
Chagas disease

Leprosy

Lymphatic filariasis

Onchocerciasis

Prospects for elimination

TDR



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PROSPECTS FOR THE ELIMINATION OF SOME TDR DISEASES

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Introduction:

Elimination or Eradication?

For the purpose of the present report, **eradication** of a disease is the reduction of worldwide incidence to zero as a result of deliberate efforts, obviating the necessity for further control measures. Similarly, **elimination** of a disease is the reduction of the morbidity to a level that does not constitute a major public health problem, but still requires a basic level of control and surveillance. This threshold varies from disease to disease and it is measured as a prevalence rate. For example, since many of the diseases have a zoonotic component they cannot be eradicated but can be controlled if they are reduced to a low target level.

Disease Elimination and Research Needs

1. There remains an unfinished TDR research agenda for each of the four diseases that can be eliminated - Chagas disease, onchocerciasis, leprosy and lymphatic filariasis - which should be continued either until elimination is achieved or until the research brings even better tools to bear on the problem, e.g. a macrofilaricide. One target is to show how to combine common interventions effectively for different diseases, e.g. bednets for malaria and filariasis, ivermectin for filariasis and onchocerciasis, and spraying for local control of the vectors of several diseases. Another is to develop more specific and sensitive tools for surveillance and evaluation of impact.
2. It will be essential to invest for a period of 8-10 years to reduce each of the four diseases - Chagas disease, leprosy, onchocerciasis and lymphatic filariasis - to a level which assures that they are unlikely to re-emerge and will no longer be major public health problems. In certain focal areas, the effort at eradication may be worth undertaking, as in the case of leprosy or onchocerciasis. The failure to make that investment will lead to real risk that elimination will not be achieved and that prior investments in research and control may be wasted.
3. The defined time to elimination as a public health problem represents a special case intervention, since the cost of eliminating the last cases of any disease is never cost-effective in itself. The framework for the economic analysis should be the savings, not in one year, but over the remaining century or more that the diseases are no longer major public health problems. Here the issue of discounting should be reconsidered, because recurrent costs are permanently eliminated or reduced.
4. The efforts directed towards elimination of TDR diseases have certain features in common, e.g. the need for tests of high specificity for surveillance, and the likelihood of the diseases remaining for long periods in remote areas and areas of conflict or declining social cohesion. There is thus good scope for cross fertilization and economization between the elimination efforts for different diseases.

5. Elimination as a public health problem will also require an increase in operational research to solve problems in the field and improve surveillance, which is essential to avoid risks of re-emergence and to assure the aims of the programmes have been achieved for a finite period. Monitoring is required as much for "disappearing diseases" as for newly emergent diseases, and sentinel sites and continuing support for the activity and flexible responses to hot spots will be required.

6. Global travel and immigration will remain continuing threats to the elimination of these diseases, and special efforts to maintain surveillance must be made.

7. While elimination implies some level of national vertical planning, to be effective, these programmes must be integrated at the district and community level. For some, treatments are sufficiently simplified and safe that they can be carried out at the community level by the community itself, e.g., onchocerciasis.

8. There are costs to a health service in terms of dislocation and disruption and diversion of personnel to elimination programmes. These should be anticipated, and planned and compensated for, from the beginning of a programme. Resources should be set aside and incorporated into elimination programmes, and used to assure that other important health and control functions are not compromised by elimination programmes. Expertise that would be difficult to redevelop in the case of future needs should also be maintained at a certain level.

9. Furthermore, there must be a plan for devolution of the disease programmes and services as the diseases are eliminated, and alternative training for scientists and health workers involved must be planned for from the beginning.

10. The development and maintenance of geographic information systems will be important for elimination activities.

11. Education and communication training and packages will be essential for assuring effective programmes at the community level.

12. Experience to date indicates the importance of modelling as a scientific and control tool; improved models can facilitate evaluation and monitoring of disease elimination both locally and globally.

13. TDR has anticipated the transition of leprosy, onchocerciasis, lymphatic filariasis and Chagas disease from major research problems to a level of research required to assure disease elimination, and they represent now less than 22% of the TDR budget.

14. At the same time, elimination of leprosy, onchocerciasis, lymphatic filariasis and Chagas disease as public health problems will require an investment of new, specially planned research funds for a finite period of time. The investment in disease elimination must be for a defined period, but one sufficient in time and magnitude to assure disease elimination, prevent recrudescence and maintain surveillance.

LEPROSY

1. The disease

Leprosy is a chronic communicable disease caused by the bacillus *Mycobacterium leprae*, which is closely related to the *M. tuberculosis* bacillus that causes tuberculosis. Both diseases are believed to be transmitted through bacteria-laden droplets from the nose and throat, and have been treated with the same or related drugs. In both cases, treatment has been lengthy; compliance has been a problem; and the development of drug resistance has threatened control. However, the two organisms have very different targets - leprosy affecting mostly the skin and peripheral nerves, and tuberculosis mostly the lungs. And whereas strains of *M. tuberculosis* have developed multi-resistance to most known drugs, mercifully leprosy is being very effectively controlled with a two- or three-drug combination.

Leprosy presents a great variety of forms depending on the individual immune response to the infection and its duration. Most infections appear to remain symptomless. At one end of the disease spectrum is *lepromatous* leprosy, in which cell-mediated immunity to leprosy is absent (though present in infections with other agents) and where *M. leprae* bacilli multiply uncontrolled, leading eventually to damage to mucous membranes, the eyes and peripheral nerves, and ultimately to deformity. At the other end of the spectrum is *tuberculoid* leprosy, in which the immune system has control of the infection, few bacteria can be found, and the symptoms are mild, often taking the form of desensitized, pale and sharply defined skin patches. *Tuberculoid* leprosy is usually self-limiting, but can sometimes lead to peripheral nerve damage. *Lepromatous* cases are thought to be the main source of transmission of the disease.

In control programmes, for choice of drug regimen, cases are generally divided into two groups: *paucibacillary* cases, which broadly coincide with cases of tuberculoid leprosy; and *multibacillary* cases, which broadly coincide with cases of lepromatous leprosy. But much finer divisions and distinctions are also possible.

2. Disease situation and trends

The prevalence of this disease has been reduced from 5.4 million in 1985 to 940 000 in 1996 and the number of patients cured with multidrug therapy (MDT) was more than 8 million at the end of 1995 (Table 1 and Figure 1).

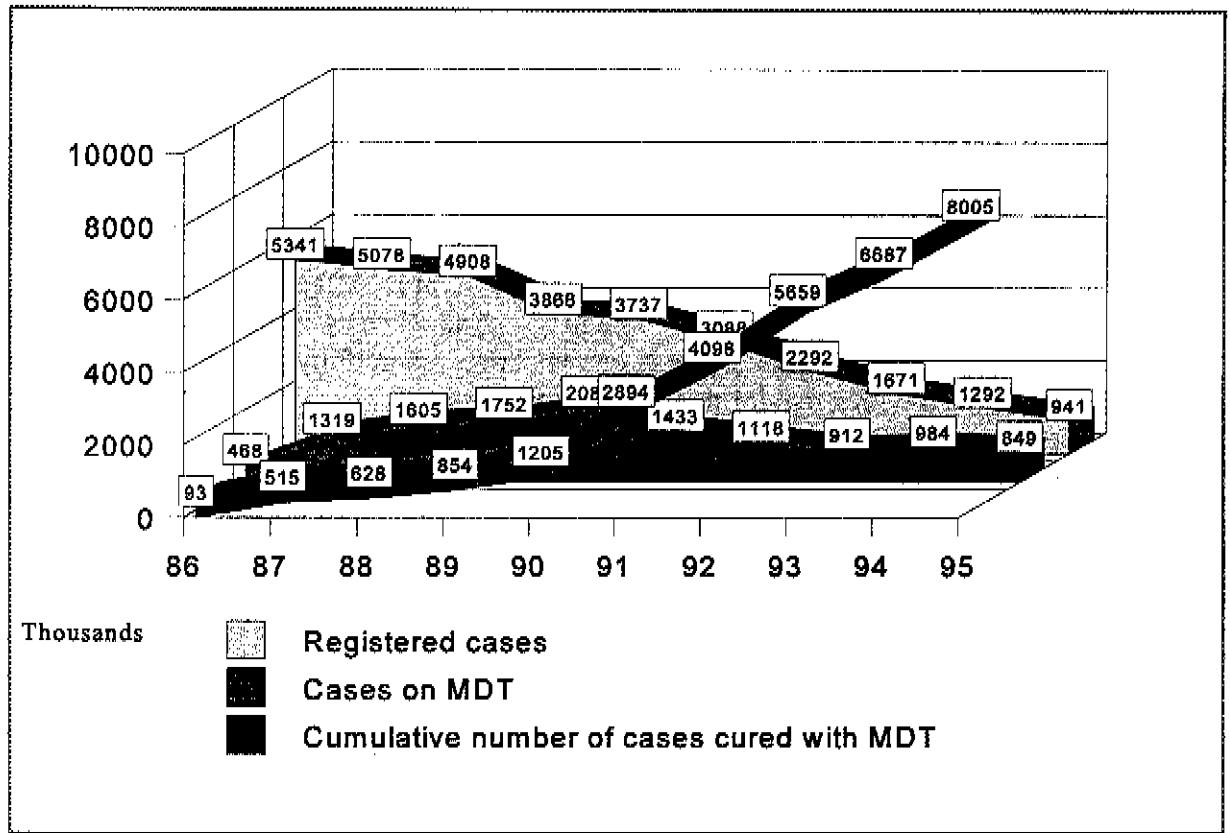


Figure 1

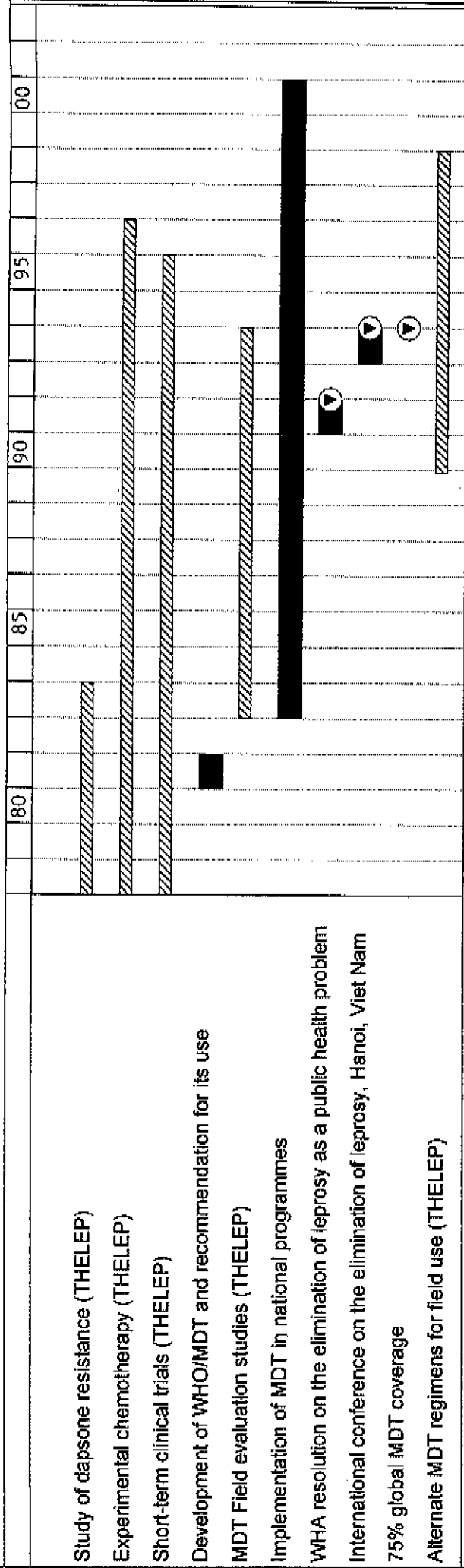
Table 1
Leprosy prevalence and MDT coverage
by WHO Region, 1996 (*)

WHO Region	Registered cases	Prevalence per 10 000	Cases on MDT	MDT coverage (%)	Cured with MDT Cumulative Total
Africa	92 517	1.70	85 942	92.9	450 877
Americas	163 277	2.15	123 366	75.6	225 450
South-East Asia	635 490	4.61	595 301	93.7	7 059 926
Eastern Mediterranean	18 188	0.43	16 738	92.0	55 919
Western Pacific	31 043	0.19	27 874	89.8	213 019
TOTAL	940 515	1.69	849 221	90.3	8 005 271

(*) excluding the European Region

Figure 2:

Towards the elimination of Leprosy: The Timetable



3. Strategy for elimination

It won't be long before the question of whether to work actively towards a leprosy eradication strategy will arise, but the tools currently available and the existing knowledge on the subject do not permit such a strategy. If eradication is to be seriously considered, the first step would be to embark on research to develop laboratory tools that can identify "at risk" groups as well as intervention tools to carry out the task.

What would be the cost-effectiveness of this research, particularly in relation to the gains to be made by completely stopping the occurrence of leprosy? If the costs of such an eradication strategy prove to be very high, investment in the research could turn out to be questionable.

On the other hand, beyond the year 2000, even with the success of the elimination strategy, there may be a felt need, at least in some parts of the world, to totally eradicate leprosy within a short period of time. This would require a strategy based on: (a) epidemiological surveillance of the small numbers of cases that may continue to occur, and, more importantly, on surveillance of subclinical infection in the population; and (b) effective interventions to abort subclinical infections apart from curing the occasional disease. The most important consideration in this strategy is cost-effectiveness, which requires that technologies for identifying subclinical infection (laboratory tests) and interventions (e.g. vaccines) be simple, affordable and acceptable to the community. As with the current elimination strategy of identifying and treating clinical leprosy, identification of and interventions for subclinical infection will be quite a challenging task for difficult-to-access areas and populations. Thus the need to invest in leprosy research even beyond the year 2000 is quite obvious.

4. The timetable towards elimination

The main landmarks are indicated in Figure 2 (control activities shown as solid bars, research activities as hatched bars) and can be summarized as follows:

1978-1984:	Study of Dapsone resistance
1978-1996:	Experimental Chemotherapy (e.g. Minocycline, Ofloxacin)
1978-1996:	Short-term clinical trials
1981-1982:	Development of MDT and recommendation for its use
1982-1994:	MDT field evaluation studies
1982-2000 and beyond:	Implementation of MDT in national programmes
1991:	WHA Resolution on the elimination of leprosy as a public health problem
1994:	International Conference on the elimination of leprosy Hanoi, Viet Nam
1995:	Achievement of 75% Global MDT coverage
1998:	Alternate MDT regimens for field use

5. Future Research Needs

Diagnostic tools to identify subclinical infection:

- to monitor transmission,

Vaccine development:

- to prevent infection/disease.

ONCHOCERCIASIS

1. The disease

Onchocerciasis is an important public health and socio-economic problem, especially in Africa where over 99% of all infected persons live. The most severe consequence of onchocerciasis is blindness, which may afflict over one third of the adult population of the most affected communities. Another important problem is severe skin disease associated with maddening itching which cause great suffering to millions of people according to recent TDR research.

2. Disease situation and trends

The Onchocerciasis Control Programme in West Africa (OCP), which was launched in 1975 and extended in 1989, covers the savanna areas of 11 West African countries. The principal control strategy has been vector control and this has been highly successful in interrupting transmission of the disease. Onchocerciasis is now under full control throughout the OCP area. Some 1.5 million people, originally infected, are no longer so; an estimated 125 000-200 000 people have been prevented from going blind; 30 million people are no longer at risk of infection and blindness, and 25 million hectares of land have been made available for settlement.

In the endemic countries in Africa outside the OCP, there are an estimated 15 million people infected with *Onchocerca volvulus*, representing 85% of all infected people in the world today. It has been estimated that, in 1990, 335 000 persons were blind as a result of onchocerciasis (40 000 new cases of blindness per year), 4-6 million were affected by skin lesions, and more than 6 million people were suffering from troublesome itching. Unfortunately, aerial larviciding was not considered technically feasible or cost-effective outside the OCP, and virtually no action used to be taken to control the disease in the non-OCP countries. This changed when ivermectin was introduced in 1987 and made available by the manufacturer, Merck, Sharp & Dohme, free of charge and for "as long as needed". Several endemic countries, supported by a group of international non-governmental organizations, have started ivermectin-based control and it was estimated that, in 1994, some 15 percent of those infected outside the OCP areas received ivermectin treatment.

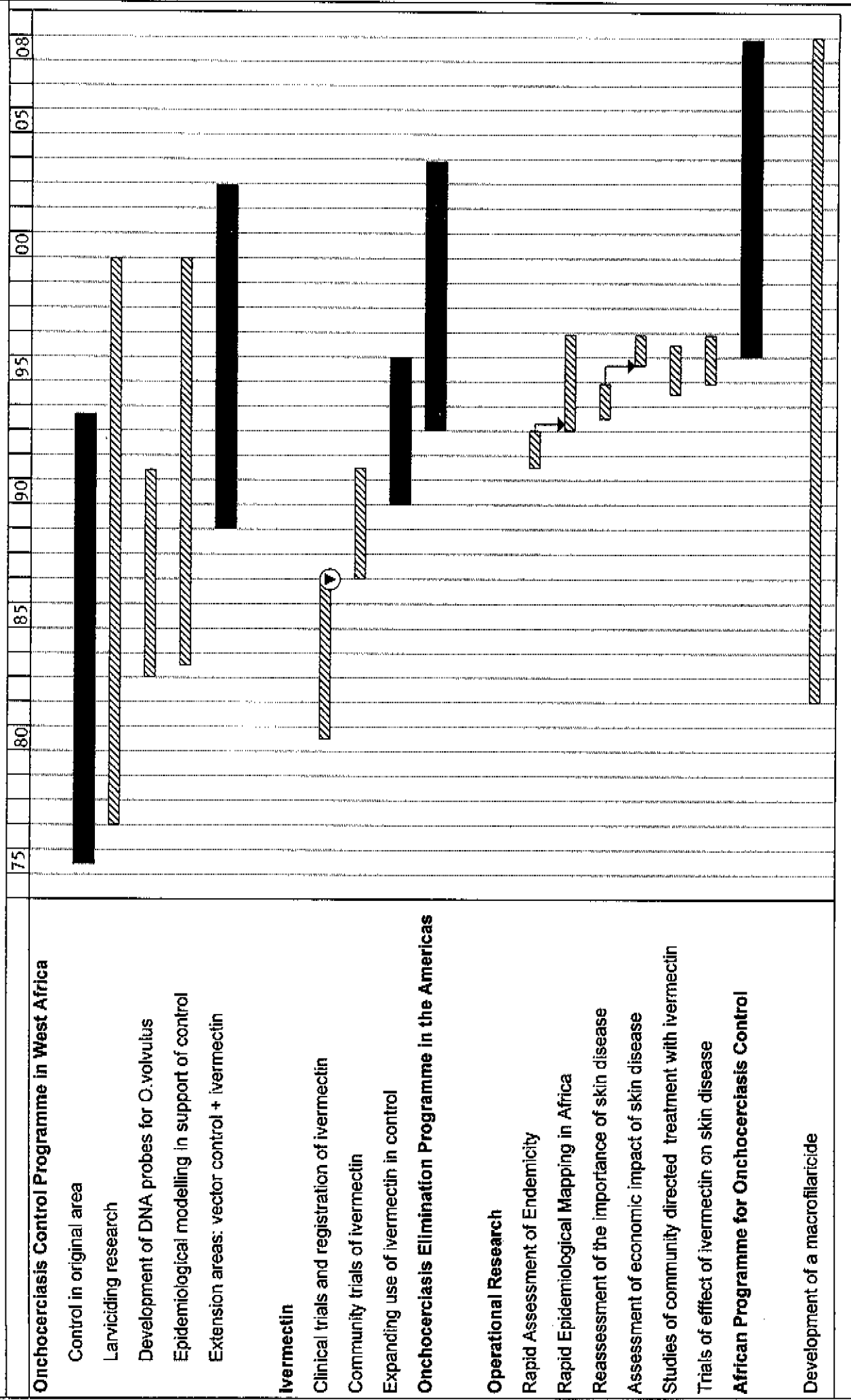
3. Strategy for elimination

It is expected that global elimination of onchocerciasis as a public health problem will be achieved during the next decade as a result of the control operations of the OCP and of two recently created international onchocerciasis control programmes. The time frame of the different control operations and of the major supporting research activities is given in Figure 3 (control shown as solid bars, research as hatched bars).

In the OCP, onchocerciasis is no longer a public health problem. Nevertheless, vector control, supported by ivermectin treatment, will continue in some areas until the year 2002 to ensure that the parasite reservoir is virtually eliminated and that the risk of recrudescence of the infection is minimal throughout the OCP area.

Towards the elimination of Onchocerciasis: The Timetable

Figure 3.



Outside the OCP, onchocerciasis control will be mainly based on ivermectin treatment. Assuming that ivermectin treatment is equally effective against the skin manifestations of onchocerciasis as it is in the prevention of ocular disease and onchocercal blindness, the disease can be eliminated as a public health problem from all communities where adequate ivermectin treatment coverage is achieved and sustained. However, large-scale ivermectin treatment does not result in interruption of transmission and treatment will therefore have to continue for a very long time, even after the disease is no longer a problem of public health importance.

In 1993, the Onchocerciasis Elimination Programme in the Americas (OEPA) was launched. OEPA covers all six endemic countries in the Americas and the control strategy is also based on ivermectin treatment. OEPA is scheduled to come to an end after a period of 10 to 15 years. The residual control activities required after this period have not yet been defined.

A new African Programme for Onchocerciasis Control (APOC) has been created to cover all endemic African countries outside the OCP area. It has the objective: "to establish, within a period of 12 years, effective and self-sustainable community-based ivermectin treatment throughout the remaining endemic areas in Africa and to eliminate the disease by vector control in selected foci". APOC control operations are expected to begin in 1997.

TDR undertook an extensive operational research programme to prepare the technical basis for APOC. Among the issues addressed were the development and application of rapid methods to locate all high-risk communities requiring treatment, the psycho-social and public health importance and economic impact of onchocercal skin disease, the effect of ivermectin treatment on onchocercal skin disease and troublesome itching, sustainable approaches to community-directed treatment, simple methods for monitoring control and the feasibility of vector eradication from isolated foci.

If the OCP is brought to a successful conclusion as scheduled by the year 2002, and if both APOC and OEPA achieve their objectives within the planned period, the global elimination of onchocerciasis as a public health problem will be achieved before the year 2008. However, the parasite reservoir will not have been eliminated by that time, and residual control activities will be required to ensure that the achievement of elimination is sustained.

4. Research for eradication of onchocerciasis

The risk of resistance to ivermectin is remote within the time frame of APOC and OEPA. However, the history of parasite disease control based on chemotherapy suggests a cautious approach should be adopted, and recent model simulations and molecular biological studies indicate that resistance could become a problem over a 20-30 year time period. It is important, therefore, to continue the development of alternative drugs for the treatment of onchocerciasis. Particularly useful would be a macrofilaricidal drug which kills or sterilizes the adult worms, thus ensuring a more definite impact of control on the reservoir of the parasite and possibly achieving its eradication. The development of a macrofilaricide is the mandate of the MACROFIL project which is funded jointly by OCP and TDR.

In order to assess whether the eradication of onchocerciasis would be feasible if a macrofilaricide became available, a computer simulation study was undertaken by the Centre for

Decision Sciences in Tropical Disease Control (CDTDC) of Erasmus University of Rotterdam using the microsimulation model ONCHOSIM. The long-term impact of mass treatment with a macrofilaricide on the parasite reservoir and transmission was simulated under realistic assumptions of drug efficacy (with efficacy defined as the percentage of macrofilariae killed or sterilized at each treatment) and treatment compliance. Eradication was defined as the attainment of an epidemiological situation in which the probability of recrudescence of the disease after cessation of control is less than 1%. The results of the simulations were compared with the predicted long-term impact of repeated ivermectin treatment on the parasite reservoir and transmission.

Though ivermectin is principally a microfilaricide, it also has an effect on the adult worms. In the analysis of five-year follow-up data from the community trial in Asubende (Ghana), it was found that the trends in microfilarial counts could only be explained by assuming an irreversible reduction in fecundity of female worms of about 35% (*Journal of Infectious Diseases*, 1995,172:204-10). Thus, ivermectin can also be considered a macrofilaricide but with a modest efficacy of 35%. However, according to the model predictions, it would take up to 50 years with annual ivermectin treatment at a coverage of 65% of the total population (typical for coverage with annual treatment in the OCP areas), or more than 15 years with six-monthly treatment, to achieve eradication.

The results of simulations for more powerful macrofilaricides with efficacies of between 60% and 90%, and administered at six-monthly intervals, are shown in Figure 4. The simulation is for a highly endemic focus with a community microfilarial load (CMFL) of 70 mf/skin-snip. The dashed line shows the prospects of eradication by ivermectin treatment. The solid lines show the combination of intervention period and treatment coverage required to achieve eradication using macrofilaricides with assumed efficacies of 60%, 75% and 90% respectively. When compared to ivermectin, a dramatic reduction in the required duration of control can be realized even with a drug which kills only 60% of the worms (leaving the other 40% unaffected). However, at a coverage level of 65%, a period of four years (drug efficacy 90%) to seven years (efficacy 60%) of six-monthly treatment is still needed.

The above results are based on the assumption that treatment compliance is random, i.e. that for each individual in the population, at each administration round, the probability of being treated is the same, irrespective of attendance or non-attendance at previous rounds. This is clearly not realistic and in order to explore the importance of systematic non-compliance, a second series of simulations was done using the extreme assumption that a certain percentage of the population never gets treated (because of non-compliance or contraindications against the drug). The results are shown in Figure 5. The solid line is for a macrofilaricide with 75% efficacy and random compliance, similar to that shown in Figure 4. The dashed line is for the same macrofilaricide but assuming systematic non-compliance in all cases. For this line, a coverage of 0.9 means that 90% of the population always gets treated while 10% never receives treatment. Figure 5 shows that the predicted feasibility of eradication depends greatly on the assumptions made with respect to compliance. If non-compliance is mainly systematic, eradication is not attainable under realistic assumptions of treatment coverage and within a reasonable period of time.

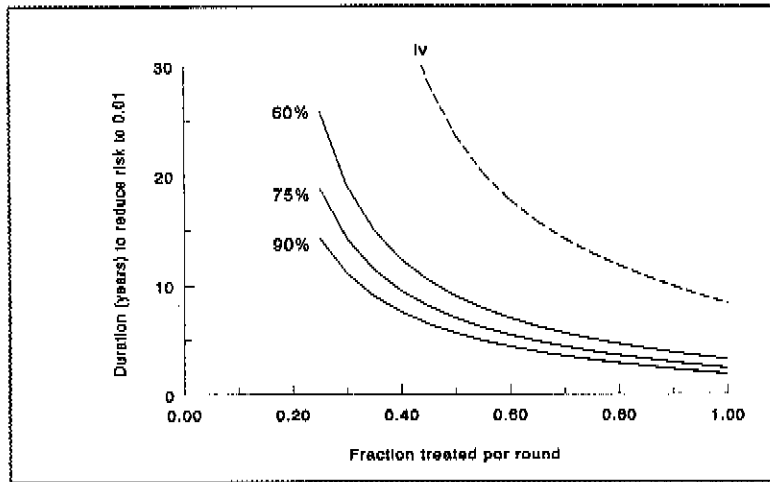


Figure 4: Potential of a macrofilaricide (solid lines) vs. ivermectin (dashed line) for the eradication of onchocerciasis. Lines indicate the combination of duration of control (Y-axis) and treatment coverage (X-axis) which leads to eradication (i.e. recrudescence risk = 1%). Above each line, eradication is almost certain; below the line, recrudescence is likely. Treatment frequency is two times per year. The percentages denote the drug-efficacy (% of worms killed per treatment).

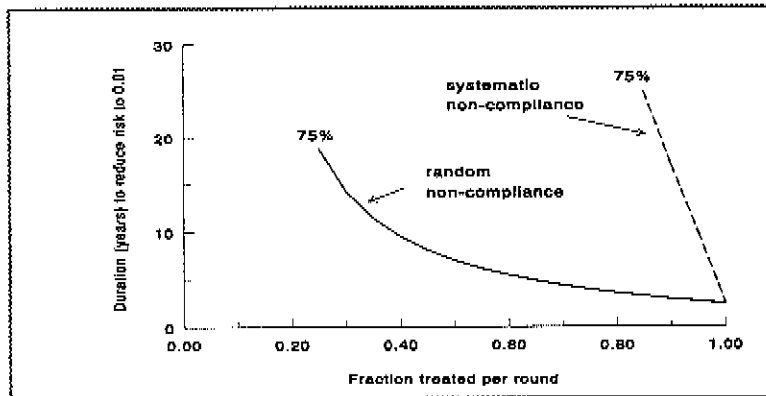


Figure 5: Potential of a macrofilaricide for the eradication of onchocerciasis. Lines indicate the combination of duration of control (Y-axis) and treatment coverage (X-axis) which leads to eradication (i.e. recrudescence risk = 1%). Above each line, eradication is almost certain; below the line, recrudescence is likely. Treatment frequency is two times per year. The drug is assumed to kill 75% of the worms per treatment. The solid line denotes a situation of random non-compliance; the dashed line a situation of systematic non-compliance (see text for details).

In conclusion, when eradication of the parasite is the primary objective of control, there is a definite role for a macrofilaricide in addition to ivermectin. However, an important requirement for such a drug is that it should not have major contraindications which would lead to systematic exclusion of certain population groups, and it should not be accompanied by severe side effects which could lead to non-compliance at later treatment rounds. These operational aspects, in addition to the need for obtaining and maintaining a high treatment coverage, appear more important for the feasibility of eradication than improvements of 5%-10% in the macrofilaricidal efficacy of the drug.

5. The timetable towards elimination

The main landmarks are indicated in Figure 3 (control activities shown as solid bars, research activities as hatched bars) and can be summarized as follows:

Onchocerciasis Control Programme in West Africa

- 1975-1993: Control in original OCP area
- 1977-1999: Larviciding research
- 1983-1992: Development of DNA probes for *O. volvulus*
- 1983-1999: Epidemiological mapping in support of control
- 1989-2002: Vector control+ivermectin in extension areas

Ivermectin

- 1980-1986: Clinical trials and registration of ivermectin
- 1987-1991: Community trials of ivermectin
- 1990-1995: Expanding use of ivermectin in control
- 1993-2003: Onchocerciasis Elimination Control Programme in the Americas

Operational Research

- 1991-1992: Rapid assessment of endemicity
- 1993-1996: Rapid epidemiological mapping in Africa
- 1993-1994: Reassessment of the importance of skin disease
- 1995-1996: Assessment of economic impact of skin disease
- 1994-1996: Studies of community-directed treatment with ivermectin
- 1995-1996: Trials of effect of ivermectin on skin disease
- 1996-2008: African Programme for Onchocerciasis Control
- 1982-2008: Development of a macrofilaricide

LYMPHATIC FILARIASIS

1. The disease

Infection with filarial parasites may lead to elephantiasis, a dramatically disfiguring disease usually affecting one or both legs, or to hydrocele, an equally grotesque inflation of the testicles. Infection can also cause acute fevers, inflammation of the lymphatic system, and the bronchial-asthmatic condition known as "tropical pulmonary eosinophilia".

The most widespread filarial parasite is *Wuchereria bancrofti*, which affects about 106 million people in the tropical areas of Africa, India, South-East Asia, the Pacific Islands, and South and Central America. India has by far the largest number of cases. The closely related *Brugia malayi* and *Brugia timori* affect 12.5 million people in South-East Asia.

The parasites are transmitted by mosquitos. In rural areas, particularly in Africa, *W. bancrofti* is transmitted by *Anopheles* mosquitos - a genus which also includes species that transmit malaria. In cities, widespread species of *Culex* mosquito, which can breed in latrines, sewage, and ditches, are major vectors. In the Pacific region, *Aedes*, a genus which includes species that transmit yellow fever, dengue, and dengue haemorrhagic fever, and which can breed in tiny amounts of clean water in the axils of plants, up-turned containers or old tyres, transmit the parasite. *B. malayi* is mostly transmitted by *Mansonia* mosquitos.

Adult worms or "macrofilariae", both male and female, settle into the lymphatic system and take 3-15 months to mature. They survive in the body for 4-8 years. Once established and fertilized, the females constantly produce large numbers of larvae known as "microfilariae", which invade the blood stream. From there, the mosquito host can ingest them with a blood meal and transmit them to another person. The larvae metamorphose through a sequence of larval forms before becoming adults.

The vast majority - millions - of microfilariae, however, remain in the body as immature forms, and die after some six months to two years. These sizable creatures - each up to a third of a millimetre long (and times some millions, that amounts to several kilometres of worm) - moving, secreting, excreting and dying as foreign bodies, can do immense damage and place an enormous burden on the host. The adults are several centimetres long and block lymphatic ducts. A combination of these effects, complicated by bacterial super-infections, causes the symptoms and pathology of the disease.

2. Disease situation and trends

Figures on global prevalence of infected and disease cases are shown in Table 2 below. The burden of disease due to lymphatic filariasis amounted to 0.85 million DALYs (0.56 million for men and 0.29 million for women) in 1990, and the disease has been identified as the second leading cause of permanent and long-term disability (WHO World Health Report, 1995).

3. Strategy for elimination

The following points are considered as the basis for the future development of a global strategy aimed at the elimination of this disease:

- The most important recent achievement leading to new optimism for successful control of lymphatic filariasis is the simplification of the recommended therapeutic regimens. Specifically, it is now recognized that a *single* dose of DEC (6 mg/kg) achieves essentially the same result as the long-recommended two-week course of this drug, i.e., a 90-95% reduction of circulating microfilariae even one or two years after treatment. Single-dose ivermectin (400 mcg/kg) is equally effective as single-dose DEC, and the *combination* of single doses of these two drugs appears to be the most effective regimen tested so far (with reductions to less than 2% of pre-treatment microfilaraemia levels two years after treatment). Actual utilization of these single-dose, once-yearly regimens in community treatment programmes has confirmed both their therapeutic effectiveness (figures 6 and 7) and their social acceptability. Thus, use of DEC or ivermectin alone or in combination once a year is a newly recognized control strategy for lymphatic filariasis that promises to be at least as effective as the once-a-year dose of ivermectin currently in use for onchocerciasis.

Table 2: Prevalence of lymphatic filariasis infection and disease

Disease due to <i>Wuchereria bancrofti</i> (figures in thousands)			
WHO Region	Population at risk of infection	Population infected	Number of disabled ^a
AFRO	260 300	40 424	14 800
AMRO	6 680	395	90
EMRO	3 700	342	117
SEARO	518 880	54 967	21 220
WPRO	113 270	10 483	3 690
Total <i>Wuchereria bancrofti</i>	902 830	106 611	39 917
Disease due to <i>Brugia malayi</i>			
SEARO	203 060	6 946	1 890
WPRO	83 790	5 544	920
Total <i>Brugia malayi</i>	286 850	12 490	2 810
Total of all lymphatic filariasis	1 094 060 ^b	119 101	42 727

(a) For *Wuchereria bancrofti* infections: only lymphoedema/elephantiasis or hydrocele; for *Brugia malayi* infections: only lymphoedema/elephantiasis; essentially all infected individuals however have damaged lymphatics with abnormal function.

(b) The total number of persons at risk is the number at risk for *Wuchereria bancrofti* infection plus two thirds of the number of persons at risk for *Brugia malayi* infection, since approximately one third of the population at *Brugia malayi* risk lives in areas where *Wuchereria bancrofti* is also present.

- Use of table/cooking salt fortified with very low concentrations of DEC (0.15% to 0.3%) has long been recognized as an effective means to control lymphatic filarial infection in communities where the salt supply can be restricted - regularly, microfilaraemia rates decrease almost to zero and transmission is essentially halted. Recently, the first commercially prepared DEC-salt was manufactured and distributed for sale in India, and DEC-fortified salt is now an available tool with the potential for playing a major role in future filariasis control programmes.

- Control of morbidity (i.e., arresting the progression of elephantiasis and lymphoedema or their reversal) has also been greatly advanced by the observations that intensive local hygiene to an affected limb, with or without the use of topical antibiotic and antifungal agents, appreciably decreases the local inflammatory burden on a patient's compromised lymphatic system and results in dramatic clinical improvement. Preliminary evidence suggests that community-based patient self-help groups work extremely effectively to stimulate and maintain personal compliance with the vigorous hygiene regimens required for this morbidity control, and such a strategy is clearly one that can be exploited worldwide, because nowhere do patients lack the intense desire to rid themselves of their ostracizing deformities.

- Studies on control of the mosquito vectors of lymphatic filariasis, using either the toxin-elaborating *Bacillus sphaericus* or polystyrene beads in breeding sites, have demonstrated unequivocally a decrease in vector numbers and hence a decrease in the transmission of infection. Exactly how and when these vector control tools are cost-effective and useful in large-scale control programmes for lymphatic filariasis are, however, not yet clearly defined.

- Use of new technologies for diagnosis:

- Lymphoscintigraphy
- Ultrasound
- DNA probes for vector infection
- DNA probes for blood infection

The transfer of the above technologies into country control programmes has begun, e.g. in China, Sri Lanka, India Australia and Papua New Guinea.

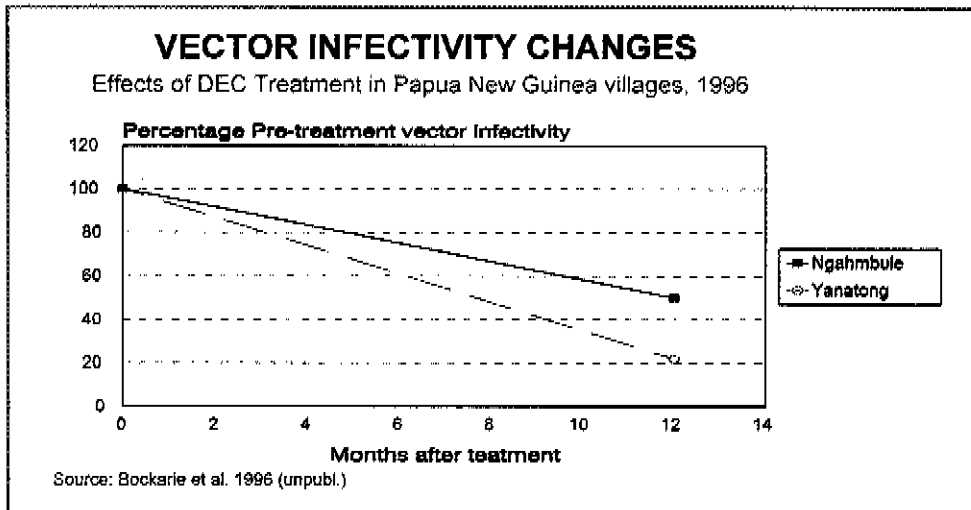


Figure 6

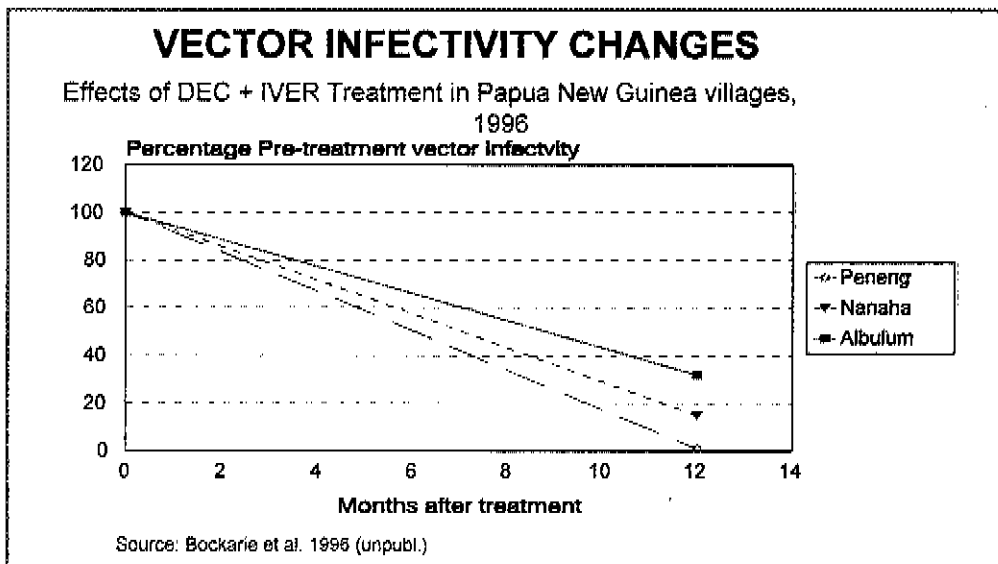


Figure 7

4. The timetable towards elimination

The main landmarks are indicated in Figure 8 (control activities shown as solid bars, research activities as hatched bars) and can be summarized as follows:

- 1989-1996: Multicentre drug (DEC, ivermectin) clinical trials
- 1990-1996: Multicentre morbidity control trials
- 1990-1993: Multicentre vector control trials
- 1990-1996: Antigen detection assays
- 1991-1996: DNA probes for detection of infection in mosquitos
- 1992-1996: Development and production of DEC-fortified salt
- 1994-1996: Enunciation of the global control strategy
- 1996-1999: Initiation of control activities by region

5. Future Research Needs

The research priorities that have been identified fall into two main areas, namely epidemiology/operational research and chemotherapy.

Epidemiology/operational research

- Geographical targeting: rapid assessment methods for mapping the distribution of infection/disease, to replace collection of blood at night.
- Design of drug delivery strategies: identification of the optimal target age group; and optimal frequency, duration and coverage of treatment. Mathematical modelling frameworks could be particularly helpful here.
- Logistics of intervention: examination of options for integrating drug delivery into existing systems (e.g. leprosy control PHC clinics) or for incorporating filarial vectors into existing vector control programmes (e.g. for malaria).
- Cost analysis: optimization of the cost-effectiveness of targeting, monitoring and intervention.

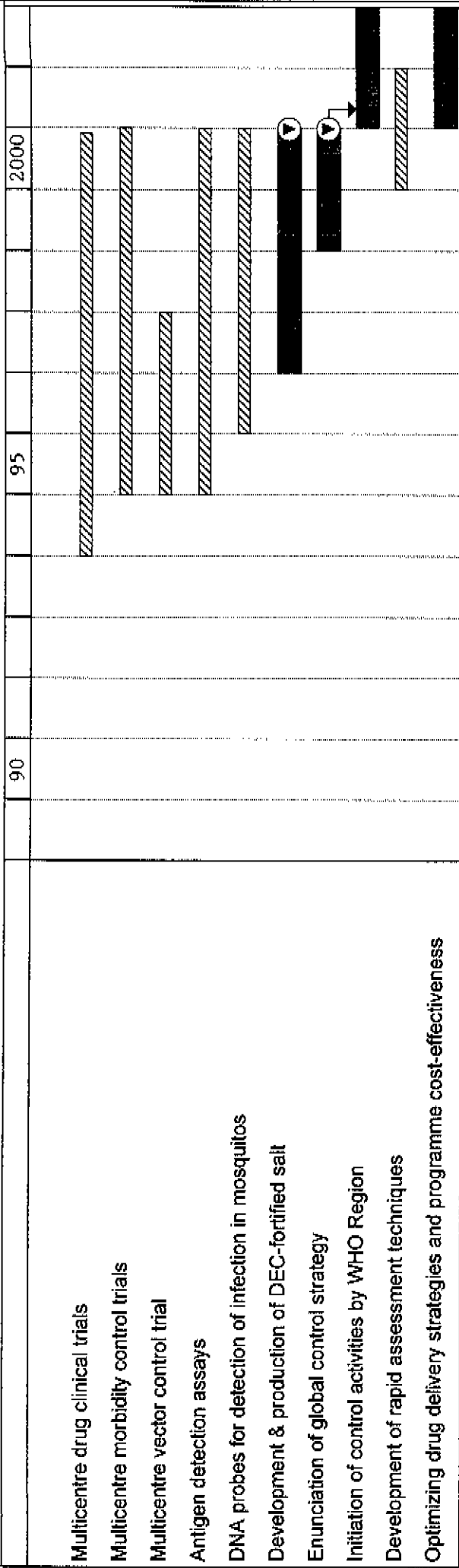
Chemotherapy

- Ivermectin is effective against lymphatic filariasis but is not yet registered for this indication. Diethylcarbamazine is also effective, and is registered, but is contraindicated in onchocerciasis (due to the Mazzotti reaction and ocular pathology). Therefore, there is no drug registered for use for lymphatic filariasis in the onchocerciasis endemic areas of Africa. Yet, paradoxically, the drug currently distributed for onchocerciasis is effective against lymphatic filariasis.

- This argues for the registration of ivermectin for lymphatic filariasis control in the African region. In this respect, negotiations are under way with Merck Sharp and Dohme Pharmaceuticals Co. in the USA.

Towards the elimination of Lymphatic Filariasis: The Timetable

Figure 8:



CHAGAS DISEASE

1. The disease

Chagas disease exists only on the American continent. There are two stages of the human disease: the acute stage, which appears shortly after the infection; and the chronic stage, which may last several years and irreversibly affects the autonomic nervous system of internal organs (heart, oesophagus and colon) and the peripheral nervous system. These incurable lesions develop some 10-20 years after the initial acute phase in one third of those infected, and include *chronic cardiopathy* (in 27% of those infected) as well as *chronic digestive lesions* (in 6%) and *neurological disorders* (in 3%). Patients with severe chronic disease become progressively sick and ultimately die, usually as a result of heart failure.

The disease is caused by a flagellate protozoan parasite, *Trypanosoma cruzi*, which is transmitted to humans by blood-sucking triatomine insects and by blood transfusion.

The risk of infection with Chagas disease is directly related to socio-economic factors: the parasite is transmitted by bugs which live in crevices in the walls of poor-quality houses in rural areas and unplanned urban developments. Rural to urban human migration is a factor which contributes to the spread of the infection by blood transfusion.

2. Disease situation and trends

Data on the prevalence and distribution of Chagas disease have improved in quality during the 1980s as a result of demographically representative cross sectional studies carried out in countries where accurate information is not available. A group of experts met in Brasilia in 1979 and devised standard protocols to carry out countrywide prevalence studies on human *T. cruzi* infection and triatomine house infestation.

These studies were carried out during the 1980s with the collaboration of the ministries of health of Chile, Colombia, Ecuador, Honduras, Nicaragua, Panama, Paraguay, Peru and Uruguay. The accurate information obtained has permitted better planning and evaluation of national control programmes by individual countries.

On the basis of these countrywide surveys it is now estimated that the overall prevalence of human *T. cruzi* infection in the 21 endemic countries is 17 million cases. Some 100 million people, i.e. 25% of all the inhabitants of Latin America, are at risk of contracting the disease.

Incidence is estimated as 1 000 000 new cases per year, and 45 000 deaths annually are due to the cardiac form of the disease.

According to the World Development Report (1993), the number of Disability-adjusted life years (DALYs) lost due to Chagas disease is 2 740 000. From a global perspective, Chagas disease represents the third largest tropical disease burden after malaria and

schistosomiasis. If, according to the UNDP Human Development Report (1994), the estimated average annual per-capita income in Latin America is US\$ 2390, the economic loss for the continent due to this disease currently amounts to US\$ 6500 million, which is equivalent to 1.3% of the external debt of the whole continent.

Infection of blood in blood banks in selected cities of the continent varies between 3% and 53%, thus showing that the prevalence of *T. cruzi* infected blood is higher than that of hepatitis B/C or HIV infection.

3. Strategy for elimination

3.1 Initiative of the southern cone countries

Since the vector of *T. cruzi*, *Triatoma infestans*, is intradomiciliary in the countries of the Southern Cone (Argentina, Brazil, Bolivia, Chile, Paraguay and Uruguay), sustained implementation of vector control measures can interrupt transmission. In 1991, the ministers of health of Argentina, Bolivia, Brazil, Chile, Paraguay and Uruguay, launched the "Southern Cone Initiative for elimination of transmission of Chagas disease".

Progress towards elimination of vectorial and transfusional transmission of Chagas disease in Uruguay, Chile, Argentina and Brazil has been documented in various scientific publications. ^{(1), (2), (3), (4), (5)}

By eliminating the transmission of Chagas disease in the above countries, the incidence of the disease in the whole of Latin America will be reduced by more than 70% (Figures 9 and 10). ⁽⁶⁾

Chagas disease is recognized as an important public health problem and is given increasing priority for control, as demonstrated by the above government initiative which is very successful and is paying high dividends. By cutting the transmission of this disease in the countries of the Southern Cone in a short period of time, the incidence of Chagas disease will be reduced by over 70%. From an estimated 1 000 000 cases per year, it will fall in 1999 to less than 300 000 cases a year for the whole of Latin America.

A total of US\$ 207 million has been allotted from national sources of the six countries for control operations since the start of the initiative in 1991. With this investment, it is estimated that the economic loss due to Chagas disease will be reduced by US\$ 4550 million.

Current data on house desinsectation, coverage of blood banks screening and serology in children and young adults indicate that the vectorial and transfusional transmission of Chagas disease will be interrupted in the following countries in the coming years: Uruguay (1997), Chile (1998), Argentina (1999), Brazil (1999), Bolivia and Paraguay (2003).

3.2 Initiative of the Andean countries and the Central American countries

As the vectors of Chagas disease in these countries are not strictly domiciliated, it is necessary to develop and test new vector control strategies for the local entomological conditions. The initial focus is on blood banks control to prevent transfusional transmission of the disease.

Thus in Colombia, Ecuador, Peru and Venezuela, the target is to adapt existing universal blood screening infrastructure, tentatively by 1996-97. In Venezuela this has already been accomplished.

In Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua and Panama, the target is to adapt existing universal blood screening infrastructures by 1997-98. In Honduras this has already been accomplished.

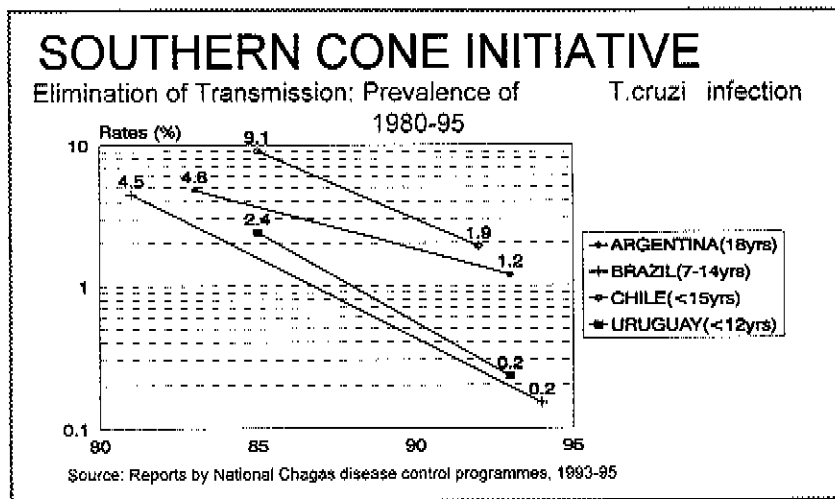


Figure 9

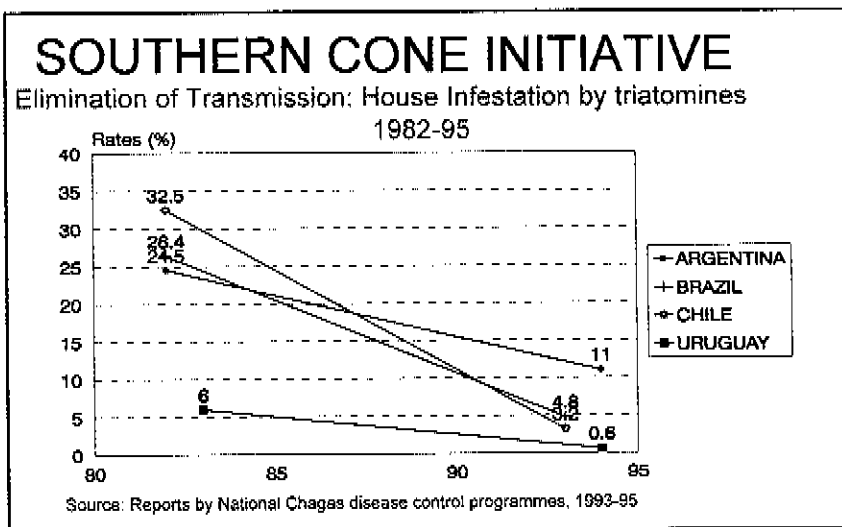


Figure 10

In these countries there are 5-6 million infected individuals and 25 million are at risk of contracting the infection.

Control activities are progressing as scheduled in Bolivia and Paraguay, but at this stage there are no entomological or epidemiological data available to assess the impact of the control programmes in these two countries or to estimate a date for interruption of transmission. These data should be available in 1999, after 4 to 5 years of continued control activities and completion of cross-sectional entomological and serological surveys.

An international independent commission has been appointed to certify the interruption of transmission in the above-mentioned countries.

3.3 Some detailed epidemiological situations

Argentina

In Argentina, transmission of Chagas disease occurs in the zones north of latitude 44°45', which cover about 60% of the country. The main vector is *Triatoma infestans*, which is a domiciliated species.

The strategy employed by the Vector Control Service until 1990 was to use highly trained personnel for the application of insecticide to houses in endemic rural areas.

As a result of field research sponsored by TDR, the control methodology was adjusted and the Vector Control Service decided to change its strategy. Community-based participation and appropriate technology replaced specialized personnel. A sensor device to detect house infestation by the vector, fumigant canisters and portable pumps for use by primary health community agents were developed and tested for efficacy.

Between 1983 and 1991, the average number of houses sprayed was 80 000 a year. Using the new approach, this number rose to 110 000 houses in 1992 and to more than 140 000 in 1994. Besides, there were more than 7500 rural agents working on this programme throughout the country in 1994.

This increase in house spraying resulted in important reductions in the proportion of houses infested by the vector in each province. The reduction ranged from 30.9% in Chaco to 94.3% in La Pampa, with an average reduction of 50.5% in house infestation in the country as a whole.

Figure 11 shows the decreasing prevalence of infection in 18-year-old males by province. There was a reduction of 75% between 1981 and 1993 in this age group.

Figure 12 shows the decrease in number of disease morbidity cases in different age groups compared with the expected figures had no control activities been carried out. In the age group of less than 18 years, an impressive decrease of 81.0% is observed, while in the age group of 18-35 the decrease is 43.6%, and in the group of 35-50 the reduction is 24.3%.

The monetary savings resulting from both direct and indirect costs for the number of human cases prevented by the control programme amount to an impressive figure of US\$ 2800 million, or about one-twentieth of the total external debt of Argentina in 1993!

To prevent transfusional transmission of Chagas disease, the screening of *T. cruzi*-infected blood has been compulsory since 1983 and the coverage of screening in blood banks of the country was 100% in 1994. Continued quality control and laboratory performance evaluation, carried out by INDIECH in provincial laboratories, ensures the high sensitivity and specificity needed for the tests used in the screening system.

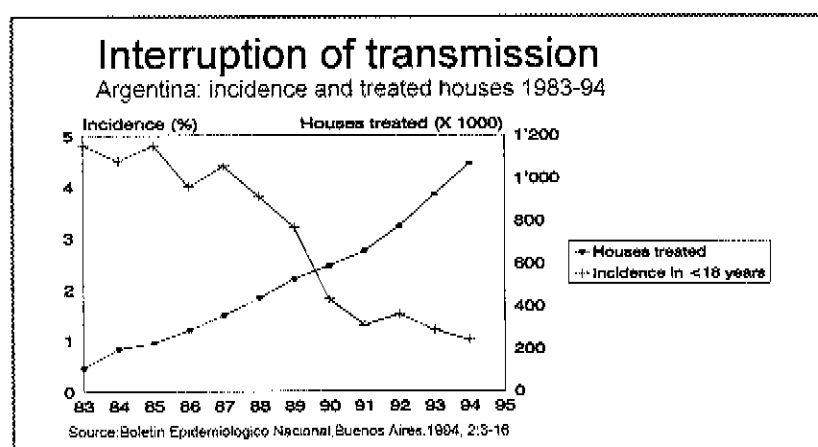


Figure 11

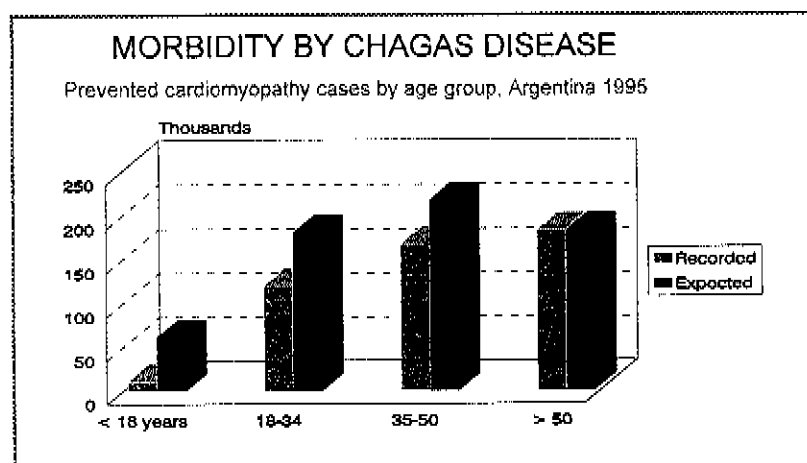


Figure 12

Brazil

In 1970, the endemic area covered over 36% of the country; 2493 districts (over 50%) were infested by *Triatoma infestans*, the main vector of the disease. A total of 49 million persons lived in the endemic zone, with 53% in rural areas. *T. infestans* is the most important species responsible for vectorial transmission of the disease. It is exclusively domestic and shows higher infection with *T. cruzi* than other species of triatomine.

The control programme has produced important results: in the State of Sao Paulo, the vector, *T. infestans*, has been eliminated from human dwellings since 1982 and no new acute cases or seropositive reactions have been detected since 1983 in the group of 1 - 4 years. In the rest of the country, there were 711 municipalities infested by *T. infestans* in the endemic states in 1983, while in 1993 there were only 83 municipalities infested, representing an 89% reduction as shown in Figure 13.

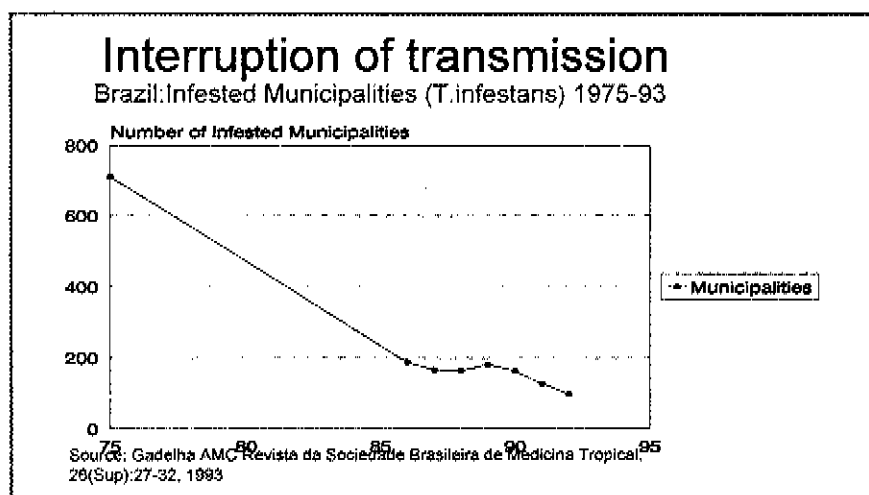


Figure 13

In 1993, only 1800 insects were captured by programme field workers in the whole country, a number that could easily be found in one single house before inception of the control programme. This represents an average of 2.5 insects in every 1000 houses, a house infestation rate far below the minimum threshold necessary to ensure transmission of the parasite.

In 8 of the 11 endemic states, a reduction of house infestation rates ranking from 100% in Mato Grosso to 20% in Goias was observed between 1983 and 1993. For the country as a whole, an average reduction of 71% in house infestation is observed. Focal areas still infested with *T. infestans* remain only in the states of Bahia, Tocantins and Rio Grande do Sul.

Sero-epidemiologic surveys carried out in 1994 in ten endemic states among 7-14 year olds showed that the incidence of infection in this age group is less than 0.5% in nine of the states, indicating a reduction of over 96.0% as compared to 1980. In other words, transmission of the disease by vector has been virtually eliminated (Table 3).

Similar trends are observed in relation to the decreasing proportion of *T. cruzi*-infected blood in blood banks between 1982 and 1991. In 1982, 6.5% of blood was found to be infected in the whole country, whereas in 1991 this proportion was only 1%. In 1995, coverage of screening in blood banks reached 98%.

Current vector control activities are targeted towards the elimination of *T. infestans* in the remaining focal areas of the states of Bahia, Goias and Rio Grande do Sul, and it is estimated that this will be achieved in 1998.

Table 3:
Percentage sero-reactivity (human infection) in 7 - 14 year olds, Brazil 1980 - 1993

STATE	1980 (%)	1993 (%)	Reduction(%)
Bahia	5.4	0.25	96.0
Goiás	7.4	0.10	99.0
Maranhao	0.1	0.00	100.0
Mato Grosso	2.8	0.18	94.0
Minas Gerais	8.8	0.06	99.0
Paraíba	3.5	0.36	99.0
Piauí	4.0	0.16	96.0
Rio Grande-Norte	1.8	0.03	98.0
Rio Grande-Sul	2.5	1.52	40.0
TOTAL	4.2	0.15	96.5

Chile

Chile extends from parallel 18° 30' to 52° 30' and has a population of 13 380 000, of whom 82% live in urban conglomerates. Approximately 1 654 000 live in the endemic area from parallel 18° 30' to parallel 34° 35' and hence are at risk of contracting the infection.

In the 1980s, the proportion of infected persons in all age groups in the country was 17.0% and the average house infestation rate was 28.8% . The prevalence of infected subjects among blood donors in 1984 was 3.6% for the whole country.

Two main species of triatomine are responsible for the vectorial transmission of Chagas disease in Chile. *Triatoma infestans*, a domestic insect, is the most important vector.

Vector control operations using insecticides with residual activity and carried out by the national programme between 1982 and 1993 have reduced the house infestation rates by 79% in Arica and by 96% in Iquique, with an average reduction for the whole country of 89.5% (Table 4). The entire country is likely to be free of insect transmission by the end of 1998.

Transmission through blood transfusion is under control, due to compulsory blood screening and 100% coverage in endemic areas.

Table 4
Prevalence of house infestation by triatomines, endemic areas, Chile, 1982 and 1993

Region	Health Services	House infestation rates (%)		
		1982	1993	Reduction (%)
I	Arica	12.5	2.6	79.2
I	Iquique	18.6	0.7	96.3
II	Antofagasta	45.7	4.1	91.0
III	Copiapo	51.2	8.0	84.4
IV	Coquimbo	49.9	2.4	95.2
V	San Felipe	18.0	2.0	89.0
V	Vina del Mar	34.6	1.6	95.4
VI	O'Higgins	28.1	1.8	79.3
Total		28.8	3.0	89.5

The marked reduction in vectorial transmission is reflected by the drop in the proportion of *T. cruzi*-infected blood donors between 1983 and 1992, as shown in Table 5.

Table 5.
Prevalence of infected blood in blood Banks, Chile, 1982 and 1993

Region	Health Services	<i>T. cruzi</i> -positive blood donors (%)	
		1982	1993
I	Arica	2.5	1.9
I	Iquique	1.6	1.2
II	Antofagasta	3.5	2.5
III	Copiapo	6.5	3.0
IV	Coquimbo	7.0	4.7
V	San Felipe	3.5	0.0
V	Vina del Mar	0.0	0.0
Metropolitan	Santiago	1.5	0.9
Total		3.6	1.3

A countrywide sero-epidemiological study was completed in Chile in 1996. It showed a prevalence rate of 1.9% in the age group of less than 15 years as compared to 9.1% in the same age group in 1983, indicating the advanced degree of control and imminent interruption of vectorial transmission in this country (Figure 14).

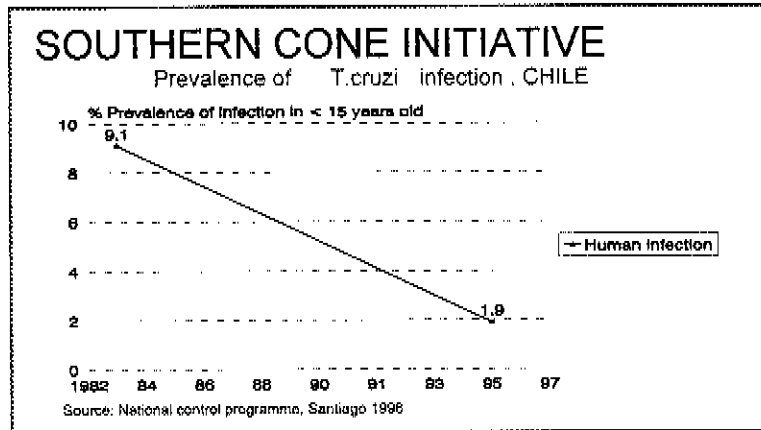


Figure 14

Uruguay

In Uruguay, domiciliary transmission is effected through *Triatoma infestans*. In 1983, this insect infested human dwellings and their annexes in the following departments: Artigas, Rivera, Tacuarembó, Salto, Paysandú, Rio Negro, Soriano, Colonia, Durazno and Cerro Largo, i.e. in 80% of the territory of Uruguay.

The National Chagas disease control programme, which was reorganized that year, carried out a spraying programme of human domiciles and peri-domiciles with residual activity insecticides. The sustained spraying helped eliminate the infestation by *T. infestans* in Artigas, Colonia, Durazno and Soriano, and markedly decreased the rate of house infestation in the remaining areas (Table 6).

In 1985, a country-wide serological survey to detect human *Trypanosoma cruzi* infection, sponsored by TDR, showed a prevalence rate of 3.4% for the whole population with a prevalence rate of 2.4% for the age group of less than 12 years.

Table 6
House Infestation Rates (%) by department, Uruguay, 1983 - 1992

Department	House Infestation Rate (%)		Reduction (%)
	1983	1992	
ARTIGAS	2.9	0.0	- 100.0
RIVERA	15.3	1.9	- 93.5
TACUAREMBO	22.2	2.3	- 90.0
SALTO	8.8	n.d.	-.-
CERRO LARGO	2.6	0.23	- 99.0
PAYSANDU	0.0	0.0	-.-
RIO NEGRO	1.4	0.06	- 96.0
COLONIA	0.9	0.0	- 100.0
DURAZNO	1.7	0.0	- 100.0
SORIANO	0.7	0.0	- 100.0

A sero-epidemiological survey carried out in 1995 in different rural areas of the endemic departments in children under twelve years old has shown very low (0.2%) or zero infection rates in this age group. This could be interpreted as confirmation of the interruption of vectorial transmission of Chagas disease in the country (Figure 15).

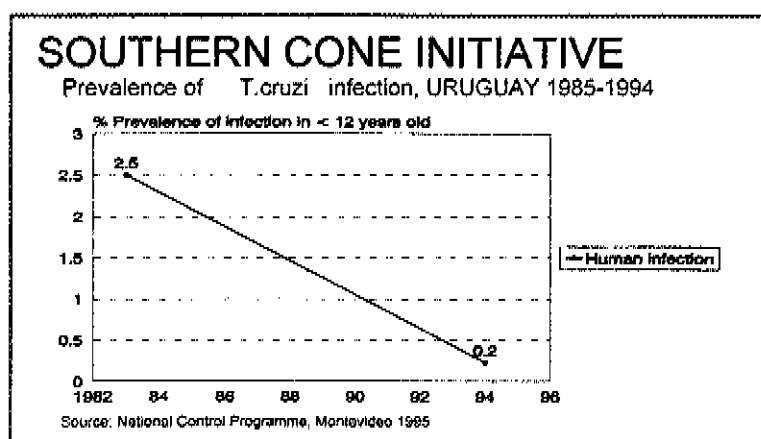


Figure 15

In addition, transmission through blood transfusion is also interrupted due to the very low number of infected donors and the 100% coverage provided by compulsory blood screening in the country.

These data mean that Uruguay is the first Southern Cone country to have accomplished the goals set by the ministries of health of Argentina, Bolivia, Brazil, Chile, Paraguay and Uruguay for the elimination of vectorial and transfusional transmission of Chagas disease since the multicountry programme was launched in Brasilia in June 1991.

4. The timetable towards elimination

The main landmarks are indicated in Figure 16 (control activities shown as solid bars, research activities as hatched bars) and can be summarized as follows:

- 1980-1985: Prevalence cross-sectional studies on human infection and house infestation in nine countries
- 1980-1985: Standardization of serological techniques and creation of a continental network of reference laboratories
- 1984-1990: Follow-up prospective studies on the course of human infection
- 1987-1989: Cloning of parasite genome and production of defined antigens for improvement of diagnostic techniques
- 1990: Industrial production of kits for blood banks control
- 1988-1992: Development of new tools for vector control
- 1988-1993: Multicountry field studies for evaluation of new vector control tools
- 1992: Industrial production of paints, canisters and sensor boxes
- 1992: Initiative of the Southern Cone countries
- 1993: Initiative of the Andean countries
- 1993: Initiative of the Central American countries
- 1995-1998: Evaluation of impact and projection of trends
- 1998-2000: Certification of interruption of transmission

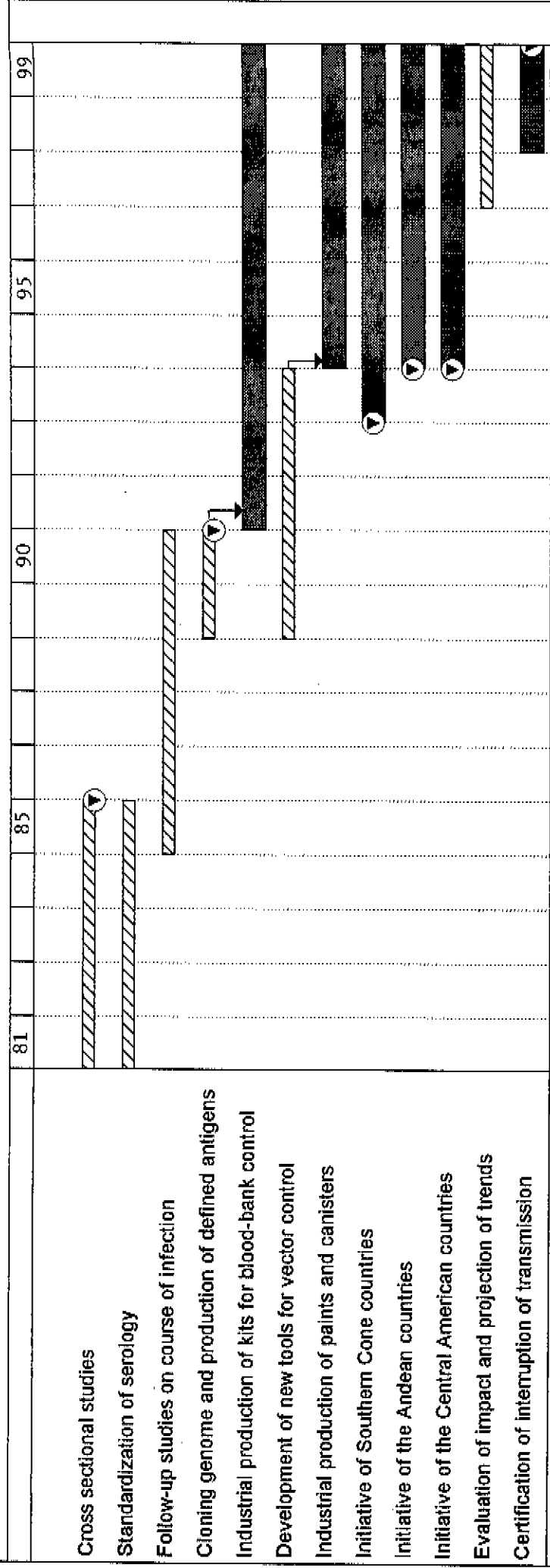
5. Future Research Needs

Future research priorities have originated from the operational questions detected by the control programme and refer to the evaluation of impact of the control activities, the monitoring of insecticide efficacy to detect possible development of vector resistance, and to the promotion of vector surveillance through the mass media. They include:

- * Studies on prevalence, clinical management and cost-effectiveness of interventions for the control of congenital transmission.
- * Monitoring of efficacy of insecticides in the national control programmes.
- * Development of techniques for detection of peri-domestic infestation.
- * Studies on periodicity of insecticide spraying based on residual density of triatomines.

Figure 16:

Towards the elimination of Chagas Disease: The Timetable



- * Evaluation of sensitivity, specificity and costs of improved kits for blood screening using defined antigens and the polymerase chain reaction (PCR) technique.
- * Improvement and assessment of methods for disinfection of blood intended for transfusion.
- * Modelling and development of indicators to assess elimination of transmission.
- * Influence of climatic changes on the populations of vectors.
- * Evaluation of the use of the media by the community for promotion of entomological surveillance.
- * Evaluation of the efficacy of control and surveillance activities carried out with active community involvement.

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