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Original Article

Elimination of visceral leishmaniasis in Nepal: Pipe-dreams and possibilities

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Abstract

Introduction: Visceral Leishmaniasis (VL) re-emerged in the Indian subcontinent in the mid-1970s after an almost complete absence in the previous fifteen or so years. The disease was first noted in Nepal in 1978 and, since 1980, it has been reported regularly in increasing numbers. Elimination of visceral leishmaniasis by 2015 has been identified as regional priority program in the level of high political commitment.

Objective: The objectives of this study are the comprehensive assessment of information related to VL on the basis of past research studies conducted in Nepal, and an assessment of the prospects of control measures.

Materials and methods: This was time line comprehensive VL epidemiological assessment study based on the research conducted by main author during the past ten years. During the period the studies were conducted using cross sectional, case control and exploratory study design. The statistical analysis was done using qualitative and quantitative methods.

Results: In our study in the visceral leishmaniasis endemic district, Siraha, in the population of 112,029, a total of 996 clinically suspected cases were reported (with fever of long duration and splenomegaly, with no malaria) during 1998-2002. In all, 283 subjects were found positive for visceral leishmaniasis by rK39 and 284 had positive bone marrow. There was no detectable difference in the density of *Phlebotomus argentipes* between high, and moderate incidence village development committees (VDC: the smallest administrative unit), but collections in the low incidence areas (in winter) were negative. *P. argentipes* was never numerous (maximum 4.4 females collected per man-hour), and was much less common than *P. papatasi*. Peaks of abundance were recorded in the March and September collections. We have found that the numbers of reported cases of visceral leishmaniasis in Nepalese villages was unaffected by indoor residual spray (IRS) indicated by parallel trends in case numbers by time series analysis in treated and untreated villages. A series of maps through ten years clearly showed that the infection can move rapidly between villages, and it is impossible to predict where transmission will occur from year to year.

Conclusion: If maximum benefit in relation to cost is the goal, it may be preferable to put all possible efforts into active case detection (ACD) with free treatment. ACD should involve the network of Village Health Workers or Female Community Health Volunteers and the rK39 dipstick test at health centre level. Surveillance of disease and vector, communication for behavioural impacts and insecticide spraying should be important component of elimination program. If IRS is to be a part of the intervention, it is essential that it is carried out effectively, both in areas where the disease has been reported and in neighbouring areas. Integrated vector management need to be monitored for its application and effectiveness for VL elimination.

Kala azar (KA) re-emerged in the Indian subcontinent in the mid-1970s after an almost complete absence in the previous fifteen or so years. Prior to that time, it had occurred in irregular epidemic waves, probably since the early nineteenth century. Napier suggested that it had been introduced, and evidence suggests that it might have come from Africa[1,2]. Since the late 1970s, the disease has spread throughout North Bihar and into neighbouring West Bengal, Bangladesh and Nepal. Despite efforts to control this spread, the number of reported cases in North Bihar alone varied between some 20000 and more than 100000 annually. In Nepal the disease was first noted in 1978, and since 1980 it has been reported regularly, in increasing numbers. Between 1980 and 2003, 24,178 cases were reported from the 16 affected districts, all in the eastern Terai (Table 1).

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Table 1: Year-wise distribution of reported visceral leishmaniasis cases and deaths[3]

Year	Number of cases	Incidence per 100000	Number of deaths	Case fatality rate (percent)
1980	51	1.50	3	5.88
1981	133	3.95	1	0.75
1982	266	7.90	35	13.16
1983	60	1.78	4	6.67
1984	94	2.79	5	5.32
1985	95	3.65	0	0.0
1986	199	9.27	6	3.02
1987	169	6.48	8	4.73
1988	442	17.18	1	0.23
1989	291	9.01	5	1.72
1990	446	12.45	34	7.62
1991	870	17.45	56	6.44
1992	1395	20.96	8	0.57
1993	1368	34.08	5	0.37
1994	1976	49.03	9	0.46
1995	1787	44.60	65	3.50
1996	1571	39.14	55	3.50
1997	1342	33.23	36	2.68
1998	1409	33.88	42	2.98
1999	1794	43.14	24	1.34
2000	2090	50.26	50	2.39
2001	2020	48.56	22	1.09
2002	2389	59.9	18	0.75
2003	1921	43.6	23	1.20
2004	1526	27.7	15	0.98
2005	1564		21	1.34
Total	27268		551	2.02

Kala-azar elimination programme has been identified as priority programme in India, Nepal and Bangladesh and committed to eliminate it by 2015 from the region. For this, as of high level of political commitment, a Memorandum of Understanding (MoU) calling for the elimination of VL through inter country cooperation was signed. Key partners reached a consensus on the five strategic pillars for elimination of kala-azar and recommended preparation of operational plans by Bangladesh, India and Nepal.

With this motivation, here, we examine the prospects for elimination in the light of recent studies, mainly one carried out in the Terai area of Nepal between 1994 and 2003. We include some published results as well as data that have previously been reported in a final report to TDR.[4]

Background knowledge

Here we present some of the available information on VL that is essential to the design of intervention, and raise some of the outstanding questions.

Epidemiology of visceral leishmaniasis

VL in Nepal is mainly confined to the southern plain of the eastern and central regions, bordering VL endemic districts of Bihar State in India. Occasional sporadic cases occur elsewhere. Around 5.5 million people live in the affected areas, so are classified as "at risk". A total of 25704 cases with 530 deaths were reported between 1980 and 2004 (440 cases per 100,000 in 20 years: average about 20 per 100,000 per year), and the case fatality rate in reported cases varied between 0.23 and 13.6 percent.

Vector and transmission

The only vector is *Phlebotomus argentipes* and any non-vector-borne transmission is epidemiologically irrelevant. Although *Phlebotomus papatasi* and *Sergentomyia babu* are much more abundant than *P. argentipes* in the area, there is good experimental evidence that they are not vectors.[5] Transfusion, venereal and transplacental transmission are all very rare.

P. argentipes (in the endemic areas) is largely restricted to domestic and peridomestic habitats, on alluvial floodplains. Studies in West Bengal and Nepal further define the habitat in terms of high soil moisture.[5,6] While the breeding sites are poorly described, breeding has been detected in humid ground rich in organic content, mainly in animal shelters. *P. argentipes* feeds preferentially on cattle and man, and does not readily feed on dogs. Further details are given below.

P. argentipes is susceptible to most relevant insecticides. Visceral leishmaniasisis not zoonotic. Good evidence that most if not all, transmission is from person to person, comes from the finding that increasing numbers of cases in Bihar are resistant to antimony.[7,8] Treatment of humans cannot produce selection pressure on a zoonotic parasite. For drug resistant clones to spread in the human population, they must be passed from person to person.

Visceral Leishmaniasis was, effectively, eliminated in the 1960s, as a side effect of the use of insecticides for malaria control. The evidence for this is largely circumstantial, but the analysis by Kalra in 1985, is very convincing, especially in that, in the places where malaria control has continued (Assam and Tamil-Nadu), VL has not returned.[9]

Disease spectrum

Subclinical infection, leading directly to immunity or (rarely) to PKDL occurs at a significant but unknown rate. This rate can best be measured (presumptively) by a combination of serology and skin testing. In African studies it varied between 25% and more than 90%.[10,11] There are no comparable studies in India or Nepal.

Patients with symptomatic visceral disease and with PKDL are infective, but sub-clinical and cured cases are assumed not to be. This assumption is integral to the elimination strategy, but has not been fully substantiated.

Co-infection with HIV may reduce the proportion of sub-clinical infections, and may hasten the progress of the disease. There is no information on the rate of progress to PKDL in co-infections. Co-infection has been very well studied in areas where infantile visceral leishmaniasis occurs, especially in the Mediterranean basin. Amastigotes have been found in the blood, and the localisation of the lesions is frequently atypical. This leads to atypical disease, in which thorough parasitological diagnosis is essential.[12] There is no reason to suppose that the extrapolation of these results to VLis justified.

Diagnosis

In most instances, diagnosis depends on clinical signs and symptoms supported by the aldehyde test, but the rK39 dipstick test is being introduced in district, regional and central health facilities. The rK39 dipstick diagnostic method is remarkably simple, and can be used at village clinic level. So far, it has proved reliable in the conditions of Nepal.[13] The sensitivity of the direct agglutination test was 100% and the specificity was 99.2%. The direct agglutination test had positive and negative predictive values of 100% and 99.2% respectively. The direct agglutination test has been found to be simple, rapid, reliable, economic, safe and adaptable to micro-techniques using microtiter plates.[14]

Treatment

While sodium antimony gluconate (SAG) remains the first-line drug with amphotericinB as second line, Miltefosine (paromomycin), which is given orally, represents an important advance in case management[8]. However, there is no reduction in the time required for cure, and the expense is greater than for existing drugs. Moreover, Miltefosine is teratogenic, so cannot be used in pregnancy.

These pre-existing and new technical advances, combined with current priorities in development (e.g. the alleviation of poverty, equity, and decentralisation of public services), have justified a re-evaluation of VL as a candidate for increased intervention efforts.

The Nepal plan

The Visceral Leishmaniasis Elimination Plan proposed in 2002 aims at reducing the annual morbidity to less than one per one hundred thousand population at risk, by 2015.[15] It is also hoped to eliminate PKDL by 2018. This will be achieved by reducing morbidity by 10% per year and preventing all mortality, by strengthening health services and by vector control measures.[15]

The incidence in 2002 was about 60 per 100 000 (range: 1.5 in 1980 - 59.9 in 2002) and incidence in 2003 was 43.6 per 100 000. Since large parts of each district, including most municipalities, are unaffected, the incidence in affected villages is much higher. The target of 1 case per 100 000 in a population of 6 million would be around 60 cases annually. Reducing morbidity by 10% annually presumably means reducing the annual number of new cases by that amount. Given a current level of 2000 cases reported annually, and a goal of just 60 cases, at a rate of reduction of 10% annually, the goal would be achieved in 33 years. To reduce the total

number of cases from 2000 to 60 in twelve years would require an annual reduction of nearly 25%.

The main thrust of the plan is to reduce the reservoir of infection by early case detection and treatment. This would be achieved by raising community awareness and improving community surveillance, by providing reliable diagnostic facilities, and by providing free treatment. This would be backed by selective indoor residual spray (IRS) and unspecified integrated vector control measures (use of impregnated bednets and eco-environmental management).

The plan does not specifically include any post-elimination maintenance phase. Clearly, the plan as proposed requires considerable expansion and development before even a feasibility study would be justified. It can only realistically be implemented after such a study has been completed.

Elimination of visceral leishmaniasis

In principle, VL can be eliminated. Indeed, it was eliminated throughout the subcontinent, for a period of fifteen years, *by mistake*!

The only relevant action taken in the initial elimination was comprehensive coverage by IRS, over a much wider area than that affected by KA. There was no special effort to enhance the normal system of case detection and treatment. Sandfly numbers were not monitored, and there was only routine monitoring of the cases.

Little can be learned from this experience. Despite the early serendipitous success, there is no sound theoretical basis for any elimination programme, much less any evidence based on practical experience.

It is generally considered that, in the absence of any non-human reservoir host, early detection and treatment of cases will reduce the reservoir of infection and prevent further transmission.[16]

On empirical grounds, however, it is generally considered that IRS should be the basis of control measures, and that it is sufficient to do this on a focal basis, concentrating on settlements from which the infection has been reported.[16]

Thirdly, it has been shown that PKDL cases potentially constitute a reservoir of infection during periods when overt VL is absent.[17] Active detection and comprehensive treatment of PKDL cases is an essential component of any elimination programme.

There is no basis to define how many houses need to be sprayed, nor how efficient the spray must be, nor what is the density (or mean longevity) of sandflies that must be reached in order to achieve the control target.

Control measures that have been undertaken have been on a trial-and-error basis, usually with inadequate monitoring, so little has been learned from them. The current strategy in Nepal is to use focal IRS in the affected village development committees (VDC: the smallest relevant rural administrative unit in Nepal), together with passive case detection and free treatment.

Our findings

Study outline

Our studies were conducted in Siraha district, one of the sixteen KA-affected districts in the eastern Terai [population: 525 840 (1991 census); 531 587 (current estimate)], from 1999 to 2001. The objective was to study the status of vector, disease and infection in relation to ecological perspectives.[4] The reported annual incidence in the study area during the study period was 13.2 per 10 000 (10.6 in 1998). We randomly selected 20 of the 109 VDCs and one of the two municipalities (population: 75 888). We used 2 VDCs in Kanchanpur, an unaffected district in western Terai, for comparative studies.

The selected VDCs were grouped according to the current annual incidence of infection:
High incidence: >20/10,000 (4 VDCs)
Moderate incidence: 6-20/ 10,000 (5 VDCs)
Low incidence: <6/10,000 (11 VDCs)
VL free: no disease (3 VDCs including the two in Kanchanpur).

Further details of the study design are described elsewhere.[4]

Key Results

Effectiveness of rK39 in active case detection

The effectiveness of rK39, a serological tool to diagnose KA, was assessed by following the VL cases in 21 infected VDCs over a 23-month period. In the population of 112,029, a total of 996 clinically suspected people were detected (with fever of long duration and splenomegaly with no malaria). These were tested by rK39 in the village, and were referred for bone marrow aspiration. Altogether 290 were positive in one or other test; 283 by rK39 and 284 by bone marrow examination.

Table 2 shows the relationship between rK39 and bone marrow results. The results show that nearly all

cases that would be detected by clinical screening followed by bone marrow aspiration could be detected by the much less invasive and simpler rK39 dipstick test.

Other workers have found this test is both sensitive and specific, but have found that patients remain positive for at least a year following cure. This will not be a problem in active case detection if a basic clinical screen is incorporated.

Table2: Relationship between rK39 and bone marrow results on clinically suspect patients in ACD

Test	BM+	BM-	Total
rK39 +	277	6	283
rK39 -	7	706	713
Total	284	712	996

rK39 Sensitivity = 97.9%, specificity = 99.2%

Vector density and behaviour

The species distribution, biting activities and feeding habits of sandflies in the affected areas were studied, and these were correlated with sero-prevalence and prevalence of VL.[18] *Phlebotomus papatasi*, *Phlebotomus argentipes* and *Sergentomyia babu* were found. *Phlebotomus papatasi* was the predominant species in all the collection sites in Siraha district, with density increasing steadily between March and September.

In our study, *P. argentipes* was found in February, March, April, June and September, but not in January. Abundance was highest in March, and there was a less well defined increase in September.[4] Ashford RW carried out a meta-analysis of three earlier studies, one by Nepali author, and two which remain unpublished.[19,20] The results were conflicting, but showed *P. argentipes* to be present in all months, but at very low density in January and February, with the highest density in April, and a small increase in September. Whole night collections showed peak biting between 8 and 10 p.m.

Blood-meal analysis detected single and multiple feeding habits in *P. argentipes*. Analysis of 257 blood meals showed that 189 flies had fed on a single host and 68 had fed on more than one animal in various combinations. Blood meals included human, ruminants, dogs, human plus human, fowl plus human, dog plus fowl. Dog blood was detected in only two of the 257 meals.[18]

There was only dubious correlation between anthropophilic sandflies and the prevalence and/or incidence of the disease in the study areas. There was no detectable difference in the density of *P. argentipes* between high, and moderate incidence VDCs; collections in the low incidence areas were negative, but these were carried out in winter, when density was low everywhere.[4]

Effectiveness of IRS

We have shown that the numbers of cases of VL in villages was unaffected by IRS.[4] Time series in treated and untreated villages showed parallel trends in case numbers (Figure 1). It should be noted, as a measure of the efficiency of the operations, that three VDCs remained unsprayed despite repeated reports of cases over five years; three other VDCs reported cases for four years continuously without being sprayed. Whatever the reasons, IRS was ineffective under the prevailing conditions.

Fig 1: Shifting of visceral leishmaniasis endemicity in Siraha district

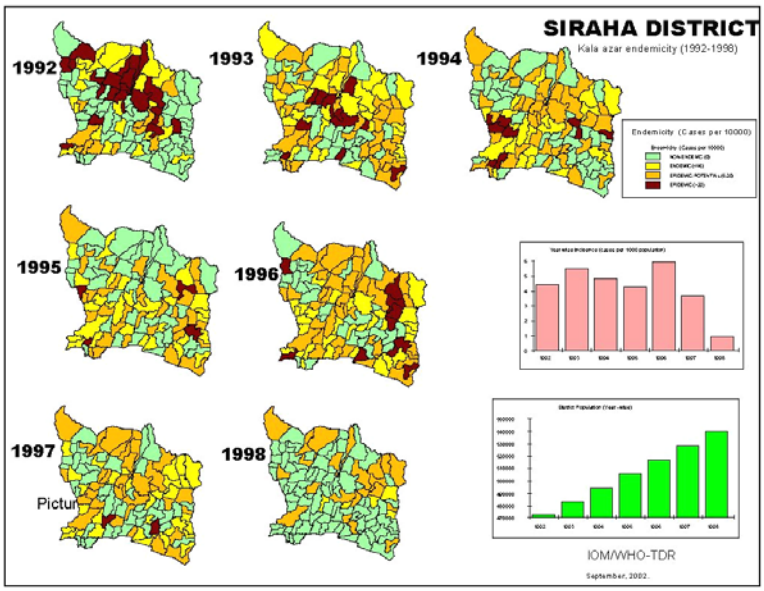
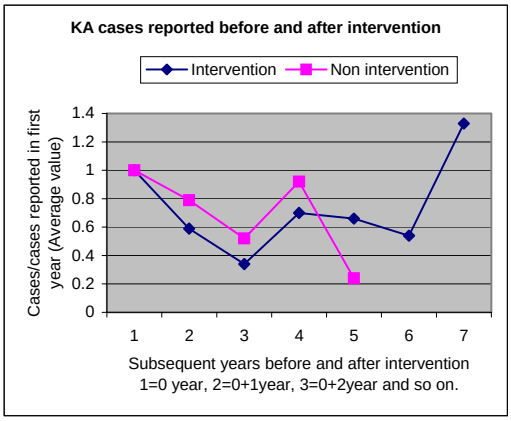


Fig 2: Analysis of effect of spraying



Effectiveness of case detection and treatment

Our study showed that under current conditions numerous villages held infected people for several years before IRS was instituted.

The role of case detection and treatment is dubious. Several relevant parameters are unknown, such as the critical mass of infections required to maintain transmission at a rate where R>1, and the infectivity of sub-clinical cases.

Mobility of the infection

In Chandra Udaypur VDC, 24 of the 911 inhabitants became infected in just five months. Of these, 22 cases occurred in a single village, Dhobiyadar (pop 136), and the 2 others were in a neighbouring village, Dharampur (pop 61).

A series of maps (Figure 2) through ten years showed that in any one year, the reported cases were strongly clustered, but that the concentrations of cases moved rapidly between VDCs.

Clearly the infection can move rapidly between villages, and it is impossible to predict where transmission will occur from year to year.

If IRS is restricted to villages where the infection is known to occur, those areas where it is incubating, or where it is present but has not yet been reported will be missed. IRS must cover not only those villages

where the infection is known, but also peripheral areas where there is a potential for transmission. Risk factor mapping at several levels of scale will possibly help to guide the spray programme.

Effectiveness of the reporting system

In-depth interviews and focus-group discussions were carried out in a VDC where the disease had been present for a long time, and questionnaires were given to VL households. These showed that most people are well aware of KA, and know that it cannot be treated by traditional medicines. Nearly all of the respondents knew to consult a medical doctor, but they were largely unaware of the transmission mechanism, or of risk factors.

Although the number of reported cases is reasonably well known, there are doubtless numerous unreported cases, whose number can only be estimated. Recent studies in Bihar have estimated that only some 25% of cases enter the government medical system, so are reported in the official statistics.[21] Many others visit traditional healers and/or private physicians. Still others probably simply die at home, for lack of funds to obtain treatment.

Not only is under-reporting a serious problem, there is no mechanism to prevent over-reporting, when patients visit more than one reporting centre.

The situation in Nepal has not been analysed, but anecdotal evidence suggests it is much the same as that in Bihar, despite the official availability of free treatment. Further, numerous patients cross the open border to India in search of treatment. In multivariable models, bed-net usage, cow or buffalo ownership, and damp floors were significantly associated with altered risk of VL. A program to increase bed-net usage could therefore decrease the incidence of VL in Nepal. [22]

Discussion

It is clear from the rising number of cases and spread of the infection through 16 districts, that the measures currently being adopted are not controlling transmission of the infection.

The current measures include passive case detection (PCD) and nominally free treatment, with focal IRS in infected areas. Our observations indicate that IRS, *as currently practised*, is valueless and that, while passive case detection can save individuals, this has not limited the spread of KA.

An important question is whether the ineffectiveness of these measures is due to inefficiency in their operation, or whether, even in theory, they could ever work. We have observed several serious shortcomings in both passive case detection with free treatment, and IRS provision, so cannot say how effective these interventions would be if they were operated perfectly.

However, we can conclude that focal IRS is inadequate to prevent transmission, due to the long sandfly season, the long incubation period, and the rapid movement of the infection between places.

We suggest that, in order to prevent transmission, all affected areas and *also peripheral areas with suitable habitats* must be sprayed. Further, the spraying activities must be much more effectively monitored. Similarly, integrated vector management (Use of impregnated bednets and eco-environmental intervention) need to be tested to assess their effectiveness to reduce the man-vector contacts, vector densities and VL incidence in endemic areas.

PCD is obviously inadequate and must be replaced with ACD. The Village Health Workers (VHWs) or Female Community Health Volunteers (FCHVs) can readily be trained to screen patients, and to refer suspects to clinics for rK39 test. If this is combined with adequate propaganda and truly free treatment, many more lives, or at least livelihoods will be saved (and a truer picture of the number of cases will emerge). The effectiveness of treatment in the control of transmission would then depend on the difference between the prepatent period (time between infection and infectiveness) and the incubation period (time between infection and symptoms), which is unknown. As long as this time is unknown, we cannot be sure that case treatment is effective in the control of transmission, even if patients under treatment were isolated from sandflies. At least, the time between onset of symptoms and treatment can be reduced to a minimum, (but not if 'fever of long duration' is used as a screening definition).

It is unfortunate that if we recommend only IRS as a control measure for VL elimination and ignore integrated vector management. Sandflies in this area are little if any nuisance, and IRS has little other benefit. ACD with free treatment might well reduce the number of cases, and would certainly save lives, so would have very positive side effects.

Guestimates of relative costs of different interventions

Alternative interventions such as comprehensive bed-net coverage, larviciding, vaccination, pheromone

traps, have been suggested but, even if they were available they would hardly be economically competitive.
Vaccination or any community intervention for rare diseases is always likely to present problems. Although a full analysis is desirable, and is a prerequisite for any elimination programme, it is possible to do a 'back-of-an-envelope' comparison between the costs of various interventions.

Let's say the crude birth rate is 4%, and the annual cost of capital is 5%. The initial cost of vaccinating 6 000 000 people, at a unit cost of **v,** can be expressed as 5% of 6 000 000**v** annually. In addition, 4% of 6 000 000**v** children would need to be vaccinated annually. The annual cost of a comprehensive vaccination programme, even if a perfect vaccine were available, would be 9% of 6 000 000**v** = 540 000**v**.

By comparison, in epidemics, a maximum incidence of 6 cases per 1 000 population is recorded: not more than 6 000 annually in the 6 000 000 population. If these were detected and treated at a unit cost of **t,** the cost of vaccination would equal that of treatment if the unit cost of treatment (**t**) were 90 (540 000 / 6 000) times that of vaccination. Vaccination would need to be remarkably cheap and effective to be economically competitive.

Comprehensive IRS coverage of affected VDCs and neighbouring ones might require 30% of all households to be treated twice annually. There are approximately 1 000 000 households in the affected districts so, at a unit cost of **s,** the cost of IRS would be 600 000**s** annually. IRS and treatment would cost the same if the unit cost of treatment were 100 (600 000 / 6 000) times greater than that of IRS.

IRS and vaccination are potentially much more expensive than treatment of individual cases.

It might be said that the additional expense of vaccination or IRS is justified as they will eradicate the infection, so can be stopped after a few years. The same could also be said case treatment, so it is by no means clear that any intervention is potentially better than another from the point of view of the elimination of the disease.

Conclusion
We see that the Government has a clear choice:

Vaccination is not available and, if it were, would not be economically viable.

In principle, IRS is the surest intervention if the goal is elimination. However, this must be comprehensive, and well monitored, at a level comparable with that of the malaria eradication campaigns. It is not certain that popular opinion would accept such intrusive intervention. Government would have to show enormous commitment for elimination by IRS to have any effect. Inadequate IRS intervention does no good, wastes money, and antagonises the people: if IRS cannot be improved to a fully effective level and attempts are not made to improve it, it should be abandoned. The possible interventions, use of impregnated bed-nets and bio-ecological interventions need to be tested to assess their effectiveness and adopt as a strategy for elimination program.

If maximum benefit in relation to cost is the goal, it may be preferable to put all possible effort into ACD with free treatment. ACD should involve the VHW or FCHVs and the rK39 dipstick test at health centre level. This will save many lives and, although the effect on incidence cannot be calculated, it is likely to be very significant. Surveillance of disease and vector and communication for behavioural impacts and operational research should be important component of elimination program. Further, the side effects, in improvement of the health service and its image, are likely to be entirely positive.

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