

Situational analysis of leprosy control in India

(envisaged as the first element of a project facilitated and financially supported by the Novartis Foundation for Sustainable Development, in order to trigger a new global effort of research to fine-tune leprosy control particularly with regard to an early detection of new cases)

Preliminary draft for feedback

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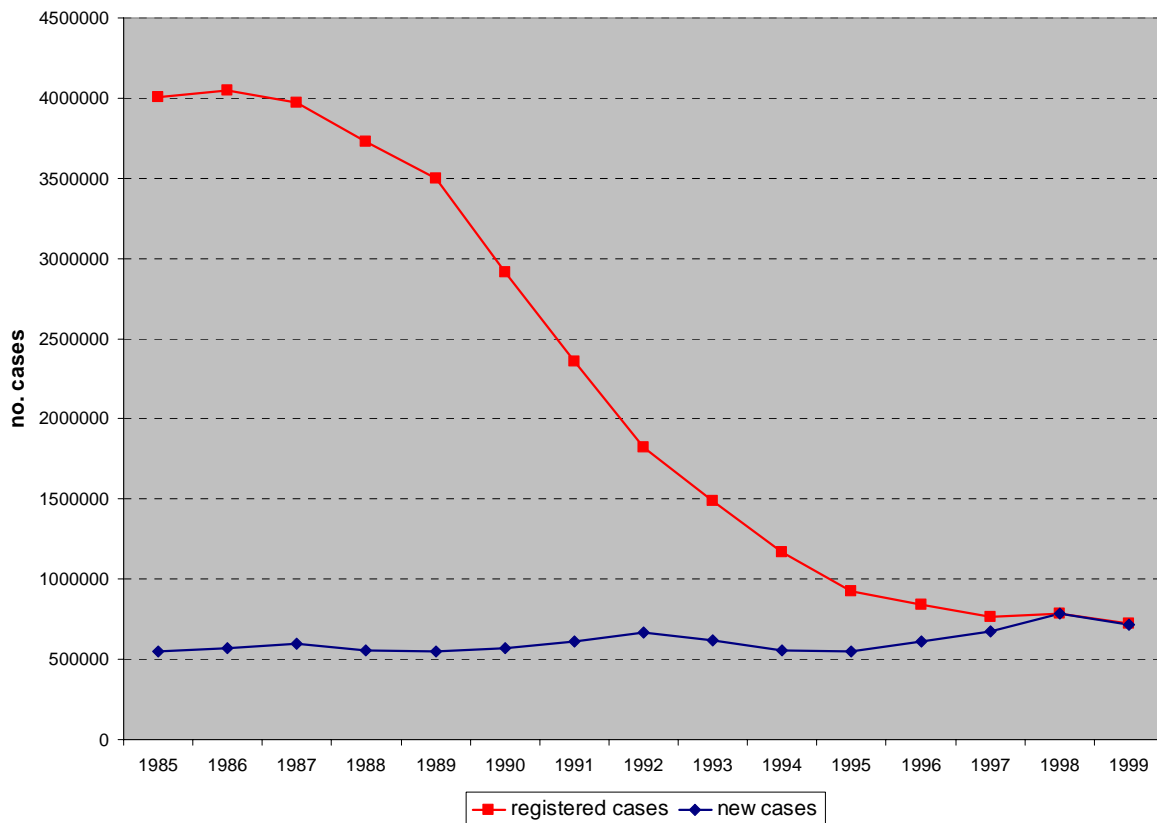
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1. Introduction

1.1. Leprosy case detection rates

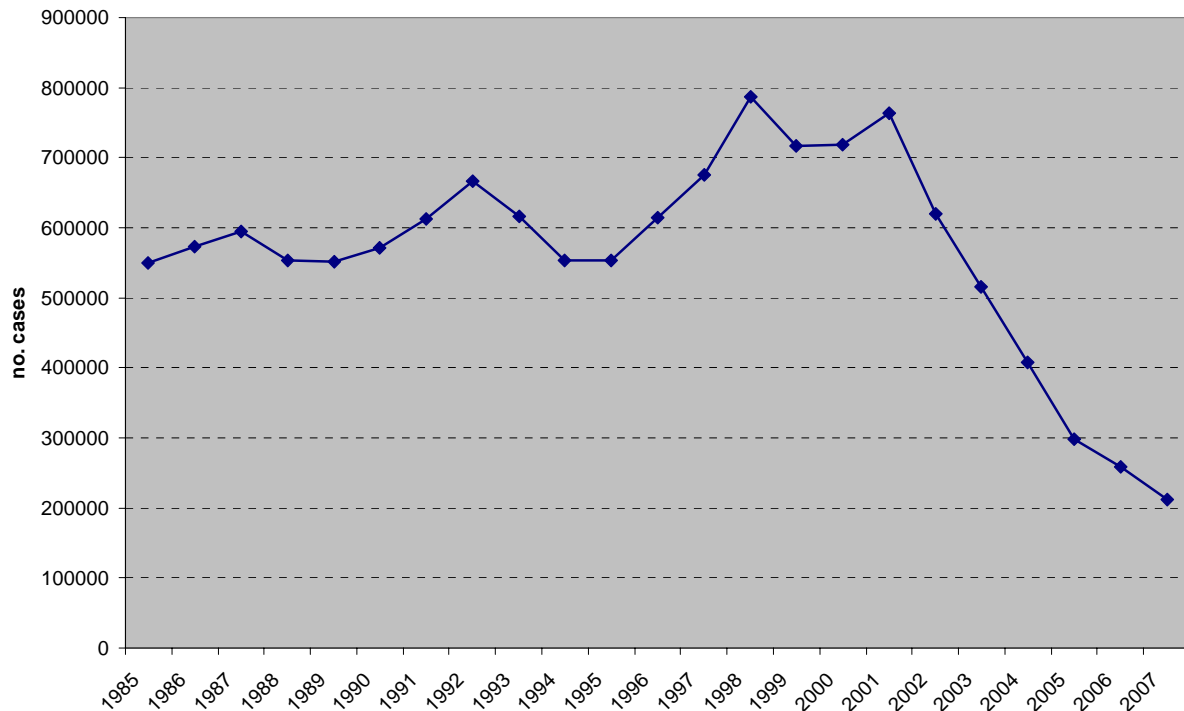
Since the introduction of Multi Drug Therapy (MDT) for leprosy in the 1980s the number of registered patients has dropped dramatically from around 4,000,000 in 1985 to around 700,000 in 1999. This was mainly due to cleaning of registers and the fact that with MDT patients are considered cured, and thus removed from the register, after they have completed their treatment. During this period the number of newly detected leprosy patients, however, has remained more or less stable at around 5-700,000 new patients per year. See Figure 1.

Figure 1: Global situation of leprosy: annual number of registered and new leprosy cases 1985-1999.



Since 2001 the number of new cases detected each year has seen a steady decline (see Figure 2). This steady decline is for the largest part due to the decline of the number of cases in India, the country where traditionally more than 60% of all leprosy patients world-wide were detected.

Figure 2: Global situation of leprosy: annual number of new leprosy cases 1985-2007 (data 2000-2007 from Weekly Epidemiological Records).



The possible interpretation of this decline was summarized by Fischer and Richardus in 2007 in a contribution to the Leprosy Mailing List (LML) (<http://www.aifo.it/english/resources/online/lml-archives/2007/260107.htm>), later also published in a modified form by Richardus and Habbema (Lepr Rev. 2007; 78: 330-337):

“We would like to reply to the messages put in the LML [...] regarding the reduction in leprosy case detection in India over the past four years. It was suggested previously in LML that such strong reduction is biologically not possible for a disease that has a 2 to 11 year gestation period. Dr. Reddy forwards the hypothesis that this is biologically not impossible and requests arguments one way or the other.

It is not helpful scientifically to approach this issue in absolute terms such as impossible. Let us consider the observation of the strong decrease in leprosy case detection and look for information and evidence that could clarify matters.

It has been documented that India experienced a drastic reduction in annual detected cases from 473,658 in 2002 to 161,457 in 2005 (Weekly Epidemiological Record 2006; 81:309-16). The annual reduction rate of leprosy case detection in this period in India was thus over 30% per year.

Meima et al. (Bull World Health Organ. 2004; 82:373-80) published a paper in 2004 in which the expected trends in incidence rates of leprosy were calculated for the period 2000-2020. In this paper, the annual reduction during this period was calculated to be between 2 and 12%, based on observed data in the period 1985-1998. In other words, if there are no drastic changes in the

epidemiological leprosy situation as observed in the period before the year 2000 (including factors such BCG vaccination coverage), the annual reduction afterwards cannot be expected to be more than 12% in the most favourable circumstances. Hence, something additional has to have happened to explain the observed 30% annual reduction of leprosy case detection in India.

Leprosy, both PB and MB, has a long and variable incubation period, with estimated averages of 3.5 and 8 years. The reduction of new case detection in India started in 2003. This would imply an intensive decrease in transmission of M.leprae that started between 1995 and 1999. It is indeed true that leprosy case detection, including active case finding, has been stepped up in this period. Finding cases early and putting them on treatment takes out sources of infection, but it is questionable whether this has such a strong impact on the ongoing transmission of M.leprae in the whole population to explain the recent annual reduction of new cases of 30%. MDT does not prevent sub-clinical cases developing disease and spreading M.leprae during their incubation period. Also, MB leprosy is hard to detect in its early stages and is often not recognized during active case finding campaigns. To our knowledge there have been no successful systematic interventions in India (or elsewhere in the world) focussing on the primary prevention of leprosy (vaccination) or on the prevention of disease in pre-clinical cases (chemoprophylaxis).

We conclude that part of the reduction in leprosy case detection in India may well be explained by a longer existing natural decline of the transmission of M.leprae in the population, possibly accelerated by the intensified control activities of the past 10 years. But it is not plausible to expect a relatively sudden annual reduction of more than 12% in the absence of any drastic nation-wide intervention with the effect of interrupting transmission of M.leprae such as vaccination or chemoprophylaxis and which would have started in the late 1990's. If such intervention existed, it would be important to know!

So while it may not be biologically impossible to achieve such drastic reduction in case detection, it is not very likely that the observed reduction is explained completely on biological or medical grounds. Other factors have probably contributed as well, including operational factors such as case finding activities and administrative factors such as registration procedures.”

All in all, it is clear that there is at the moment no consensus about the interpretation of the decline and whether this decline is due to socio-economic, biological, operational or administrative factors, or a combination of these.

1.2. Leprosy case detection rates in India – current situation

The total number of leprosy patients registered in India in the period from 1 April 2007 to 31 March 2008 was 137,684, leading to an overall detection rate of 1.17/10,000 population. The statewise New Case Detection Rate (NCDR) is given in Table 1.

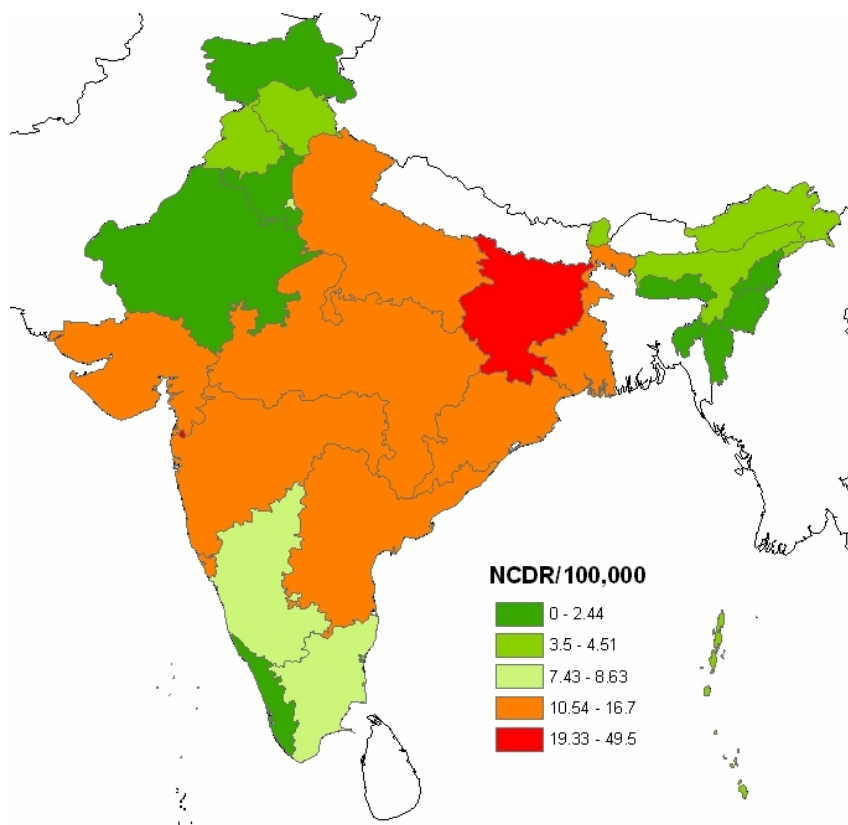
Table 1: Population, number of new cases and NCDRs for the 35 states of India (2007-8)

Group	Rank	State	Population	Cases detected	NCDR/100,000
Low	1	Lakshadweep*	67,669	0	0
	2	Meghalaya	2,763,735	14	0.51
	3	Daman&Diu	213,946	2	0.93
	4	Haryana	25,009,748	379	1.52
	5	Jammu&Kashmir	12,010,899	209	1.74
	6	Rajasthan	67,082,964	1,201	1.79
	7	Manipur	2,864,639	54	1.89
	8	Nagaland	2,792,619	54	1.93
	9	Kerala	33,899,428	778	2.30
	10	Tripura	3,531,942	85	2.41
	11	Mizoram	1,063,535	26	2.44
	12	Punjab	27,520,060	964	3.50
	13	Arunachal Pradesh	1,282,012	45	3.51
	14	Himachal Pradesh	6,800,819	246	3.62
	15	Sikkim	657,992	27	4.10
	16	Assam	30,036,654	1,268	4.22
	17	A&N Islands*	420,315	18	4.28
	18	Pondicherry	1,108,681	50	4.51
Medium	19	Delhi	17,906,774	1,331	7.43
	20	Karnataka	58,890,750	4,522	7.68
	21	Uttarakhand	9,581,049	763	7.96
	22	Tamil Nadu	66,868,808	5,511	8.24
	23	Madhya Pradesh	70,224,912	6,058	8.63
	24	Goa	1,480,349	156	10.54
	25	Maharashtra	111,443,362	12,397	11.12
	26	Andhra Pradesh	82,893,403	10,047	12.12
	27	Gujarat	58,239,804	7,228	12.41
	28	Orissa	40,682,830	5,685	13.97
High	29	West Bengal	89,899,615	13,551	15.07
	30	Uttar Pradesh	194,704,448	31,028	15.94
	31	Chandigarh	1,137,712	190	16.70
	32	Bihar	98,516,843	19,041	19.33
	33	Jharkhand	31,101,898	6,799	21.86
	34	Chhattisgarh	23,336,171	7,808	33.46
	35	D&N Haveli	303,029	150	49.50
India			1,176,339,414	137,685	11.70

* For operational and logistic reasons, the study will concentrate on mainland India, so excluding the two states covering the Lakshadweep, Anababan and Nicobar Islands.

When put on a map the situation is as follows:

Figure 3: Geographic distribution of NCDRs in India (2007-8)



The data show that the case detection rate for India as a whole is 11.7/100,000 population for 2007-2008. Twenty-three states with a total population of 442,599,950 had a registered NCDR of <10/100,000 (green in Figure 3), whereas the other 12 states with a total population of 733,739,464 the registered NCDR was >10/100,000 (orange/red in Figure 3). The states with an NCDR of >10/100,000 are concentrated in the central, most densely populated part of India.

For the purpose of this study, it will be necessary to study in-depth the trends in NCDR in the Indian states over time, if possible for the period 1998-2008. This should be done in the preparation phase of the project as described in 3.2.

1.3 Specific epidemiological characteristics of leprosy in India

Leprosy is known to be a highly clustered disease. Also in India, the leprosy new case detection rates are unequally distributed ranging from areas with high endemicity of more than 10 per 100,000 population to very low endemic areas of less than 1 per 100,000 (see Table 1 and Figure 3). These patterns often reflect historical endemicity levels, but this is not always the case.

In many of the areas, the Leprosy Control Program in India has achieved a significant reduction in leprosy prevalence through intensification of control measures such as active case-finding, implementation of Leprosy Elimination Campaigns etc. Interestingly, the decline of leprosy

prevalence rate has not been similar in all states: some states have achieved a decline of more than 70%, where in other states this decline has been less prominent. The reasons for these differences in declining levels are not clear. The performance and effect of the control program can be influenced by a number of different factors, such as patient- and health system related factors. Patient delay causing late presentation of sign and symptoms has been mentioned as one of the major determining factors, but also historical levels of endemicity and previous case-detection activities may influence current prevalence trends. In order to monitor and evaluate the progress of leprosy control in India and to forecast the future need for resources, it is necessary to obtain a better understanding of the driving and restraining forces of the decline in the leprosy case detection rates.

1.4 Leprosy prevalence studies

Actual prevalence data for leprosy, as determined by house-to-house surveys with active population screening, are largely missing, probably due to the extensive nature and high workload involved in these exercises for a relatively low prevalence disease such as leprosy.

Three recently published studies determined the actual prevalence of leprosy in relation to the registered number of cases in the area:

1. Grossi *et al.* from Brazil presented a paper at the 17th International Leprosy Congress (Hyderabad, February 2008) estimating that 28.4% of leprosy cases in Minas Gerais State were not identified by the health system between 2001 and 2005.
2. Moet *et al.* (PLoS Negl Trop Dis. 2008; 2:e198) found in a study among 20,000 people from the general population from Northwest Bangladesh that the actual prevalence (13.1/10,000) was more than 5 times higher than the registered number of patients (2.31/10,000); suspects were observed for 6 months before a definitive diagnosis was made. Five of 27 newly found patients were <15 years old (child rate 19%), indicating substantial active transmission.
3. A recent study in the Mumbai area in India showed that the actual number of leprosy patients was 3-7 fold higher than the number of cases registered by leprosy programs. A point of additional concern was that both the child leprosy rate (34%) and the number of patients with grade 2 disability (17%) were high (Shetty *et al.*, manuscript submitted).

However, it is unclear how far the data can be extrapolated to describe the leprosy situation in the countries as a whole.

1.5 Relevance of the gap between actual prevalence and NCDRs

When talking to leprosy experts, the consensus is that one will always find more leprosy patients when doing an active population survey compared to passive case detection. The question is how relevant this is from a clinical, an operational and the patient point of view:

1. The majority of patients found are single lesion paucibacillary (SLPB) patients, a group that is generally considered to be less important for transmission.
2. Part of the patients detected will be self-healing. One report from Africa by Brown (Lepr Rev. 1974; 45:104-111) indicated that this can be as high as one third of all leprosy patients. There is anecdotal evidence of one situation, where people identified with potential leprosy during an active case finding exercise were accidentally not followed up and put on treatment. When they were re-examined it was found that in 70% of the cases people had self-healed.

3. A substantial number of people will be diagnosed with “suspected leprosy”. In routine leprosy control these people are actively followed-up for a period of 3-12 months before the definitive diagnosis is made; during prevalence studies these people are often immediately diagnosed as “leprosy patients”, leading to over-diagnosis.
4. From an operational point of view one has to decide when the size of the gap between the number of patients in the community and NCDRs is such that it has an impact on health care provision, be it drug supplies, case seeking methods or staffing of leprosy-related services.
5. From a patient perspective, one has to realize that a longer detection delay increases the number and severity of impairments and handicaps, both in PB (low risk) and in MB (high risk) patients. Determining the disability rates in both patients on treatment and in undiagnosed patients will provide an opportunity to determine not only the extent, but also the gravity of the leprosy problem in the community and will provide leprosy programs with valuable information for an informed decision on the need for (additional) interventions.

From this, one may conclude that prevalence studies are probably only of limited value to answer the question what the true extent of the leprosy problem is in a community. However, they are a source of (diagnosed and undiagnosed) leprosy patients which can be included in in-depth studies to determine patient- and health system-related factors influencing the leprosy problem and to identify vulnerable groups that should receive focused attention.

In the past, a lot of emphasis has been put on over-diagnosis of leprosy, which is relatively easy to establish using re-examination of diagnosed patients by an expert leprosy medical doctor. The current study proposal will focus on under-detection, which is more difficult to ascertain as it involves both patient and health system factors.

2. Research questions

2.1. General Objective

To develop measurements for monitoring and evaluation of the progress of the leprosy control programme in India to improve further effectiveness of the leprosy control program and to forecast future treatment needs.

The ultimate aim is to develop easily applicable, standardized and validated methods that can be used globally and over time.

2.2. Research questions

1. What are the driving and restraining forces of the decline in leprosy?
2. What factors influence reported case detection rates of the leprosy control programs?
3. What measurements can be used to monitor or and evaluate leprosy control programs?
4. What measurements can be used to estimate future demand of treatment?

2.3. Specific questions

Analysis of existing data will give an answer the following questions:

1. What is the trend of CDR of leprosy in Indian states over the last 10 years?
2. Which areas can be classified as high, low and middle endemic?
3. Which areas within these strata of endemicity can be identified as areas where leprosy prevalence has declined more or less than average?

Additional research is needed to answer the following questions:

4. Which factors can explain the difference in rates of decline in leprosy prevalence in different areas and strata of endemicity?
5. Does the association of reported CDR and the extent of leprosy problem in the community differ in these areas in different endemicity strata?
6. Is there a relationship between detection delay and/or trends in CDR with the leprosy problem in the community?
7. Which indicators can reflect best the prevalence of leprosy in the community as to monitor effectiveness of the leprosy control programme?
8. How can leprosy prevalence best be estimated to assess future demand of treatment?

2.4. Other possible research

A prevalence study such as the one described here offers numerous opportunities for additional research. Some potential side studies are:

1. GIS study

With Geographic Information Systems (GIS) it is possible to look at clustering of leprosy cases within the sites and to study whether for example (a larger) distance to the nearest health post plays a role in the proportion of undetected leprosy cases. For this it is necessary to geo-reference all patients (and preferably all non-patients as well, but this can be done in a selection of the clusters) with a hand-held GPS device, obtain digitized maps of the area and use GIS-software such as ArcView or HealthMapper for data analysis. This approach can give answers either alone or in combination with a transmission study (see below).

It was mentioned that DANIDA (Danish International Development Agency) has already set up a nationwide HIS system for new leprosy patients, but this needs to be verified.

2. Biomarkers study

Biomarkers may be a valuable contribution to an assessment tool. There are efforts under way to develop an early diagnostic assay for infection and/or early disease, but it is currently premature to apply these. Even though the detection of specific antibodies to *M.leprae* (“serology”) in leprosy patients does not provide a diagnostic test, it gives an indication of the total bacterial load in the body. As one would expect this to rise with increased diagnostic delay, serology may be a proxy parameter for diagnostic delay.

3. *Transmission study*

The last few years new molecular tools have been developed for the strain differentiation of *Mycobacterium leprae*. With this technique, it would be possible to study transmission patterns, leading to a better insight into the spread of leprosy. For this study it would be necessary to collect, store and test slit skin smears from newly found patients and determine the in-depth patients' contact patterns.

3. Implementation plan

The whole study can be divided into 6 steps:

1. Seeking permission to perform the study
2. Study design
3. Preparations for study implementation
4. The actual implementation of the study
5. Data analysis
6. Results dissemination

These steps do not necessarily have to be carried out after each other:

- Step 1 and 2 can be performed at the same time and some information from step 2 (for example the detailed protocol) will probably be necessary for getting ethical permission (step 1).
- Step 2 and 3 can partially overlap once ethical clearance (either definitive or provisional) has been obtained.
- Step 5 can already start when step 4 is still under way. However, some of the major conclusions can only be drawn once all the data are available.

3.1. *Step 1: Seeking permission*

This step has two important activities:

3.1.1. *Informing stakeholders at an (inter)national level.*

National level: Indian government, Indian Council of Medical Research (see below).
International level: WHO, ILEP

In India the provision of health care facilities is the responsibility of the State rather than the country, which means that one may have to go through an additional round of stakeholder information once the States where the study will be conducted have been identified.

3.1.2. *Obtaining ethical clearance*

Ethical clearance should be obtained from the Indian Council of Medical Research (<http://icmr.nic.in/>), which asks for a detailed protocol and budget. To facilitate this process, contact can be made at an early stage, possibly as part of informing the stakeholders at the national level.

In most western countries it is also necessary to get ethical clearance from the local Medical Ethical Committee. If Novartis is officially conducting the study, it will be necessary to ascertain whether ethical clearance in Switzerland is required as well.

3.2. Step 2: Study design

The overall aim of this step is to develop a detailed study protocol. The points raised below are a first step to this.

3.2.1. Overall study design

The most appropriate study design is a cluster survey analogous to a Rapid Village Survey (RVS) with a few modifications:

- a. In the current study we will actively screen the whole population for leprosy instead of voluntary reporting of signs and symptoms indicative of leprosy to get a full representation of all leprosy patients, which is mandatory for the determination of vulnerable groups as well as the interviews.
- b. Both the previously undiagnosed leprosy patients and leprosy patients currently on treatment will be included as this covers the definition “prevalence”.

It is generally assumed that a suitable number of clusters is at least 30. These clusters can be selected in a staged sampling procedure.

3.2.2. Selection of study areas

As the study focuses on specific questions regarding the association between trends in the reported New Case Detection Rates and the extent of leprosy problem in the community, it will apply a purposeful sampling scheme.

The sampling unit will consist of an administrative area of about one million persons with specific characteristics of endemicity and decline in leprosy over the last 10 years. For operational and logistic reasons, the study will concentrate on mainland India, so excluding the two states covering the Lakshadweep, Anababan and Nicobar Islands.

Table 2: Characteristics of study sites

Endemicity	Declining Rates last 10 years		
	<i>z-score</i> < -2.0	<i>z-score</i> -1 to +1	<i>z-score</i> > 2
<i>z-score</i> < -2.0	Site 1	Site 2	Site 3
<i>z-score</i> -1 to +1	Site 4	Site 5	Site 6
<i>z-score</i> > 2	Site 7	Site 8	Site 9

The z-score calculates the level of extremeness: a z-score < -2.0 means extremely low, -1 to +1 average and > 2 extremely high. The exact thresholds will need to be determined from further analysis of available NCDR data for the period 1998-2008.

3.2.3. Sample size calculations

In each of the nine study sites a cluster sampling scheme will be used, to calculate area specific point community prevalence within 95% confidence intervals. This will provide a study population of leprosy patients (both currently on treatment and undiagnosed cases) to answer the questions posed in chapter 2.

3.2.3.1 Determining the difference between NCDR and community prevalence

Assumptions:

One-sided 95%

Alpha: 1.64

Power: 80% = beta = 0.842

If one has an NCDR of 10 per 100,000 and one wants to show that the prevalence in the community is >3 times the NCDR, one needs a sample size of 60,503, the community prevalence is then 30/100,000 and one may expect 18 patients (Table 3).

All this is not corrected for design effect, which may differ for different situations. From an operational point of view a cluster will probably be no more than 3,000 persons, see 3.2.4. Where large numbers of people need to be examined one needs multiple clusters which means that the design effect is lower than in areas where only one or a few clusters will need to be examined.

Leprosy is a clustered disease, but the leprosy clusters are generally quite small (Bakker *et al.* Int J Epidemiol. 2004; 33:1329-1336), at least much smaller than the size of the clusters mentioned for this study. This means that the design effect is probably close to 1, but this needs to be calculated from previously collected data (Moet *et al.* PLoS Negl Trop Dis. 2008; 2:e198; Bakker *et al.* Int J Epidemiol. 2004; 33:1329-1336).

Table 3: Sample size calculations

NCDR	Patients per 100,000	Samples size per factor considered to be not acceptable (Community prevalence is factor 1.5 - 5 x higher than NCDR)				
		5	4	3	2	1.5
0.0005	50	4,612	6,715	12,090	36,281	120,955
0.0001	10	23,093	33,611	60,503	181,520	605,083
0.00007	7	32,994	48,019	86,438	259,326	864,438
0.00003	3	76,996	112,057	201,707	605,132	2,017,123
0.00001	1	231,004	336,191	605,147	1,815,452	6,051,523
NCDR	Patients per 100,000	Number of expected patients per factor (Community prevalence is 1.5 - 5 x higher than NCDR)				
		5	4	3	2	1.5
0.0005	50	250	200	150	100	75
0.0001	10	50	40	30	20	15
0.00007	7	35	28	21	14	11
0.00003	3	15	12	9	6	5
0.00001	1	5	4	3	2	2
Expected cases		12	13	18	36	91
		12	13	18	36	91
		12	13	18	36	91
		12	13	18	36	91

The numbers in Table 3 need to be further verified by an epidemiologist or bio-statistician. It will also be necessary to correct for the discrepancy between point prevalence as measured by a population survey compared to an NCDR, which is a proxy for yearly prevalence. However, the numbers needed will be similar to the numbers mentioned in the table.

The size of the study population as well as the number of patients available for interviewing depend heavily on the difference between the NCDR and the actual leprosy burden that one wants to detect. This is a fundamental decision (see above), but also at least partially depends on the available budget.

3.2.4. Cluster size calculation

The number of clusters should be at least 30, but can be higher as the size of a cluster should be manageable from an operational point of view. One team of two persons can check, under favourable conditions, around 100 persons per day. Assuming that circumstances will not always be optimal, that the teams need time to travel to/from the study area and that there are 10 teams in one regional team, the cluster size should be around 10 teams x 4 days x 75 persons/day = 3000 persons.

3.2.5. Partner selection

A strong Indian collaborating institute with scientific staff experienced in leprosy research will be crucial as they know the situation in India, have their network and can help to identify potential problems at an early stage. This institute should also take up the day-to-day overall management of the study as well as the quality control.

Once the areas where the study will be carried out have been selected, it is necessary to select suitable partners for performing the field survey. Partners can be from larger NGOs or institutions, but the staff involved should preferably come from the area (state or district) where the study is performed, as they know the local situation and speak the local language(s). The partner should be experienced in leprosy and preferably have some experience with research.

3.2.6. Protocol development

Based on all of the above, a detailed protocol document will need to be developed, which will also be the basis for the ethical clearance application. Further literature review is needed for the study protocol to identify and analyse previous studies and already available methodologies.

Chapters for this detailed study protocol should include:

1. Protocol summary
2. Background information and scientific rationale, including potential risks and benefits
3. Objectives
4. Study design
5. Study population, including selection and inclusion/exclusion criteria
6. Study procedures, including:
 - a. for all study subjects: field survey and demographic data to be collected
 - b. for patients and suspects: clinical examinations, laboratory examinations, history of leprosy and questionnaires
 - c. quality control mechanisms
7. Data handling and record keeping, including data collection
8. Statistical considerations, including data analysis plan

9. Subject confidentiality
10. Protection of human subjects (informed consent)
11. Literature references

Plus any information (such as partners, time tables and budgets) required by the Ethical Committee or other relevant bodies.

3.2.7. Additional activities

These should include:

1. Informing regional and local authorities
2. Design of informed consent forms, data forms, questionnaires and database(s): consent forms and questionnaires should be designed in English, translated into the local languages and translated back to English to check for accuracy.
3. Development of detailed data analysis plan
4. Design of quality control mechanisms for the field survey, the laboratory and clinical examinations and the data collection and entry
5. Design of training materials

3.3. Step 3: Preparation of study implementation

During this phase all staff involved in the study follows a standardized training program to ensure that everybody has the same information. Staff will include the management, clinicians, health workers, data clerks, laboratory personnel, physio technicians, study nurses and interviewers. It should be possible to use a Training of Trainers approach for this.

After this, the procedures and materials will be pilot tested on a limited scale to check for any shortcomings in the protocols or forms. These shortcomings will be amended at this stage.

3.4. Step 4: Study implementation

During this phase the teams will actually go into the field, to perform a situational analysis, screen the total population for leprosy and interview the confirmed patients according to procedures described the protocol. The stages of the study will be roughly as follows;

1. Situational analysis of the health system (see 3.4.1)
2. Population census:
This can be done as the survey proceeds. One should aim at a coverage of at least 80% of the population
3. Informed consent
4. Collect basic data
5. Full body check for leprosy:
 - Currently on treatment: confirmation by doctor (including pictures) and interview
 - Yes: confirmation by doctor (including pictures), collection of clinical and laboratory data, interview, referral for treatment (see 3.4.2).
 - Suspect: assessment by doctor (if leprosy go to “yes”), if necessary return after 3-6 months
 - No
6. Interviews with patients (see 3.4.3)
7. Quality control of data, clinical results and laboratory test outcomes. It should be discussed whether it is operationally feasible to perform quality control of the full body check in non-

leprosy study subjects. Also, one needs to determine whether it is culturally acceptable, as re-checking may lower the credibility of the health workers to the population.

If the inclusion rate is high (>80%) it will not be necessary to check the patient records of the public and private sector as all study subjects will be asked whether they are currently on leprosy treatment.

3.4.1. *Situational analysis of the health system in the area*

Apart from the formal public health system, there is probably also extensive private, traditional and alternative health care provision in the areas. It will be important to map the total health system and the type of contribution (referral, diagnosis, treatment) as well as the extent and quality of leprosy care provided by each of these groups. A situational analysis of the capacity of the health system in the various sites to provide leprosy care will need to be carried out. This can be done by site visits and interviews aiming at identifying driving and restraining forces for quality leprosy control. This would include a description of the facilities (both public and private) with respect to trained leprosy staff, MDT and prednisolon (for reactions) stocks, provision of health education, reporting, data quality etc.

3.4.2. *Patient characteristics*

Data will be analyzed as described in the detailed data analysis plan that will be prepared in step 2 (see 3.2.7). The data will give information on factors that are considered to be indicators for leprosy prevalence and transmission as well as control programme performance. These include child rates, disability rates, MB/PB ratios, general age distributions, registered/unregistered patient ratios, public/private sector treatment ratios, male/female ratios, etc.

These data can give more in-depth information on leprosy diagnosis and treatment and identify groups that are especially vulnerable to have undetected leprosy. If opportune, these groups could then be singled out for targeted interventions in future.

3.4.3. *Interviews with patients*

Once patients are identified (both those on treatment and undiagnosed), the most important stage of the study starts: the identification of patient- and health-system related delays and barriers for the diagnosis and treatment of by (semi-) structured interviews. Nicholls *et al.* (Lepr Rev. 2005; 76:35-47) performed a similar study in West Bengal which could provide the basis for the questionnaires used here. Important questions to answer are:

- *What is the leprosy care seeking behaviour of leprosy patients?*
If patients have not sought health care: why not?
If patients have sought health care: which route(s) did they follow through the informal, public and private systems? What was the delay between first signs/symptoms and the start of care seeking? Did they receive diagnosis and treatment? And if yes: how long did it take them from the start of care seeking? Is the treatment they receive adequate (official MDT regimen, MB/PB)?
- *What are the patient-related delay and barriers to seeking diagnosis and treatment of leprosy?*
How long is the patient delay and which factors in the patient's knowledge, attitude and

social-economic situation impede or expedite seeking timely diagnosis and treatment?

- *What are the health system-related barriers as perceived by the patients to getting timely diagnosis and treatment of leprosy?*
Are there factors that make the health system better or less accessible or adequate in dealing with leprosy as perceived by the patient?

3.5. Step 5: Data analysis

Data will be analyzed according the data analysis plan described in the detailed study protocol (see 3.2.7).

3.6. Step 6: Dissemination of results

Dissemination of results can take several forms:

- Workshop(s)
- Policy document(s)
- Scientific publications and presentations

This needs to be decided at a later stage. It will also be important to involve the (inter)national, national, regional and local stakeholders in this.

4. Logistics and management

A prevalence study of this size requires meticulous preparation and planning. Detailed planning will need to wait until the detailed protocol has been developed, but a number of issues can already be set in motion once the study areas and the collaborating center in India have been selected:

- Study oversight and management procedures
- Arrangement of quality control procedures
- Staffing
- Arrangement of transportation
- Setting up of data entry and storage facilities (local or centralized?)
- Arrangement of laboratory facilities for smear, histopathology and quality control

4.1. Staffing

There will be several layers of staff:

4.1.1. Scientific committee

The Scientific committee will consist of scientists from India and abroad and will be involved in the study design and analysis, will from a distance guide the central team, the regional teams and critically assess the activities.

4.1.2. Central team

The central team should consist of at least:

- a principal investigator with leprosy research experience
- a medical doctor of a leprosy reference center

- a medical anthropologist or sociologist
- a laboratory supervisor of a leprosy reference center
- an epidemiologist / biostatistician
- a data manager.

Some of these functions could be combined in one person.

This team will be responsible for the overall day-to-day management and performance of the study, the quality of the data and the quality control activities and will actively take part in both the study preparation and the data analysis.

4.1.3. Regional teams

The regional team performs the actual field surveys. As this involves nine study sites, probably in different parts of the country, it will be necessary to set up multiple regional teams consisting of staff from the local partners, possible with the addition of some temporary staff.

The regional team with study-specific training as described in 3.3 will consist of:

- A number of survey teams. Each survey team should consist of a male and a female health worker with leprosy experience. One regional team can check one cluster of 3000 persons per week (see 3.2.4). Once the sites have been identified and the number of study subjects has been calculated, a forecast of manpower needed can be made.
- A medical doctor with leprosy experience
- A laboratory technician with experience in reading Ziehl Neelsen-stained slit skin smears (histopathology for all samples and possibly other (biomarker) tests will be performed at a central level)
- Possibly a physiotherapist to perform the nerve and muscle function tests
- One or more data entry clerks
- One or more interviewers with relevant experience.
- Auxiliary staff such as drivers, cooks, messenger boys etc.

This team is responsible for the performing the actual field surveys according to the and the timely transfer of data to the central level

4.1.4. Additional personnel

- At the central level an experienced histopathologist is needed to read all the slides from patients and suspects.
- One or more study nurses could be trained to perform the overseeing activities involved in quality control. These could be stationed at a central place and travel from team to team to perform the quality control activities.
- For data analysis the experience of specialized epidemiologists, statisticians and social scientists, either from India or from abroad will need to be sought.

4.2. Equipment and consumables

It may be necessary to buy, hire or lease the following items:

- Computers for the regional and central level and possibly a server.
- Stationary and forms (these could be replaced by PDAs).
- Cars for transportation of the regional teams.

- Laboratory equipment and consumables for the regional and central level for collection, staining and reading of smears and biopsies.
- Digital cameras for leprosy confirmation.
- Means of communication (mobile phones, modems).
- ...and probably a lot of other items one cannot even envisage at the moment.

5. Time frame

It is difficult to determine exactly how long this study will take. However, some indications can be given, see Annex 1.

6. Budget

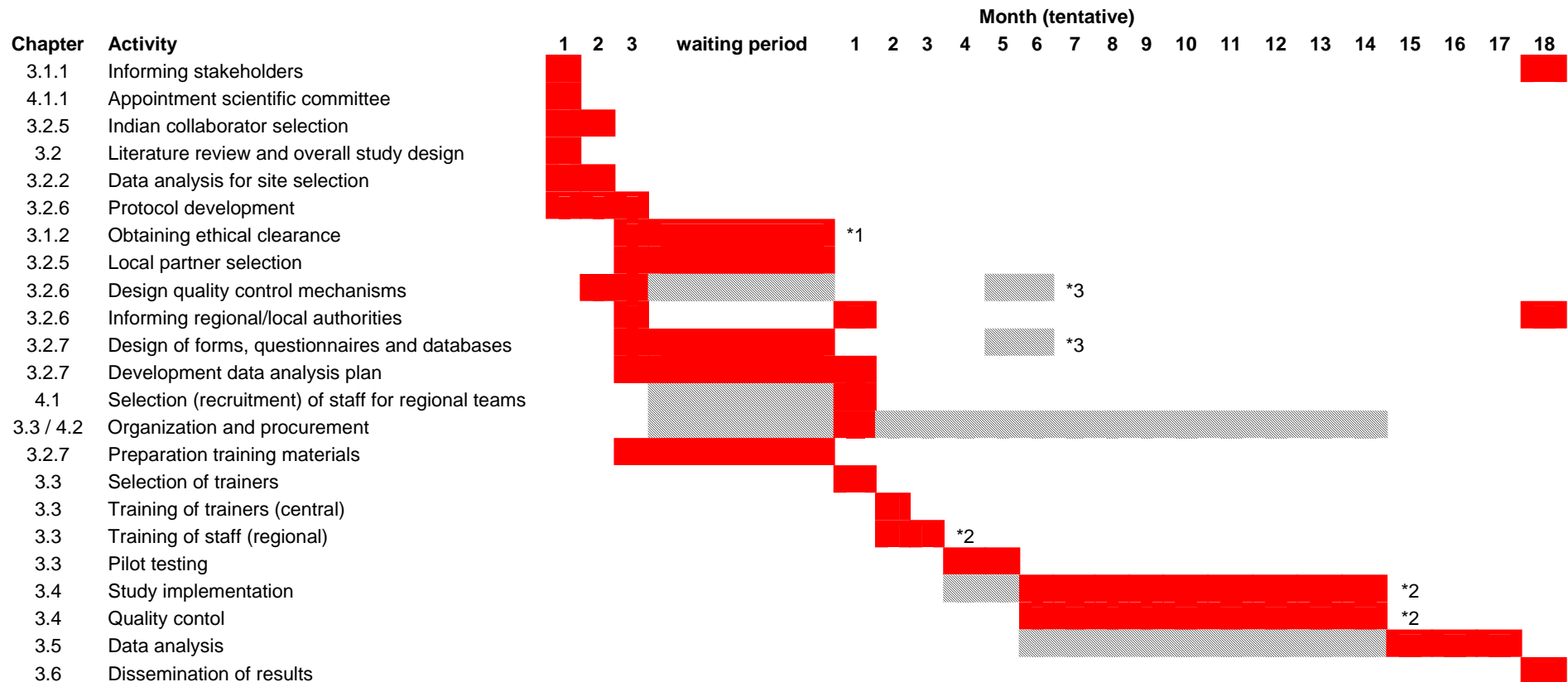
To be calculated during the writing of the detailed study protocol.

7. Acknowledgments

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Annex 1: Tentative time schedule



*1 waiting period depends on ethical clearance procedure

*2 will depend on number of clusters and staff needed

*3 protocol, forms, quality control mechanisms, questionnaires and databases will be amended based on outcomes pilot study