Clinical Trial Perspective

CLINICAL INVESTIGATION

Considerations in the design of clinical trials for multibacillary leprosy treatment

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In 1991, the World Health Assembly adopted a resolution to attain the goal of global elimination of leprosy as a public health problem by the year 2000, based on universal access to multidrug therapy established by the WHO. The WHO multidrug therapy recommendation was not based on clinical trial results, but was based on all scientific knowledge available at the time and incorporated some financial constraints, such as the impossibility of daily rifampin use. Further decisions regarding treatment duration were needed to allow the World Health Assembly resolution target to be reached, which was set without a deep epidemiological evaluation. At present there are many uncertainties about leprosy treatment, including for instance, its ideal duration including decisions concerning daily or intermittent use of drugs, the use of immune modulators with antibacterial drugs as prophylaxis, and treatment of reactions during and after chemotherapy. To advance our knowledge of leprosy treatment, knowledge revision of the available research would be the first step to develop comprehensive Bayesian clinical trials designed to shed light on these uncertainties.

Keywords: adaptive clinical trial • Bayesian statistics • clinical trial • impairment • leprosy • neglected infectious disease • relapse • treatment

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Leprosy is a chronic disease, caused by *Mycobacterium leprae,* which affects skin and nerves, often resulting in physical disabilities. Unlike other neglected diseases that have a definite geographic distribution, leprosy has been found around the world, meaning that transmission occurs regardless of climate.

Nevertheless, disease transmission has ended in nearly all developed nations, most likely as a consequence of socioeconomic development. Currently, new autochthonous cases can be found in all tropical countries, with India and Brazil having the highest number of newly detected cases annually. Some insular countries located in the Pacific and Indian Oceans have the highest rates of new case detection, indicating a high risk of transmission [1].

In the gulf region of the USA, mostly in the states of Louisiana and Texas, native cases are still diagnosed. There are armadillos (*Dasypus novemcinctus*) in the area that are naturally infected with strains of *M. leprae* found also in autochthonous human cases. This suggests that leprosy might be a regional zoonosis, even though *M. leprae* was introduced into the Americas by Europeans and Africans [2]. There are also records of *M. leprae* infection in armadillos in Central and South America [3,4]. Furthermore, cases in African chimpanzees raise the possibility that these animals could be helping to maintain leprosy transmission in Africa [5] . The actual importance of nonhumans in leprosy epidemiological dynamics is unknown.

The mechanisms of leprosy transmission are not well known due to the fact that there is no test to diagnose infection. It is presumed that infection is much more

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frequent than actual disease in endemic areas. The incubation period can vary from a few months to 20 years [6].

Leprosy has always carried a huge stigma and was considered by many cultures a divine punishment. The description of the bacillus by Hansen did not eliminate stigma but aggregated to it the fear of contagion. Isolation as the main control policy to avoid contagion was the same to the layman as the banishment of the diseased to avoid impurity before germ theory.

Sulphones discovery in the 1940s created an optimistic expectancy of rapid leprosy control, but patients from the lepromatous pole of the disease had a high risk of relapse, around 25%, even after many decades of sulphone therapy. Lepromatous patients could have their disease controlled with lifelong sulphone therapy, but the development of sulfone resistance could render the disease untreatable.

Sulphone resistance was identified clinically in the 1950s and has been confirmed in many parts of the world since 1964 [7]. Rifampicin showed high bactericidal activity on *M. leprae* in the 1970s, which allowed a big improvement of leprosy therapy and the beginning of multidrug regimen clinical trials [8].

Before the completion of these clinical trials, in 1981 the WHO established two multidrug treatment regimens for two different groups of patients: paucibacillar (PB) and multibacillar (MB) patients (Table 1) [9].

In 1993, for the first time chemotherapy treatment for MB leprosy patients had fixed duration regardless of the results of bacteriological examinations or the presence of clinical symptoms.

This paper's intention is to point out the uncertainties concerning MB leprosy treatment and to suggest possible new research approaches. First the paper will briefly place leprosy treatment into the context of the WHO's policy for leprosy control and elimination since the 1990s and presents the rationale for WHO multidrug therapy (MDT). Although leprosy control is not the central focus of this paper, it is impossible to think about leprosy treatment development without addressing leprosy control policies. Then the possible outcomes to be measured in clinical trials, a central point in the evaluation of any treatment, will be examined. The discussion of published clinical trials is the following section. Finally, this paper proposes some new, controversial research approaches. It will most likely pose more questions than answers. The author intends to open a debate about adaptive Bayesian clinical trials among those who work with neglected diseases.

Leprosy & WHO policy in the 1990s

In 1990, many patients still lived in leprosy colonies in the developing world, without access to rifampicin-containing treatment. The WHO-MDT regimen was considered efficient enough to allow patients to be released from treatment and from isolation, but many countries gave priority to the new cases for the use of the WHO-MDT, a treatment more expensive than dapsone monotherapy.

The implementation of WHO-MDT turned a previously lifelong disease into one that was curable. A rapid and important reduction of known prevalence was observed in the countries that implemented MDT for all patients, due to the shorter disease duration allowing the release of patients from leprosy institutions, however, many endemic countries did not introduce WHO-MDT to their control programs.

In May 1991, the 44th World Health Assembly (WHA) adopted the resolution 44.9, declaring the commitment of the WHO to attain the goal of global elimination of leprosy as a public health problem by the year 2000. The goal was to reduce the known prevalence of leprosy to below 1/10,000 inhabitants. From 1995 on, WHO supplied free of cost, MDT for all the endemic countries with the support of Sasakawa Nippon Foundation's (Akasaka, Tokyo) support until 2010 and Novatis's (Basel, Switzerland) support since then.

The establishment of this goal intended to increase political and financial support for leprosy control. As the target was based on known prevalence, an indicator that is a function of know incidence (new case detection

Table 1. WHO multidrug therapy regimen and its duration.

Bacillary level	Rifampicin	Dapsone	Clofazimine	Duration
Paucibacillary	Two capsules of 300 mg once a month (supervised)	One tablet of 100 mg/day (self-administered)	–	6 months
Multibacillary	Two capsules of 300 mg once a month (supervised)	One tablet of 100 mg/day (self-administered)	Three capsules of 100 mg once a month (supervised) + one capsule of 50 mg/day	1981–1993: 24 months or until slit skin smear negativity 1993–1997: 24 months fixed duration 1997 onwards: 12 months fixed duration

rate) and the duration of the disease, it demanded a fixed duration of the treatment in all countries to allow comparisons and analysis of time trends. WHO-MDT for MB patients was defined as a 24-month treatment in 1993.

Unfortunately the new case detection rate in many parts of the world would not allow this target to be reached by 2000 if the duration of WHO-MDT were maintained at 2 years. In 1997, without strong evidence, the WHO recommended the reduction of MB leprosy treatment from 24 to 12 months, even though the WHO Expert Committee on Leprosy, which met a few months before, was not clear about this point. The meeting report states that the committee considered the recommendation of 24 months treatment still valid and also that "it is possible that the duration of the current MDT regimen for multibacillary leprosy could be shortened to 12 months" [10].

This new treatment duration reduction allowed the global elimination target to be achieved by the end of the year 2000.

Without further WHA resolution and ignoring the fact that after many years of using MDT there was no evidence of its impact on transmission [11] and that the crude death rate magnitude influences prevalence, the WHO then "established its own more radical targets of reaching elimination at national and then sub-national levels" by 2005 [101], which was postponed to 2010 for those countries that did not reach the target by then. This more radical target had no feasibility in some countries, which generated discussions about the accuracy of the numbers reported to the WHO [12–15] and also suffered criticism [16–24]. The 8th WHO Expert Committee on Leprosy meeting in Geneva, (Switzerland) changed the political emphasis from elimination to reducing disabilities and ensuring the quality and sustainability of leprosy services and moved on from the dispute about prevalence numbers to recommend new targets based on case detection and disability prevention [25].

WHO multidrug therapy: rationale, evidence & criticisms

The rationale for any treatment for mycobacterial diseases is to use more than one drug to avoid resistance and to treat long enough to guarantee that the number of persisting bacilli is sufficiently low in order to be controlled by the immune system. The probability of the presence of resistant bacilli to one drug is proportional to the bacillary load. Persistent bacteria are dormant bacteria with low metabolic activity but which are sensitive to drugs and still viable. The persistent bacilli may revert to a normal division rate in the absence of chemotherapy and produce relapses. The use of bactericidal drugs should allow the reduction of treatment duration since they act on bacilli with low division rate that are less susceptible to the action of bacteriostatic drugs. Those remaining bacilli may persist in hostile intracellular microenvironments, where they can evade the immune system [26,27], where drugs may not achieve a high concentration or where pH is low and affects drug action.

Although leprosy as a clinical entity cannot be reduced to its bacteriological aspects, since symptoms and incapacities are produced by the interaction of the patient immune system with the bacilli and its antigens, the evaluation of WHO-MDT was based only on the risk of relapses. While the two objectives of leprosy control programs are transmission reduction and incapacity prevention, many patients treated with WHO-MDT develop new nerve function impairment during and after the chemotherapy [28].

It is important to evaluate the issues discussed here in the context of public health history. In the 1980s, disease control programs had their focus only on the interruption of transmission and not on reduction of disease lethality or patients suffering relief. An important example of the changes of disease control policies in the last 35 years is malaria control, which in the 1980s did not include treatment of the disease but only vector control. Brown *et al.* published an important paper on the history of WHO and public health policy that may be useful for those interested in this issue [29].

The lifelong treatment of leprosy imposed a huge burden to health systems as most countries isolated patients and treated them with dapsone monotherapy. This policy needed to be changed for it did not fulfill the patient's best interests or provide the society the best protection. Some issues that supported this policy choice are listed below:

- Available resources were spent on chronically ill patients with unknown bacteriologic status and with incapacities, leaving no resources to give better treatment to new patients, such as rifampicin, which was available;
- Stigma was reinforced by isolation even of patients with inactive disease and the threat of the growth of dapsone resistance was real;
- Very good results were observed with the combination of dapsone and rifampicin, and there were some evidence of the equivalence of once a month rifampicin with everyday regimen [30–32];
- To wait 20 years for a precise and accurate estimation of the relapse rate of a fixed time treatment was not an option.

The decision regarding the new leprosy treatment recommended by the WHO in 1981 used all the scientific

knowledge available then and incorporated some financial constraints, such as the impossibility of the use of rifampin on a daily basis [7]. Further decisions regarding treatment were needed to reach the WHA resolution target that was set without a deep epidemiological evaluation.

Nowadays the WHO-MDT should be considered based on an evidence grade 5 in the Oxford Centre for Evidence-Based Medicine criteria. As stronger evidence is needed, two issues are important in the discussion of the WHO-MDT for MB patients. The first is whether daily doses of rifampicin would lead to better results and the second is what the impact is of treatment being shortened to 1-year duration compared with the 24-month treatment.

The resolution about the monthly use of rifampicin was based on the very high cost of rifampicin in the 1980s and the huge number of those to be treated, as it included all patients previously treated with dapsone monoterapy, that is, a huge number of prevalent patients; 10–12 million cases in the mid-1980s [33]. The elimination of the backlog of old leprosy cases was the biggest achievement of WHO elimination campaign. A smaller number of cases to be treated allows the definition of the best possible treatment with less financial constraint.

The 24-month WHO-MDT for MB patients showed an acceptable relapse rate estimated as 3.9% in 15 years based in the follow up of a cohort in the Philippines [34]. These data were completed and reviewed estimating a cumulative relapse rate of 6.6% at 16 years after completing chemotherapy [35]. Both studies used a criterion for relapse with high specificity. As an example how this criterion is important, a retrospective cohort from Colombia estimated a relapse rate of more than 25% after at least 24 months of treatment [36].

The only paper that was found that follows a cohort after 1-year WHO-MDT refers to only one relapse in 300 MB patients after a mean follow-up time of 6.4 years [37]. As this cohort was studied in the same center as the previous 24-month cohort, it is worth pointing out that in this last cohort, relapse only begun at 6 years after treatment conclusion.

Some authors emphasize the importance of the identification of patients with high risk of relapses for a better treatment approach [38,39]. Patients with high bacilloscopic index are believed to have a higher risk for relapse.

A difficulty to evaluate different results of observational cohort relapses rates are not only the differences in relapse definition but also what are considered MB cases. In 1982, the classification of leprosy patients as PB or MB meant a simplification *vis a vis* the Ridley–Jopling classification. This classification used the bacterial index (BI) ≥2 as a discrimination criteria and its rationale was that bigger bacterial burden requires more drugs to avoid the selection of resistant strains and longer treatment to deal with persistent bacilli. In 1988, probably because of lack of accuracy in the field bacterioscopy, the cut-off point was changed to BI >0 in any skin smear site. Slit skin smear (SSS) is considered 1+ if one to ten bacilli are observed in 100 fields [102]. Traditionally, fewer than ten bacilli in a smear were considered as a probable contamination of the microscopic slide, because slides used in bacilloscopies with negative results may be reused. This change modifies the composition of the MB group, reducing the risk of relapse. A further simplification was introduced in 1995 where the PB or MB classification became based on a proxy clinical sign – the number of skin lesions [7].

The accuracy of this classification method is unknown, but it is so widely used that papers exist in which a patient with more than five lesions is not considered a patient classified as MB with this criterion but as a MB patient by definition. It is important for the sake of precision to clarify that MB is not the same as a multilesion patient, but some papers are not explicit with the criteria for MB classification.

It is important to emphasize that this paper is not discussing the adequacy of the simplification of leprosy classification to be used in the field, but how the incorporation of new criterion for MB classification in the academic work introduced heterogeneity in the set of papers evaluating WHO-MDT. This heterogeneity makes it difficult to combine or compare the results of different studies. We can conclude that despite all the uncertainties discussed above, the WHO-MDT for MB patients has reached consensus in an important portion of health professionals, including medical doctors worldwide, as it has been recommended by many leprosy control programs, not only those from poor and middle-income countries, but also by the US CDC for immigrant candidates with leprosy, by the BMJ Evidence Centre product "Best Practice" (with the comment about treatment duration: "…or longer as prescribed by the physician") and the Australian Center of Disease Control (exception for those with BI ≥ 4: treatment duration of 24 months) [40].

The American Leprosy Control Program recommends a different treatment for American residents with daily rifampicin for PB and MB patients for 12 months for PB patients and 24 months for MB. Their evaluation about relapses shows smaller risk than those published with intermittent rifampicin regimens [41].

Measuring bacteriological & clinical outcomes in MB leprosy treatment

Leprosy control is based on early diagnosis and treatment to interrupt transmission and prevent nerve damage, which leads to disabilities.

The usual strategy to interrupt transmission is to cure the disease, eliminating the source of infection. However, sometimes elimination of the source of infection is not the same as curing the disease. This happens in many viral infections, such as measles, influenza or dengue fever, where the infectious period is not the same as the symptomatic period [42].

Traditionally leprosy treatment is followed up through BI from SSS and logarithm BI (LBI) skin biopsy.

At present we lack a criterion for leprosy bacteriological cure. It is known that SSS will be negative some years after the end of MDT for the majority of patients. The fall in BI is unrelated to the potency of the therapy and the SSS negativity also does not predict the risk of relapse [7]. The conclusion is that BI is not a useful end point for leprosy clinical trials.

There is not a clear criterion for treatment failure that could be a result of low compliance or resistance. The lack of an accurate definition of bacteriological cure, other than treatment conclusion, impacts the definition of an accurate criterion for relapse.

As a bacteriologic criterion is related not only to the patient's health but also with transmission, BI of skin surface and nasal secretion could be relevant end points in treatment regimen evaluation [43]. Ebenezer *et al.* showed that MB patients treated with WHO-MDT for 24 months with positive SSS had granuloma fractions in nasal mucosa biopsy that exceeded those seen in the skin specimens. However, mouse footpad studies from the nasal mucosa biopsy specimens did not demonstrate any growth of *M. leprae* [44]. Some old treatment evaluation studies used BI from nasal secretion and LBI of skin biopsies [31]. BI of skin surface and nasal secretion are end points that could be further explored in future clinical trials, as these outcomes had rarely been used in recent research.

Detection of persisting *M. leprae* by inoculating the footpad of immune-suppressed neonataly thimectomized Lewis rat was used in the THELEP studies [45].

Disability prevention through treatment is a reality if we compare patients nowadays with those from the dapsone monotherapy era. However, patients present new nerve damage during and after chemotherapy, raising the question whether the present treatment is the best treatment for disability prevention.

How to incorporate this dimension in the clinical trials is an important issue. The INFIR study measured new nerve function impairment (NFI), defined as the presence of NFI measured by clinical examination on nerves without previous evidence of impairment [28].

The Screening of Activity Limitation and Safety Awareness scale could also be used as a measure of the functional impact of nerve damage [46–48]. Other measures, such as the eye-hand-foot impairment score, although less sensitive to nerve function variation, could also be considered [49,50].

The WHO disability grade is not a sensitive tool for measuring the progress of NFI. It is an indicator of late diagnostic and a proxy for health care coverage – very important features of leprosy control programs.

The frequency of leprosy reactions has been considered a relevant end point in some studies [51–55] as well as the quantity and duration of corticosteroids use [56].

Current designs & issues

In September 2012, a published editorial in *Leprosy Review* pointed to the need of new leprosy treatments for MB patients and proposed a randomized trial to compare a monthly dose of rifamficin, ofloxacin and minociclin (ROM) for 12 months with WHO-MDT for MB patients [57].

A small clinical trial with ten MB patients on ROM and 11 on WHO-MDT, both for 24 months, was reported in 2004 [58]. Its outcomes were lesions resolution, BI from SSS, LBI of biopsies and a histological grading method for leprosy incorporating bacillary load and tissue reaction (bacillary index × granuloma fraction). Leprosy reactions were promptly treated with tapering doses of oral prednisolone. No difference was observed between the treatment groups, but it should be remembered that the power of the sample is small.

Some clinical trials focus on erythema nodosum leprosum (ENL) and have as outcome the remission of symptoms and recurrence of reaction [59]. One of the possible treatments used for ENL is clofazimine, which is bacteriostatic, and may contribute to the smaller reincidence rate observed in some studies [59,60]. Other clinical trials focus on corticosteroid treatment of neuritis or decompressive surgery with impairment the main outcome [61–64].

It is important to notice the separation of the disease into two areas concerning its pathology and its treatment: the bacteriological and the immunological. Clinical trials dealing with chemotherapy regimens seldom standardize the management of reactions. Reactions after the patients finish the chemotherapy regimen, when the patient is said to be released from treatment, are often not considered to be related to any bacteriological aspect of the disease. Some authors correlate type 1 reactions after chemotherapy with persistent bacteria multiplication [65] and there is evidence of a positive correlation between the presence of viable *M. leprae* and type 1 reactions [66].

A steroid prophylactic randomized trial demonstrated a 75% reduction in outcome after 4 months of low dose

steroid [67], but at 12 months of WHO-MDT treatment the difference became statistically insignificant. A longer period of steroid prophylaxis along with MDT has not been yet studied. Predicting MB patients with high-risk of new NFI is possible [28,68], and the strongest predictor is previous NFI, which reinforces the need of early diagnosis. Factors associated with the presence of ENL were also studied [69].

Design alternatives

In the first trimester of 2012 there were 181,941 prevalent leprosy cases in the world while 219,075 new leprosy cases were diagnosed during 2011 [70]. These numbers express a huge victory of the implementation of WHO-MDT universal access and also give another dimension to the demand of leprosy treatment, allowing the implementation of new multidrug regimens with higher financial cost, at least in middle-income countries such as Brazil and India, responsible for the diagnosis of nearly 80% of the world reported new cases.

It is important at this point to emphasize that leprosy patients have the same right as other citizens in a specific country. If Brazil distributes highly active antiretroviral therapy for around 250,000 patients each year with twice a year CD4 and viral load testing for each patient, the country can consider leprosy patients to merit the best available technology for their treatment. The health policy to respond to neglected tropical diseases should not reinforce marginalization of affected people or neglect knowledge and evidence production.

The editorial of the March 2012 issue of *Leprosy Review*, the last journal dedicated to leprosy as the main subject, encourages the development of large trials on new treatment regimen [57]. This paper intends to introduce the idea of a comprehensive randomized clinical trial (RCT) to this debate.

It could be very important to develop a RCT with factorial design; the first factor being the immunological portion of treatment and the second the bacteriological portion.

The immunological question to be answered could be whether extending the duration of steroid prophylaxis from 4 to 8 months would block this effect and achieve a similar level of reduction at 12 months [67]. The bacteriological factor involves two questions to be answered: first, "what is the difference between daily and monthly drugs intake?" and second, "when should the antibacterial drug be stopped?" Should a single drug for 6 or 12 months complete the treatment? Should a single drug be added to corticosteroids or other immune modulator in the treatment of reaction after the end of MDT?

In the frequentist framework for RCT, this is an insane and megalomaniac idea, for its cost in money and time. However, if we think about a Bayesian adaptive RCT design, such a study is feasible and viable.

The frequentist approach considers that the unknown parameter is a fixed value, not a random variable. Samples are used to know something about the parameter and samples are random. It would estimate the probability of observing the actual sample value or more extreme results given the hypothesis.

The bayesian approach deals with uncertainty and all uncertainties are measured by probabilities;that is, the probability of the parameter given the sample. This approach allows multiple tests that make it possible to work with an adaptive sample size, that is, the sample size may not be chosen in advance, but based on the knowledge about the parameter that is updated at each group of observations. Other adaptive aspects of a Bayesian RCT is the arm drop strategy, which allows the beginning of a trial with multiple arms that are dropped if its probability of success is very low, or if the difference of predicted probability of a trial success of two arms is smaller than a predetermined value [71,72]. For instance, in the case of treatment A with low cost compared with treatment B with high cost, B would be dropped if its predicted probability of success is less than 20% greater than that for treatment A. Otherwise, treatment A would be dropped. This rule is unbalanced in favor of the low cost treatment.

This example shows that setting decision criteria is part of the design of a Bayesian adaptive clinical trial. In a traditional trial, once the outcomes are defined, the question that remains for the statistical analysis is if the outcome frequency difference between the treatment groups could be explained by chance. In a Bayesian design, the size of the acceptable difference and the probability that will be considered big enough to end the trial must be set.

The main point of controversy about a Bayesian approach is the need of a prior probability distribution that, with the observed data, will result in the posteriori distribution. This prior distribution may be subjective, based on previous data or may be a noninformative prior. Of course, sensitivity analysis about the prior distribution is very important to make the results more robust [73].

The term neglected diseases was meant to point to the lack of permanent control policies and the lack of interest in the study of these diseases. The result is a lot of uncertainties forcing medical conduct and epidemiological control to be based on opinions. Those opinions are based on scientific hypotheses but not on sound evidence. Taking the present weak evidences and expert opinions to build a prior distribution and to settle a set of adaptive rules for a comprehensive RCT would likely produce stronger evidence about leprosy treatment.

A draft of an example of a Bayesian design RCT to help the beginning of discussion follows:

One factor would be a prophylactic immune modulator compared with placebo, the second factor would be the antibacterial drug regimen (intermittent ROM×WHO-MDT or intermittent ROM×daily ROM or the three regimens), and a third factor could be maintenance of one antibacterial drug or different treatment protocols for late reaction episodes. Outcomes would be bacteriological and new NFI. In the beginning of the randomization to include the third factor, probably one of the two arms of the first factor – immune modulator or placebo – will be dropped. Before conclusion of the study, one or two arms of the second factor will probably be dropped. In other words the study becomes simpler as its progress. Any arm drop will likely only be possible based on NFI and not on relapse or SSS results.

The criticism of subjectivism that is currently layed at the door of Bayesian clinical trials can be answered with the sensitivity analysis and with the argument that if you use all disposable information and update it continuously, you will reach the right answer for your questions [74]. The criticism to public health and healthcare subjectivism can only be answered with the argument of tradition.

To use Bayesian approach for a context with many questions, as in neglected tropical diseases, is also an opportunity to test if this approach is really capable of generating good evidence in a setting of financial constraint.

The design of a Bayesian clinical trial requires a skilled statistician as part of the research team. The software WINBUGS developed by the Bayesian inference 'Using Gibbs Sampling' project is a flexible software for the Bayesian analysis of complex statistical models using Markov chain Monte Carlo methods [75].

Facing the health needs of MB patients; leprosy treatment should be handled as a dynamic treatment regime because it requires many other decisions besides the MDT. Dynamic treatment regime is defined as a sequence of decision rules for adapting a treatment plan to the time-varying state of an individual patient [76]. This is the case of the use of any immune modulator and other measures to avoid nerve impairment and to treat reactions.

The main advantage of Bayesian RCT is its adaptive aspect that allows smaller samples, continuous evaluation as the data are produced and early end for futility. The main limitation is the control of the overall type I error rate and the fact that the use of different prior may lead to different conclusions that demands an *a priori* definition of priors.

Some consideration about adaptation of diagnosis & treatment procedures to field conditions in developing countries

Leprosy control is based on early diagnosis and treatment. Theoretically, the elimination of infection sources would result in transmission reduction. Early treatment would also reduce impairments.

The challenge of leprosy control is to diagnose and treat patients who are the poorest among the poor and very often live in areas with little health resources. Leprosy is a stigmatizing condition and therefore the search of medical help is sometimes difficult. Local solutions must be found to face these problems and will involve health education, socioeconomic development, simplification of diagnoses and treatment tools to guarantee population coverage. Today leprosy control is part of primary health care.

The need for sound evidence is coherent with the need for simplification of actions to be conducted in field work. RCTs are instruments to evaluate the efficacy of a treatment and are usually conducted in ideal settings with cooperative patients in order to guarantee compliance with the treatment. The intent is to produce a precise and accurate evaluation of efficacy. Of course the efficacy will not be reproduced in the health system routine usually referred to the field. The result to be observed in the field is considered the effectivity. The effectivity is the efficacy reduced by constrains of field reality that includes access, compliance, equipment and human resources problems. Public health decision makers may trade efficacy for compliance. For instance, a treatment with a 10% lower efficacy may have a 20% higher compliance. However, we have to be aware that the decisions that simplify procedures or reduce costs also reduce the efficacy; and for those decisions to be ethically supported we most know what the trade is. No effectivity is higher than the efficacy, which makes the argument defending the effectivity on procedures with unknown efficacy a hollow one.

Future perspective

In the last two decades, important improvements happened: leprosy is no longer a lifelong disease and leprosy colonies for patient isolation are part of public health history, but leprosy is still a public health problem in many parts of the world due to its high incidence and transmission. The changes on leprosy magnitude in high-incidence areas will probably be apparent many years from now, meaning that the need for patients care will continue for some decades.

The routine treatment of MB leprosy will likely change in a couple of years with MDT that includes more active and less toxic drugs. The huge decrease of case prevalence allows having a more expensive treatment per patient without the need of a important increase of leprosy control budget. The leprosy research community is aware of the need to develop a solid evidences base to support changes of the current practices.

The Bayesian approach is ideal for informed decision making and allows RCT design to include strategies for quantifying the cost of simplification. To advance in leprosy treatment knowledge; revision of the available research would be the first step, for it will allow the establishment of prior distributions to be used in the development of a comprehensive Bayesian clinical trial designed to shed light in those uncertainties.

This moment is an opportunity to change two paradigms. The first is the lack of feasibility to generate sound evidence about leprosy treatment and, the second, the hegemony of frequentist statistical approach.

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Executive summary

- Multidrug therapy including rifampicin to treat multibacillary leprosy created huge optimism for short-term leprosy control. In May 1991, the 44th World Health Assembly adopted resolution 44.9, declaring the commitment of the WHO to attain the goal of global elimination of leprosy as a public health problem by the year 2000. The goal was to reduce the known prevalence of leprosy to below 1/10,000 inhabitants. The pressure to attain this goal resulted in reduction of treatment duration without sound evidence.
- In the last three decades there have been few randomized clinical trials on leprosy treatment. Cohort studies are the base for relapse frequency knowledge. Studies are divided between bacteriological (leprosy treatment) and immunological aspects (reaction treatment) of the disease.
- There is not at present a bacteriological end point to be observed at the end of the treatment; as negativity of slit skin smear takes years to be achieved.
- The assumption that the classification as multibacillary should be based on skin lesion numbers means cohort data are not comparable with older studies.
- Reaction treatment trials have many end points. One important end point used is new nerve function impairment that measures the progression of the neural damage and by consequence impairment progression.
- It is important to develop a randomized clinical trial with factorial design. One factor could be a prophylactic immune modulator compared with placebo, the second factor would be the antibacterial drug regimen (intermittent × daily × WHO-multidrug therapy), and a third factor could be maintenance of one antibacterial drug or different treatment protocols for late reaction episodes.
- Such a study is feasible and viable with a Bayesian adaptive randomized clinical trial design.

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