

The International Tuberculosis Surveillance Research Unit (TSRU): the first 30 years

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THE TSRU is a monument. It is a monument of collaborative efforts, a monument of findings, a monument of consequences, a monument of potential for the future.

THE BEGINNING

The TSRU originated from questions which preoccupied the late Dr. John Meijer, former Director of the Royal Netherlands Tuberculosis Association (KNCV), in the mid-sixties, such as: "What were and would be the most active measures for moving from high to low tuberculosis prevalence in a country? . . ." Dr. Meijer asked a small group of experts to formulate views on the future of the tuberculosis control programme in The Netherlands. These discussions indicated that the problems faced by The Netherlands were also confronting other countries and that the greatest problem in planning future policies in tuberculosis control was the lack of reliable epidemiological information.

Dr. Halfdan Mahler, then chief of the World Health Organization (WHO) Tuberculosis Unit, and later the Director General of the WHO, and Dr. Johannes Holm, then Executive Director of the IUAT* (the former organizer of the International Tuberculosis Campaign and well known for his managerial skills), both showed great interest in the issues. Together with the National Tuberculosis Associations of four countries, they proposed the creation of an international research body under the joint auspices of the WHO and the IUAT: the Tuberculosis Surveillance Research Unit, or TSRU. Seeking a director for the unit, they were impressed by the competence and skill of Dr. Karel Styblo, the co-ordinator of the subsequently famous Kolin study, sponsored by the WHO in Czechoslovakia. They visited Dr. Styblo, and after an hour-long discussion they were convinced that *he* was the man they needed as Research Director of the TSRU.

The main aim of the TSRU is to study tuberculosis epidemiology relevant to tuberculosis control and surveillance. Multiple interactions take place between the tubercle bacillus and its host, but most of them had not yet been characterized at the time. For a long time after the discovery of the tubercle bacillus by Koch, only two phenomena were recognised: overt disease and death from it. In particular, the transmission of tubercle bacilli in a community, the probabilities of developing active tuberculosis consequent to primary infection, the risk of endogenous reactivation or the likelihood of reinfection with virulent tubercle bacilli were not clearly understood. It was particularly important to study these interactions under natural conditions, without interference by direct or indirect control measures such as case-finding and chemotherapy, and then to assess the impact of these measures.

Initially, the research was to be undertaken in *low prevalence* countries to determine what means and procedures had helped these countries to reach a stage of low prevalence. Relevant problems included the interruption of certain measures or the introduction of new approaches in order to attain definitive elimination in their area. In these countries such studies were feasible by virtue of the availability of data, facilities and personnel.

It was understood from the beginning that the studies should be planned in such a way as to facilitate tuberculosis control in *high prevalence* countries as well, by identifying the best policies for tuberculosis control and by avoiding previous errors and the instigation of unnecessary measures. Thus, on request by the WHO in 1980, TSRU included high prevalence countries in their early studies.

The TSRU was thus conceived in 1965 by a handful of concerned tuberculosis workers and born in 1966, with Dr. Karel Styblo as Principal Investigator. The KNCV, with its legendary generosity, provided a working place, administrative support and sustained financial contributions. It also provided an abundance of data from The Netherlands, as well as the input of its tuberculosis officers and researchers. These

* In 1986 the IUAT became the International Union Against Tuberculosis and Lung Disease (IUATLD).

are also provided by the other nations that join the TSRU.

The TSRU is run by the TSRU Directing Committee, which consists of representatives of the IUATLD, the WHO, two representatives of the member countries, the advisors and the Scientific Director of the TSRU. TSRU meetings are held at 12- or 18-monthly intervals. A Progress Report with papers on all items to be discussed is sent to participants prior to meeting.

The TSRU is self-supporting, through contributions of the Tuberculosis Associations or countries that are members. Projects are planned and prepared with the TSRU Director, but are financed by the national bodies. They are analysed by the researchers of the respective countries, in consultation with the TSRU Research Director.

COLLABORATIVE EFFORTS

Collaborative efforts to date have involved 13 countries: the original four—The Netherlands, Canada, Norway and ex-Czechoslovakia—were joined by Sweden, France, Japan, Finland, Germany and Switzerland, and subsequently Algeria, Korea and Tanzania.

The TSRU has benefited greatly from the consultancy of Professor Ian Sutherland of the UK Medical Research Council (MRC) (he was a partner in the risk of infection paper, and he collected and analysed the data on the control group in the MRC BCG trial which helped to characterize the probability of developing tuberculosis after primary infection); from statistical support and computerized data management from Drs. Eva Svandova, Joseph Radkovsky and M. Sampalik of Czechoslovakia; and from data and mathematical modelling by Hans Waaler of Norway (many of the parameters for modelling TB were unknown in the mid 1960s, and studies were undertaken to explore the various indices). Other useful data have been provided by other countries such as Denmark, the UK, the USA, Tanzania, Benin, Uganda, Kenya, and others. Valuable support has also been provided by the successive officers of the WHO TB Unit.

The International Tuberculosis Surveillance Centre (ITSC), a branch of the TSRU, was established in 1972 for *tuberculin surveys*, with Dr. Mattheus Bleiker as Director and Miss Ozrenka Mislejnovic and Miss Ilse Blijker as the reference testers and trainers.

In addition we should acknowledge other well-known contributors to the tuberculosis community who have passed away. Besides Dr. Meijer and Dr. Holm, we cannot forget Dr. Herman van Geuns of The Netherlands who always focused on helping underprivileged countries; Professor Georges Canetti of France, who from the outset stressed with Dr. Holm and Dr. Styblo the importance of the role of the bacillus, providing an excellent understanding of the role of super-infection; Dr. Otto Galtung Hansen of Norway, who gathered such a wealth of basic statistical

data in his country; Dr. Ingela Sojgren of Sweden who, among other things, provided—in a paper on the risk of infection in Sweden—a brilliant study on the role of bovine tuberculosis in human beings; Professor Karel Raska of Czechoslovakia, whose Institute in Prague was involved in the Kolin study and other TSRU activities; and Professor Stefan Grzybowski with his paper on a very successful tuberculosis control programme among the Inuit in the North-Western territories of Canada, and his analyses of tuberculosis infection and disease among Canadian and Inuit contacts. Mention should also be made of Lida, Dr. Karel Styblo's wife, who sacrificed many of her own interests in her devotion to Dr. Styblo and his work.

THE MANY FINDINGS

What is this 'monument' of findings produced by the TSRU? Here are but a few. The TSRU:

- showed the importance of the classification, in different categories, of the various types of cases of tuberculosis—new cases (infectious, sputum smear positive, culture positive, or non-infectious), relapse cases, chronic cases—and it proposed workable definitions for them;
- developed an epidemiological index, the annual risk of infection, which is widely recognised as perhaps the best single index allowing for the dynamic assessment of tuberculosis trends in a community. This index measures transmission, and as such is an extremely useful surrogate marker of the prevalence of sputum smear positive cases in the community;
- calculated the ratio between the annual risk of infection and the rate of incidence of infectious (smear positive) cases, so countries could now accurately assess the dimensions of their tuberculosis morbidity and project their needs for supplies in the national tuberculosis programme;
- translated into quantitative terms the natural history of tuberculosis in the individual and in society: in particular, it calculated the risks from infection to disease and from disease to recovery or death in humans, and it analyzed in depth, especially through population cohorts analysis, the process of elimination of tuberculosis;
- clarified the issue of endogenous exacerbation versus exogenous origin of the development of tuberculosis disease in humans and showed their respective roles;
- made forecasts about the trend, the size and various other aspects of the disease in society, including the impact of the human immunodeficiency virus (HIV) on tuberculosis;
- calculated the 'natural' decline of the disease and the impact of various approaches in detection, prevention and treatment, both in terms of interrupt-

ing the chain of transmission and of relieving human suffering, as well as the yield and worth of various measures and procedures.

Dr. Styblo and colleagues also:

- showed definitively the relatively modest role of BCG in preventing transmission of the disease in the community, the low yield of indiscriminate mass X-ray examinations and tuberculin testing, and the lack of utility of long-term systematic follow-up of patients after completion of a correct course of treatment;
- examined the problem of the patient's delay and the doctor's delay for diagnosis under routine conditions;
- demonstrated the overwhelmingly important role of adequate treatment: curing those patients already detected has priority over further detection of new cases;
- proposed a rationale on the interaction of the tubercle bacillus and humans in the environment of the latter, and I cannot but think that these postulates complement Koch's postulates on the demonstration of the causative role of an infectious agent.

Karel Styblo's postulates were as follows:

- 1 the infectious agent of tuberculosis is in humans, not in the environment;
- 2 the tubercle bacilli can be identified in human sputum;
- 3 sputum can be rendered non-infectious by proper treatment;
- 4 any such reductions in the sources of infection will inevitably reduce the risk of infection and improve the epidemiological situation;
- 5 BCG has only a very minor role in interrupting the chain of transmission, but it can protect children against severe forms of the disease.

Through the above findings, Dr. Styblo made various proposals concerning the main components of a national tuberculosis programme, as regards the monitoring of its functioning and its evaluation (both epidemiological and qualitative). In particular, he drew attention to the interest of cohort analyses of results of treatment among patients, a crucial aspect largely neglected in most health programmes against many infectious diseases.

The Mutual Assistance Programme of the IUATLD,¹ a programme essentially developed by Dr. Styblo, provided the opportunity to put into practice and assess under actual field conditions the various proposed components of a National Tuberculosis Programme, integrated within the general health infrastructure. The Tuberculosis Guide, first published in 1978,² describes both the hierarchy and the alloca-

tion of responsibilities within a national programme; it explains the practical execution of the tasks and evaluation of the programme, including patient cohort assessment, and provides recording and reporting documents.

Dr. Styblo also:

- upheld and initiated the application of short course chemotherapy of tuberculosis in low-resource countries within the framework of the above-mentioned National Tuberculosis Programme. This ensured the efficacy of the therapeutic regimens in the individual patient and on a national scale, and guarded against emergence of resistance of the bacilli. Between 1978 and 1991—when Dr. Styblo retired from the IUATLD—nine such National Tuberculosis Programmes supported by the IUATLD were running in high prevalence, resource-poor countries; these programmes yielded high, never-before obtained therapeutic effectiveness. Indeed, nation-wide levels of cure were obtained year after year, and under the most adverse environmental conditions: over 85% documented quiescence of the disease, with very low levels of failures or relapses, and no increase in measured drug resistance.
- studied the interactions between tuberculosis and HIV infection in humans and in the community. In particular, data collected nation-wide during the past decade in a number of countries with a high prevalence of the two infections have provided a unique basis for analysing the epidemiological and clinical interferences of the two diseases. Moreover, National Tuberculosis Programmes conducted in these countries provide useful operational ideas on the delivery of measures against these two scourges.

THE PRACTICAL CONSEQUENCES

Virtually all of the predictions about the trends for tuberculosis, some of which were made several decades ago, have turned out to be valid and accurate, including Styblo's assessment of the roles of HIV infection and other social and economic factors on the present resurgence of tuberculosis disease in developing and industrialized countries. Furthermore, his proposed target percentages of cure (85%) and detection of smear positive cases (70%) in a community, estimated as the most cost-effective model to limit tuberculosis transmission,² were included in the World Health Assembly Resolution on Tuberculosis (Resolution 44.8) of 13 May 1991.

Here are two different examples of the long-ranging practical consequences of TSRU findings:

- 1 For industrialised, low prevalence countries. The Netherlands may be seen as an example. It was the first country to show the way in the practical application of the TSRU's recommendations. Following

¹ Now in its 4th edition, with 15 000 copies distributed by the IUATLD, in English, French and Spanish.

TSRU findings, the health authorities have, in the past ten to fifteen years:

- discontinued the annual tuberculin testing of schoolchildren (600–700 000 tests/year);
- discontinued systematic, routine X-ray examination of the population;
- discontinued the annual radiological check-up of previously treated tuberculosis cases and of patients with fibrotic lesions of the lung;
- discontinued systematic X-ray examination of teachers;
- discontinued routine drug susceptibility testing on all new tuberculosis isolates;
- introduced universal short-course chemotherapy in the 1970s;
- distinguished, since the early 1970s, data on new cases and relapses among the Dutch and foreign-born populations. Through this practice it was observed in the early 1970s that immigrants had a substantial effect on slowing the downward trend in national tuberculosis *notification* rates, in particular in children and young adults. On the other hand, the trend in the *risk of infection* was hardly influenced, if at all, by the wave of immigrant tuberculosis;
- introduced regular assessment of the application of modern rules for diagnosis and treatment of cases (in particular to attempt to reduce patients' and doctors' delays);
- limited contact examination to the close family circle (extending the circles of investigation only if there were cases in the family).

These decisions resulted in the complete reorganisation of the tuberculosis programme and network of facilities in The Netherlands, freeing in particular many nursing positions, now used for other diseases or conditions. A small number of highly specialized centres has been maintained to sustain expertise. In short, greater efficacy has resulted, together with considerable economic savings. In the last few years the efforts of the specialised centres have focused on immigrants from high prevalence countries, resulting in intensive (active) case-finding and a high (>90%) cure-rate.

- 2 For low resource, high prevalence countries, Tanzania would be an example. This country benefited from the first new model National Tuberculosis Programme which is now being employed nationwide in more than 20 other countries. These programmes constitute the prototype National Tuberculosis Programme which was endorsed by the WHO in its Global Tuberculosis Programme. It has also been advocated by the United Nations Development Programme, by the World Bank and by an increasing number of governmental and non-governmental health agencies.

The TSRU studies have helped to define the current understanding of the epidemiology of tuberculosis, and particularly the transmission of infection. The TSRU model represents a new paradigm for tuberculosis control and elimination, putting clarity, order, logic and priority into the process. It has given us indices to follow and guidelines for monitoring surveillance and elimination. Perhaps most importantly, it has provided this sound prototype for National Tuberculosis Programmes: without this model, we would be in no position to face the present world tuberculosis crisis. Moreover, such programmes, properly sustained over the years, may, it is hoped, be sufficient to curtail the disastrous effects of HIV infection on the transmission of tuberculous infection.

Two more remarks:

- The TSRU has in a way re-established the central importance of epidemiology and statistics, in the preparation and assessment of most public health undertakings, demonstrating how the quantified parameters of the natural history of any disease can provide the clinician with the necessary basis for assessing and choosing new methods of treatment, prevention and detection;
- TSRU studies have been conducted along the traditional principles of all IUATLD undertakings: internationality, independence and apoliticism, multi-centred collaboration, mutual stimulation, quality together with a pioneering approach, partnership with the WHO, and extremely low costs, a remarkable characteristic in the light of the scope of the achievements.

THE DRIVING FORCE

How has this been at all possible?

These accomplishments may be attributed largely to the contributions of Karel Styblo as Director of TSRU. Dr. Styblo's intelligence, competence, skill, lucidity, insight and firmness of purpose were complemented by his incredibly hard work, unflinching courage and energy.

While the TSRU has been a collaborative effort, to which many contribute, it was Karel Styblo who cemented everything together. He is the one who piloted this unprecedented international venture in the field of applied epidemiology, making it so successful and of such wide significance.

The TSRU challenged a number of traditional concepts, occasionally making its findings—and its Scientific Director—unpopular. One example is Styblo and Meijer's paper on the impact of BCG vaccination programmes in children and young adults on the tuberculosis problem.³ The proposition that BCG did little to curtail transmission and the conclusion that mass BCG would not influence the epidemiological patterns were such heretical concepts that even other

TSRU members were sceptical, initially opposing the publication of the paper. With the usual tenacity he displayed once he was convinced of the scientific correctness of his views, Dr. Styblo fought to obtain enough money to start applying short-course chemotherapy (from 1983 onward) in the National Tuberculosis Programme of a low resource country, Tanzania. Associated with improved management of the programme, this step was so successful in improving treatment results and epidemiological patterns that his methods were universally recognised and adopted.

Although his TSRU analyses and National Tuberculosis Programme approach dealt with population groups and communities, the driving principle from which Dr. Styblo never departed is the overwhelming importance of the individual patient or person at risk. This focus has always remained central to Dr. Styblo's fundamental thinking and to his conduct of field interventions. The TSRU has been of extraordinary value for humanity, saving tens of millions of lives and resulting in substantial economic savings.

THE FUTURE

Industrialised nations which are focusing upon elimination of tuberculosis need further guidance. High

prevalence, resource-poor countries need immense support and guidance. The world must be made aware of the bitter risk that tuberculosis may once again become an untreatable, unmanageable plague if the rising tide of man-made multidrug resistant tuberculosis is not stopped promptly and at the global level.

Dr. Styblo has retired. A continuing, vivid TSRU remains a must. It is essential not to lose pace and stamina in these efforts.

Note: A comprehensive list of TSRU publications and reports of sessions can be obtained from KNCV at the following address: KNCV, Riouwstraat 7, Postbus 146, 2501 CC's Gravenhage, The Netherlands.

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