospitalised for the full duration of the treatment and received their tablets under DOT conditions.

Ethical considerations

Decision on diagnosis and treatment was entirely under the responsibility of the prescribing doctor of the health centre/hospital, and thus in line with the national guidelines, without interference from the investigators. No biological samples were taken from patients other than those prescribed for clinical reasons by the health staff. Only patients who gave informed consent were enrolled. The protocol of this study was approved by the ethical committees of Nepal Health Research Council, Kathmandu, Nepal, Banaras Hindu University India, and the corresponding bodies at the University Antwerp (UZA), Antwerp, Belgium.

Monitoring toolkit

The two data collection tools used in the novel monitoring system were a patient register and specific reporting forms. The register (Figure 1) is a line listing of each new patient. All basic data for identification and for epidemiological purposes (name, ID, age, sex, address, contact (mobile phone number) are recorded and so are data on diagnosis and treatment history, and current treatment choice (drug, dosage). In the next columns, treatment outcomes are recorded at two or three different moments in the follow-up, that is, at the end of the treatment, at six (and eventually at twelve) months. Registered treatment outcomes had to comply with the standardised case definitions for VL (TDR 2010) that also features on the lower part of the page.

The second tool is the reporting form (Figure 2) that summarises the outcomes collected over the past quarter, that is, (i) the end-of-treatment (EoT) outcomes of the most recently completed quarter and (ii) the 6M post-treatment outcomes of the cohort that was closed 7 months earlier.

These outcomes were calculated from the register at the earliest one month after the last day of the quarter in question, that is, when all patients started on treatment had completed their 28-day treatment regimen, EoT visits had taken place and outcomes had been recorded. At the same time, late (6M) treatment outcomes could be calculated from the line listing of the cohort that was closed 7 months earlier provided that these patients have presented themselves for their 6 month post-treatment follow-up visit. If they have not, they must be traced by telephone contact or home visit. If 12 months post-treatment outcomes are collected, a similar report can be drawn.

Training

We organised training workshops for the PHC staff and other stakeholders at the start of the project, halfway and at the end. Supervision and discussion with participating and supervising staff enabled us to improve the tools, identify the obstacles, and give feedback to the users. In February 2012, the results were presented in a validation workshop in Faridabad, India to stakeholders: representatives from the Ministries of Health of India and Nepal, WHO and NGO's, and scientists. After this workshop, the tools were finalised into generic forms (Figures 1 and 2) that are freely accessible on the website www.leishrisk.net/kaladrug.

Data analysis

We computed and plotted treatment outcomes on a quarterly basis. Secondly, we calculated the EoT and 6M post-treatment (6MpT) cure rates in the different settings to appreciate the effectiveness of Miltefosine (and other drugs) used under routine care conditions, and this in a cumulative cohort that was censored on 31st May 2011 to allow us to collect 6M post-treatment outcomes.

Case definitions were taken from recent WHO/TDR guidelines and presented in Table 1. The final cure rate was calculated as the number of patients that were assessed as cured (no VL symptoms) at 6M divided by the total number that started treatment. For treatment

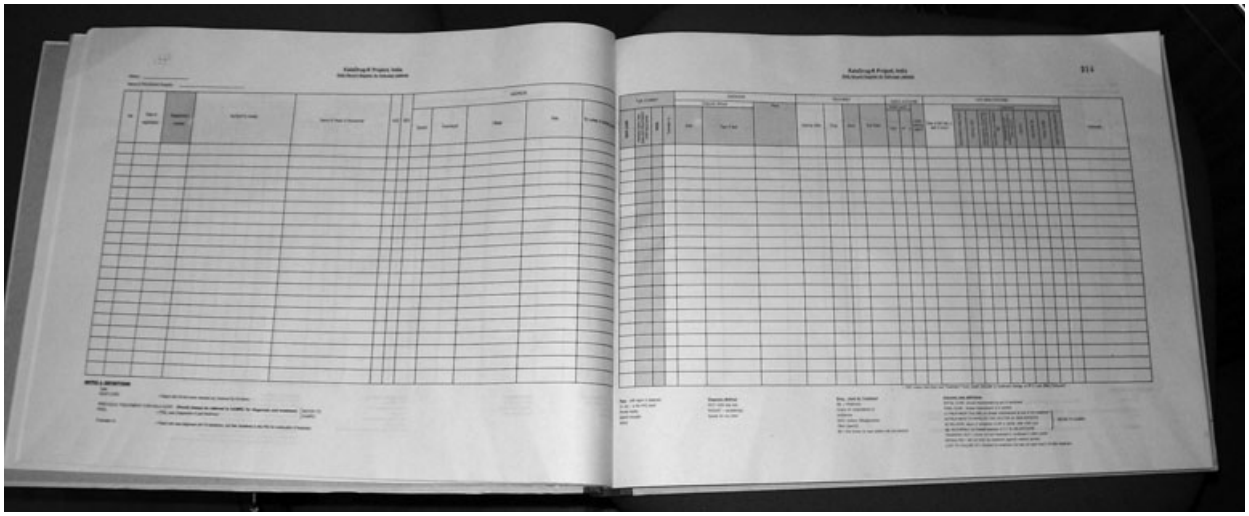

Figure 1 VL register book.

failure rate, we divided the number of non-responders + number of relapses + number of deaths, and divided by the number that was started on treatment.

Results

The total number of patients treated in the three PHCs in India was 310; in the two district hospitals in Nepal 289, and at BPKIHS in Nepal 232. For KAMRC in Muzaffarpur, we only report on the outcomes of the 566 patients treated on Miltefosine only. Treatments provided at the PHCs in India were either Miltefosine (68.7%) or Sodium Stibo-Gluconate (SSG, 31.3%), the latter despite the fact that it had officially been abandoned for its known lack of efficacy. In the two Nepalese district hospitals, the treatment of choice was Miltefosine (69.2%) with Amphotericin B as alternative in case of contraindication or Serious Adverse Events (30.8%). At BPKIHS, 58.6% received Miltefosine, 39.6% Amphotericin B and 1.7% liposomal amphotericin B (four patients).

Overall, early and late (6M) treatment outcomes in the different clinical settings and with the different drugs prescribed, on a cumulative cohort up to May 2011, are given in Table 2 and 3: Treatment completion rate (which corresponds with early cure rates because we define cure as treatment completion with clinical improvement) with Miltefosine in the two district hospitals in Nepal was 87.0%, and in the three PHCs in India 84.0%. Defaulter rates for Miltefosine-treated patients were 2.5% in Nepal and 14% in India. In Nepal, three patients were switched to second-line treatment because of non-response to Miltefosine treatment on clinical grounds. No aspiration and Giemsa staining was performed to formally confirm this as treatment failures.

For the late treatment outcomes, routine data collection could not be installed as planned as hardly any patient returned for the follow-up visit at six months post-treatment. Active tracing through telephone contacts and home visits was organised by the research teams, with good results in India. In Nepal, however, this was particularly time intensive because of the large distance between the team's headquarter and the two hospitals. Moreover, in the border district Mahottari, more than 50% of the VL patients were Indian citizens seeking treatment across the border, whereby often only a temporary address in Nepal was recorded in the register, resulting in high loss-to-follow-up rates. The final cure rate obtained despite active tracing therefore was 38.0% for patients treated with Miltefosine, against 76.1% in India. Treatment failure rates were 1.5% and 5.6%, respectively.

In contrast, the RQCM approach yielded more complete information in the research centres BPKIHS for Nepal and KAMRC for Bihar. End-of-treatment cure rates with Miltefosine in BPKIHS were 90.4% and 98.1% under DOT in KAMRC; defaulter rates were resp. 7.4% and 0.7%. Late treatment outcomes here were much more complete with minimal loss-to-follow-up rates, and showed 77.9% cure and 8.8% relapse in BPKIHS Dharan and 90.6% cure and 6.7% relapse at KAMRC Muzaffarpur (Sundar *et al.* 2012).

In Figure 3, we plotted out the quarterly outcomes by cohort in Miltefosine-treated patients from BPKIHS, where systematic follow-up was done up to 12 months

QUARTERLY REPORT ON VL TREATMENT OUTCOME		
Name of Institution:	Name of (District) VL coordinator:	Date of completion of this form:
District n°:	Signature:	

EARLY OUTCOME	Patients registered during ___quarter of year _____	From (date) To

1. NEW CASES (1st time treated)		Total number registered	Initial Cure	Non-response (early treatment failure)	Defaulter	Treatment stopped for SAE	Others (e.g Transfer out)	Death
New KA Cases	MIL							
	Ampho B							
	SAG							
Total								

2. OTHER CASES (history of recent ttm)		Total number registered	Initial Cure	Non-response (early treatment failure)	Defaulter	Treatment stopped for SAE	Others	Death
Re-Treatment after Failure, Default, SAE or Relapse	MIL							
	Ampho B							
	...							

QUARTERLY REPORT ON VL TREATMENT OUTCOME		
Name of Institution:	Name of (District) VL coordinator:	Date of completion of this form:
District n°:	Signature:	

FINAL OUTCOME	Patients registered during ___quarter of year _____	From To

(in dark gray: same numbers as reported on the early treatment outcome report of this cohort)

1. NEW CASES (1st time treated)		Total number registered	Final Cure	Non-response	Defaulter	Treatment stopped for SAE	Others	Death	Relapse	Lost to Follow-up
New KA Cases	MIL									
	Ampho B									
	SAG									
Total										

2.OTHER CASES (history of recent ttm)		Total number registered	Final Cure	Non-response	Defaulter	Treatment stopped for SAE	Others	Death	Relapse	Lost to Follow-up
Retreatment after Failure, default, SAE, Relapse	MIL									
	Ampho B									
	...									

Figure 2 Example of the blank report form.

Table 1 Case definitions for the outcome recording of VL patients

Early treatment outcomes	
Initial cure:	Treatment completed, clinical improvement (absence of fever, regression of enlarged spleen + return of appetite and/or gain in body weight)
Non-response:	Signs and symptoms of VL persist or recur + confirmation by a positive
Defaulter:	VL case who did not complete the 28-day treatment regimen of Miltefosine and/or did not present for assessment after treatment in the facility where they were enrolled
Side effects-related switch	Side effects requiring Miltefosine stop and change of treatment
Death	Any death, whether or not related to KA
Late treatment outcomes	
Definite cure:	VL case with initial cure and no clinical signs (fever, or increase in spleen size since last visit), six months after completion of therapy
Relapse:	VL case with initial cure but with reappearance of clinical symptoms and/or signs along with smear positive for LD bodies during the six-month follow-up
Lost to follow- up:	VL patient who completed therapy but who did not present/could not be traced for assessment at six months post-treatment
Death	Any death, whether or not related to KA

Treatment failure: includes both non-response and relapse. Adapted from TDR/WHO. Indicators for monitoring and evaluation of the kala-azar elimination programme. 2010.

post-treatment, showing trends in cure rates over time, and revealing an increase in the relapse rate from 8.8% at 6M to 16.2% at 12 months.

Discussion

The main objective of this study was to develop and optimise new tools for monitoring VL treatment outcomes and test them in the primary healthcare setting. Retrospective cohort monitoring is considered a good tool for monitoring care outcomes in long treatments and chronic diseases within the health system (Khader *et al.* 2012a,b; UNRWA 2009). As the data are collected by the providers and can be analysed at an intermediate (district) level, immediate feedback to providers and remedial action is possible, for example, in case of a high defaulter rate. A potential benefit of the monitoring is that it stimulates the PHC staff to improve counselling on follow-up visits– and consequently on treatment adherence, as shown in TB and HIV/AIDS programmes (Lowrance *et al.* 2007; Volmink & Garner 2007).

With the proposed tools initial and final cure rates, defaulter rates and failure rates, as done in TB programmes, can be calculated. Their implementation, however, requires commitment and strategies to systematically monitor and register early and late treatment outcomes of all patients diagnosed and treated.

By piloting this method in the different settings and comparing outcome indicators, we were also able to make a series of observations: The data obtained in our study provided a snapshot picture of the status of implementation of the current treatment guidelines with

Table 2 Early treatment outcomes in cumulative cohort from 2009 to May 2011 early treatment outcomes

Setting											
Piloting centres	Country	DRUG	Early cure	Defaulter	Death	Treatment switch for non-response	Referral	Treatment switch for SAE	Grand total	Treatment completion rate %	Defaulter rate %
District hospitals	Nepal	MILTEFOSINE	174	5	0	3	10	8	200	87.0	2.5
		Amphotericin B	81	0	1	0	7	0	89	91.0	0.0
PHCs	India	MILTEFOSINE	179	30	2	0	2	0	213	84.0	14.1
		SSG (SAG)	72	21	1	1	2	0	97	74.2	21.6
Reference centres											
BPKIHS	Nepal	MILTEFOSINE	123	10	0	0	0	3	136	90.4	7.4
		Amphotericin B	89	3	0	0	0	0	92	96.7	3.3
		AmBisome	4	–	–	–	–	–	4	100.0	–
KAMRC (DOTS)	India	MILTEFOSINE	555	4	2	0	0	5	566	98.1	0.7

Treatments: MIL: 50 mg BID (for >25 kg BW) or OD (for <25 kg BW) for 28 days; children (2–11 years): 2.5 mg/kg daily for 28 days. Ampho B: 1 mg/kg/day for 14 days. SSG: 20 mg/kg/day for 30 days.

Table 3 Late (6 m) treatment outcomes in cumulative cohort from 2009 to May 2011 early treatment outcomes

Setting													
Piloting centres:	Country	DRUG	Final cure	Defaulter	Death	Treatment switch for non-response	Referral	Treatment switch for SAE	Relapse	Lost to follow	Grand total	Cure rate %	Treatment failure rate %
District Hospitals	Nepal	MILTEFOSINE	76	5	0	3	12	8	0	96	200	38.0	1.5
		Amphotericin B	5	0	1	0	7	0	3	73	89	5.6*	4.5
PHCs	India	MILTEFOSINE	162	30	2	0	2	0	10	7	213	76.1	5.6
		SSG (SAG)	69	21	2	1	2	0	2	0	97	71.1	5.2
Reference centres:													
BPKIHS	Nepal	MILTEFOSINE	106	10	3	0	0	3	12	2	136	77.9	11.8
		Amphotericin B	64	2	0	0	0	0	0	26	92	69.6	0.0
		AmBisome	4	–	–	–	–	–	–	–	4	100.0	–
KAMRC (DOTS)	India	MILTEFOSINE	513	4	4	0	0	5	38	2	566	90.6	7.4

*No active 6M post-treatment tracing done.

Miltefosine as first-line drug regimen. In routine practice, the proportion of patients receiving recommended first-line treatment was around 60–70% in Nepal, related to the absence of paediatric formulae and availability of Amphotericin B. In Indian PHCs, the proportion fluctuated in relation to supply, with periods of SSG being used.

PHCs in India have only access to first-line treatment and therefore have a high referral rate, in contrast to the District hospitals in Nepal with access to second line and more lab facilities. Non-response and treatment switch for serious adverse events are rarely reported, because these patients are referred to second line, so they end up classified as referral, or they simply default and seek treatment elsewhere.

The cure rates of Miltefosine obtained in this piloting study give a first evaluation of the effectiveness of the current first-line policy with unsupervised ambulatory treatment (as applied in the three PHCs in India, and the two district hospitals as well as the reference hospital in Nepal): Early treatment outcomes show treatment completion rates from 84,0–90, 4% and call for efforts to reduce defaulter rates. The late (6 months) treatment outcomes that were complete for the PHCs in India and BPKIHS in Nepal were 76.1% and 76.5%, respectively, which is worryingly low, especially given the data from BPKIHS, indicating a considerable number of relapses beyond six months (Figure 3).

Given the relatively small number of patients, there will be a large variation in, for example, cure rates from one quarter to another in a given PHC, but calculating the outcomes on a quarterly basis forces to reflect on performance and leads to initiatives for improvement (Maher 2012).

The majority of patients adhered to the treatment follow-up including the EoT evaluation, probably encouraged by the financial incentive provided by the VL programme. The return visit scheduled at six months post-treatment was not respected, and treatment outcomes presented here were obtained through active tracing of the project staff and not by the clinic staff. Tracing patients who default during treatment or for the follow-up visits should be the role of the District Health Office (DHO) through the existing network of village health volunteers such as Accredited Social Health Activists (ASHAs) and Auxiliary Nurses/Midwives (ANMs), and the use of mobile phones to transfer the missing data on outcome (Malaviya *et al.* 2013). Involvement of community health workers in VL control activities has been advocated by others (Joshi *et al.* 2006; Malaviya *et al.* 2011; Singh *et al.* 2011; Malaviya *et al.* 2013), as they can help to identify suspected VL cases at community

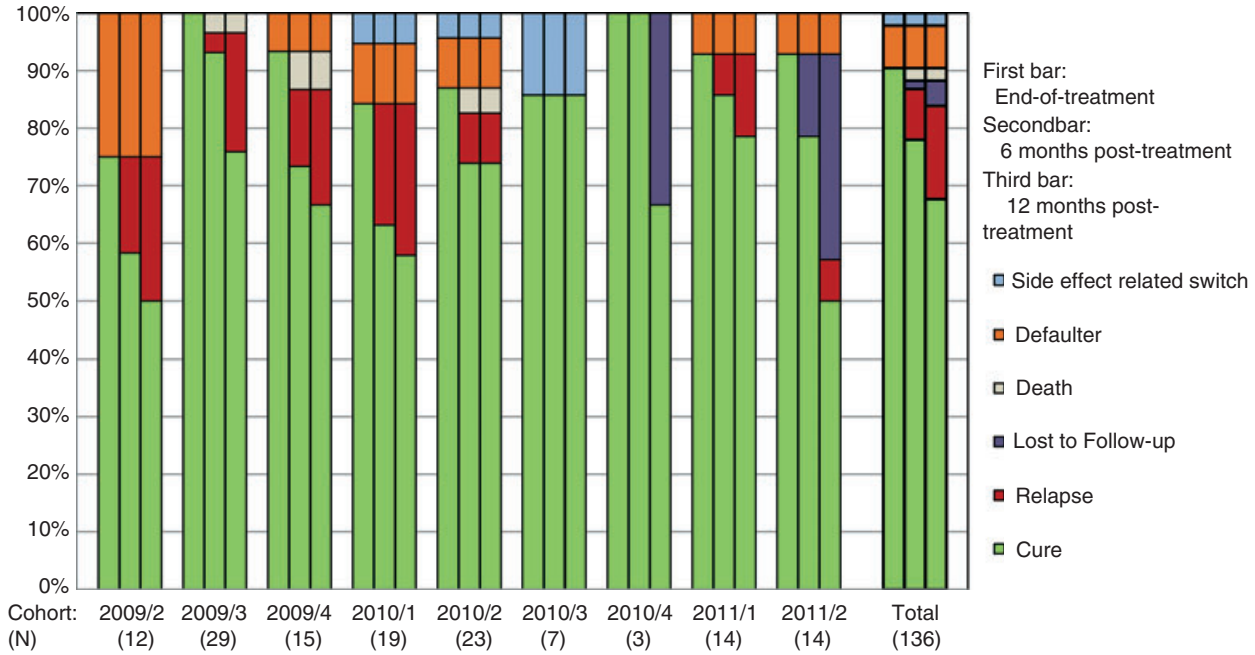

Figure 3 Quarterly cohort outcomes of Miltefosine-treated VL patients at end of treatment, at six months and at twelve months after treatment in BPKIHS, Dharan, 2009–2011.

level, and refer or eventually even use a rapid diagnostic test for screening on the spot when adequately trained.

An alternative to routine collection of treatment outcomes at the primary healthcare level would be through spaced surveys. Hasker *et al.* (2010) performed such a survey, by tracing formerly treated patients and questioning them on clinical events since treatment. They found that 40% of SSG-treated patients and 15% of miltefosine-treated patients had taken a second VL treatment since. Compared to retrospective cohort monitoring, the survey method may have the advantage of being independent and punctual but it was costly, and may be biased by a high number of patients that cannot be retrieved if addresses are not recorded in detail (Malaviya *et al.* 2011).

Implications for public health and research

Based on a standard methodology applied in TB programs, we propose a treatment outcome monitoring tool for VL that can be routinely used at primary healthcare level. All the tools (register, report forms, manuals) can be downloaded from the website www.leishrisk.net/kaladrug. To implement the system requires (i) minimal training on treatment outcome definitions for PHC staff and (ii) a dedicated team at the district health office to organise the collection of late treatment outcomes with possibly the involvement of community health workers.

District health office staff acquainted with the tuberculosis programme should have no problem in applying the same RQCM methodology on VL. The tools can be used by any VL treatment programme in the world, regardless of the treatment protocol(s) used. It should help in comparing the effectiveness in real-life conditions of different treatment options, as well as monitoring the effectiveness of current treatment strategies over time in the light of possible emergence of resistance.

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