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THE PEOPLE'S DEMOCRATIC REPUBLIC OF ALGERIA

MINISTRY OF HEALTH, POPULATION AND HOSPITAL REFORM

Proposal for new and innovative sources of financing to stimulate research and development (R&D) in respect of diseases disproportionately affecting developing countries

For the attention of Dr E. Renganathan, Secretary of the Expert Working Group, with our compliments and the assurances of our highest consideration

New and innovative sources of financing to stimulate research and development (R&D) in respect of diseases disproportionately affecting developing countries

Most diseases (regardless of classification as Type I, II or III) may **disproportionately affect developing countries** unless measures are taken to prevent, diagnose or treat them using a country-specific approach.

Developing countries increasingly bear a double disease burden: **injuries and noncommunicable diseases** compound the ongoing scourge of communicable diseases and nutritional deficiencies.

In addition, against a backdrop of globalization and increased mobility, no communicable disease can be considered as confined to a specific geographical area. Demographic and economic trends have made the world more vulnerable to epidemics such as tuberculosis, SARS or avian flu, which could affect millions of people in developed and developing countries alike.

The increasing incidence of noncommunicable diseases should also be mentioned. Many new medicines, for example to treat cardiovascular diseases and cancer, could benefit patients in developing countries but are costly and difficult to administer.

Besides treatment, it might be more cost-effective in terms of improving health care in developing countries to explore other approaches such as **inexpensive early diagnostic tools and epidemiological research into etiology and prevention strategies**. It is therefore clear that research priorities regarding **Type I diseases** from the standpoint of resource-poor developing countries will probably differ from those of developed countries.

Act No. 08-05 of 23 February 2008 amending and supplementing General Principles Act 98-11 of 22 August 1998 containing the five-year plan for scientific research and technical development in the period 1998-2002 offers an ideal opportunity to institute root-and-branch reforms made necessary by advances in research in an ever-changing world. The five-year period from 1998 to 2002 specified in Act No. 98-11 of 22 August 1998 has been superseded by a new five-year period (2008-2012).

This Act validates the role of intersectoral commissions as an invaluable tool for the elaboration of relevant national programmes and their periodic implementation, including allocation of financing.

In Algeria, research arrangements differ from foreign models in several important respects. **Financing** is basically provided by the **State**; business, whether public- or private-sector, provides practically no financing.

Innovative sources of financing could involve business, private-sector foundations in the context of public/private-sector partnerships and existing research foundations.

Such initiatives would boost the availability of resources and ensure sustainability. It is vital to increase resources to ensure that research activities are maintained at a constant level, and to establish arrangements to facilitate the mobilization of new financial flows and heighten their impact. A monitoring and evaluation mechanism also needs to be set in place.

It is therefore **vital to invest in health research and health care** to promote economic and social development and roll back poverty.

In the light of the foregoing, **the sustainability of financing** for health research is and remains a **crucial issue**.

Two diseases have been selected as R&D targets, namely cancer (Type I disease) and tuberculosis (Type II disease).

A. Cancer : diagnostic and treatment strategies

The pace of progress throughout the world necessitates and justifies the updating of knowledge and techniques in health training and research, specifically in the field of cancer.

The Algerian Health Ministry attaches particular importance to the introduction of effective arrangements to treat cancer.

To this end, it advocates **training** for health workers who are expected to keep abreast of technical and technological progress in order to be able to provide **at local level** cancer treatment that requires high-tech resources.

The payoff is fewer referrals for treatment abroad, which formerly represented a heavy financial burden for Algeria and was psychosocially traumatic for patients.

The long-term objective is to effect technology transfer via **training**, technical assistance and comparison of experience.

The treatment of cancer in Algeria has made major strides, both at existing facilities and at the new cancer treatment centres which are planned. About 15 cancer treatment centres are planned as one-stop facilities offering a full range of functional investigative techniques (biological and anatomopathology, medical imaging, nuclear medicine) and an extensive range of treatment approaches (radiotherapy, surgery and chemotherapy).

This self-contained approach will facilitate concentration of specialized cancer treatment teams and promote efficient and cost-effective working methods thanks to the **development of consensus-based treatment protocols**.

Accordingly, three major objectives are planned in the course of the next 5 years:

- Institution of a full range of standardized technical facilities in the majority of major population centres and hospitals/cancer treatment clinics to facilitate screening campaigns and early diagnosis;

- Offer patients high-quality treatment for the most commonly occurring forms of cancer in Algeria, perform early diagnosis and thereby improve survival rates among cancer patients;

- Develop new treatment protocols for cancer patients based on advanced or adapted exploratory work or therapies with a view to improving survival rates among cancer patients.

The need for new techniques is reflected first and foremost in the adoption of new treatments, whether technical (e.g. radiotherapy) or surgical, or in the availability of new chemotherapy protocols.

This programme is backed up by international cooperation, for example with the International Atomic Energy Agency (IAEA) (oncology, radiotherapy, nuclear medicine and medical imaging), through bilateral projects that are useful for the purposes of **training and expertise**.

In the context of the Millennium Development Goals, comprehensive control and treatment of cancer will ensure wider accessibility to diagnostic tools and health care, irrespective of geographical location. It will also enable diagnosis and treatment of cancer to aspire to the technical level necessary **for the most effective possible management of this public health problem.** The adoption of new technologies presupposes the medium-term development of diagnostic tools and the availability of new isolated or combined treatment protocols.

Training on cancer treatment intended for substantial numbers of specialists in all disciplines remains a core objective because it will enable Algeria to acquire the human resources it needs to complete its development.

Lastly, the compilation of statistics and the determination of assessment parameters will reflect this policy of developing cancer treatment. The number of patients, their geographical distribution, the average age at diagnosis, the survival rate and the number of diagnostic and treatment procedures will be evaluation criteria.

B. Tuberculosis: diagnostic strategy:

Tuberculosis is a public health priority. A clarification and study protocol will be outlined under the topic of **tuberculosis in Algeria in 2009.**

Extent of the problem

Since independence in 1962, tuberculosis has emerged as a public-health priority in Algeria. In 1964 the annual risk of tuberculosis infection was estimated at 4%, and the incidence of smear-positive pulmonary tuberculosis was very high, estimated at between 250-300 cases per 100 000 of population.

Considerable efforts and resources were subsequently invested to eradicate this scourge. Appropriate political measures were taken very early on by the Ministry of Health. The Tuberculosis Office was inaugurated on 1 June 1964 and the Central Tuberculosis Laboratory in March 1969. In June and July 1969, two decrees made BCG vaccination at birth mandatory and established the principle of free diagnosis, treatment and monitoring of tuberculosis.

The National Tuberculosis Control Programme was inaugurated in 1972, and to ensure decentralization of diagnosis, treatment and administration of the BCG vaccination, the Ministry of Health promoted «health sectorization» in the same year. 210 health sectors were thus created to administer tuberculosis control activities.

The two most reliable epidemiological indicators indicate tuberculosis trends in Algeria and demonstrate the progress made by our country in this area:

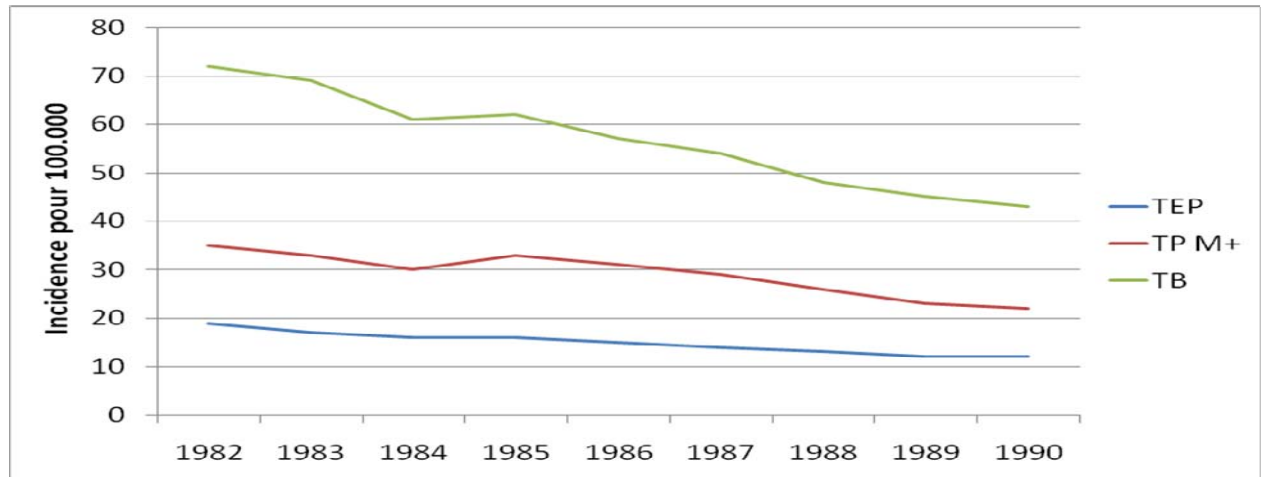
1. The annual risk of infection and the trend over time have been calculated using national tuberculin surveys carried out in Algeria between 1976 and 1989.
2. The prevalence and incidence of tuberculosis calculated by centralized case reporting, in the context of assessment of the national tuberculosis control programme instituted in 1982.

The annual risk of tuberculosis infection fell from approximately 4% in 1966 to 0.22% in 1987, with an annual rate of decline of 7.8% (1).

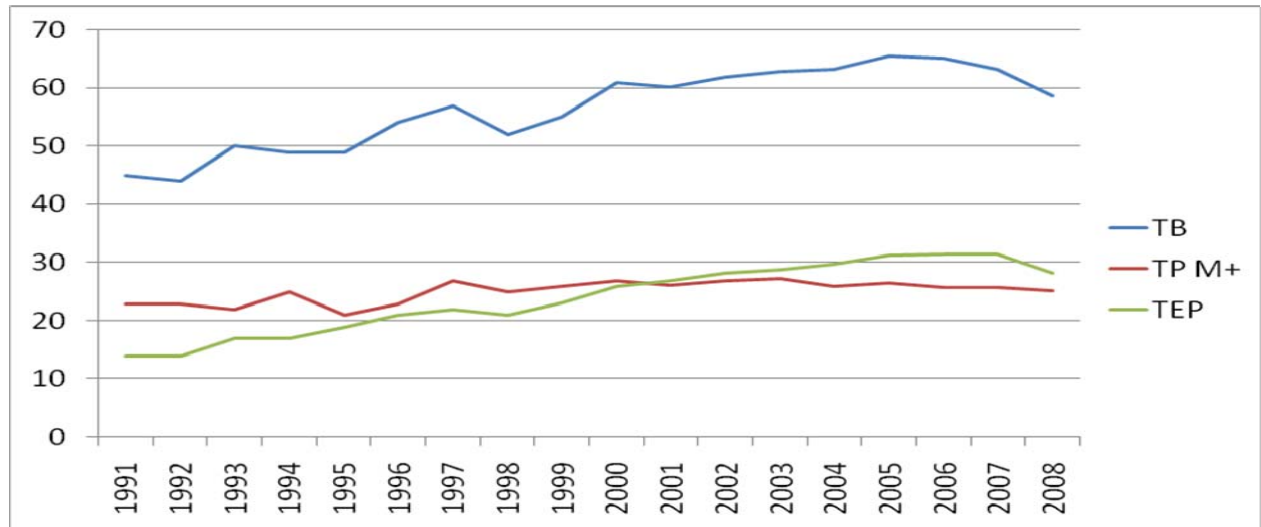
National case reporting results confirm the decline in the annual risk of infection. Between 1982 and 1990, the annual incidence of new smear-positive pulmonary tuberculosis cases per 100 000 of population fell from 35 cases in 1982 to 22 cases per 100 000 of population in 1990, i.e. an annual decline of 7.1% (2).

However, since 1992, centralized reporting of cases has indicated an increase in the overall number of cases of all forms of tuberculosis, whether pulmonary or extrapulmonary.

Evolution des incidences de la tuberculose (pour 100.000 habitants) de 1982 à 1990



Evolution des incidences de la tuberculose (pour 100.000 habitants) de 1991 à 2008



[Top graph: Incidence of TB (per 100 000 of population), 1982-1990

y axis: Incidence per 100 000

legend: EPTB, PTB+, TB

Bottom graph: Incidence of TB (per 100 000 of population), 1991-2008

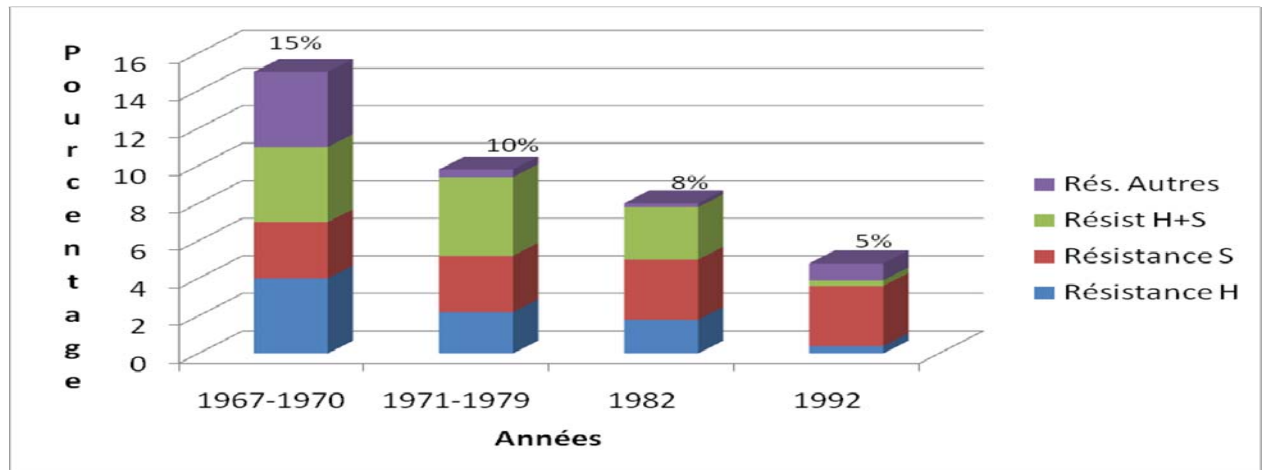
legend: EPTB, PTB+, TB]

Thus the incidence of all forms of TB increased from 45 per 100 000 of population in 1991 to 63 in 2003, whereas the incidence of smear-positive pulmonary tuberculosis increased from 23 to 27.3 between 1991 and 2003 before receding to 25 per 100 000 of population in 2008.

Rural population movements and the deterioration of socioeconomic conditions in urban settings since 1972 cannot alone account for the increase in the incidence of cases of all forms of tuberculosis, especially given that tuberculosis control facilities have carried out their mandate to treat the disease, bolstered by the arrival of increasing numbers of newly trained physicians and public-health specialists. Furthermore, the cumulative prevalence of HIV/AIDS is low in Algeria and its impact on the incidence of tuberculosis is negligible.

In addition, rates of resistance of mycobacterium tuberculosis (or BK) to antibiotics have steadily decreased since the inauguration of the national tuberculosis programme, as the following graph indicates (3):

Evolution de la résistance primaire de 1967 à 1992



[Primary resistance trends, 1967-1992

y axis: %

x axis: Years

legend: Resistance to other drugs, Resistance to H + S, Resistance to S, Resistance to H]

This steady reduction in primary resistance is attributable to standardized regimens of antituberculosis chemotherapy and their widespread application.

The very favourable rates of multidrug resistant tuberculosis (MDR-TB), namely 1.2% in 1988 and 1.4% in 2004, **are below the critical threshold of 3% defined by WHO** and are testimony to the quality of the tuberculosis treatment provided under the national programme.

However, as we have seen above, the incidence of tuberculosis increased between 1991 and 2003 and then stabilized by 2008, when the incidence of all forms of tuberculosis was 58 per 100 000 of population and the incidence of new cases revealed by smear-positive microscopy was 25 per 100 000 of population (Ministry of Public Health, Population and Hospital Reform, Tuberculosis Office).

Although the National Tuberculosis Programme instituted in 1972 has demonstrated its importance and effectiveness, **the current situation requires re-evaluation and further action.**

Work needs to be done in various fields, focusing on:

A- Quality control

1- Tuberculosis case reporting should be monitored both upstream and downstream, from the peripheral level where information is collected to the tuberculosis and respiratory disease monitoring facility, then at the intermediate level at the département-based epidemiology and public-health unit, and finally at the central level. The quality of the data received and the systematic detection of double (or triple) reporting should be priority considerations.

2- Improvement of diagnostic methods through quality control of laboratory microscopy and culturing. Nowadays examination of BK cultures plays a fairly negligible role in diagnosing tuberculosis.

3- Informing and raising awareness of medical and paramedical workers through ongoing feedback of explanatory information and organization of regional and/or national seminars.

B- Epidemiological surveys

Estimation of annual risk of tuberculosis infection and trends over time

It would be useful to carry out a national tuberculin survey using the standard WHO methodology on the same representative samples of population as those randomly selected for the 1980-1989 surveys (1).

C- Research

This has two components :

- Diagnostic methods

New tests are currently available and many researchers use **gamma interferon** to diagnose tuberculosis.

A research project in the form of a doctoral thesis is currently being carried out (Bab El Oued Hospital Chest Medicine Unit). The aim of the project is to compare **the diagnostic value of gamma interferon with the classic tuberculin intradermoreaction test in tuberculous pleurisy.**

There is no doubt that this work would lead to improved diagnosis of extrapulmonary tuberculosis, elimination of overdiagnosis and avoidance of useless and costly treatment for many patients.

- Directed basic research

In recent years molecular epidemiology techniques have prompted considerable interest (21, 22, 23). They are a useful complement to surveys focusing on infectious tuberculosis cases and confirm small localized epidemics of recent, common-source origin arising from one and the same bacterial strain. Comparing data from the conventional epidemiological survey, the socioeconomic survey and the molecular biology findings will give a clear picture of the chain of transmission and the route of infection.

Thus, in the light of the foregoing, we intend to carry out a study entitled **«Long-term survey of tuberculosis in families : the respective roles of socioeconomic conditions,**

genetic factors and histocompatibility» at the Bab El Oued Hospital Chest Medicine Unit in Algiers.

Study protocol

Background

Tuberculosis is a disease of poverty and overcrowding. However, even though the infectiousness of the disease due to the microorganism is the underlying factor in transmission, individual genetic factors almost certainly contribute to the onset of tuberculosis (10, 14,15, 18).

What is the relative significance of these three factors?

The answer to this question will certainly help to break the chain of BK in the community, identify individuals at high risk and prevent the onset of the disease.

The study of tissue groups (HLA) in the onset of tuberculosis has shown a direct relationship between the individual's susceptibility or lack of susceptibility to tuberculosis and his or her family genetic history; however, **contradictory results** obtained by other teams have not enabled these groups to be identified conclusively (4, 5, 6, 11, 12).

The HLA groups most commonly implicated in Europe and Asia are **HLA DR2**, identified as being the most likely to **favour tuberculosis** (12, 13, 19) and **HLA DW3 as protecting against it** (20). On the other hand, in Africa and in the Mediterranean basin, **the groups most frequently implicated are HLA B27 in Greece and HLA A2 and HLA B5 in Egypt** (7).

No work on this subject has been published in North Africa.

However, these findings provide no information about the socioeconomic conditions in which patients live, which is an essential element in the transmission and onset of the disease.

Meanwhile, **molecular biology techniques** have become routine. These supplement the findings of conventional epidemiology, make it possible to trace the path taken by BK through a community and determine whether the infection was recent or the resurgence of a dormant infection.

A study was carried out in Algiers in 1993 to try to identify possible human, socioeconomic and genetic factors that might account for these differences (8). The study involved 186 cases of pulmonary tuberculosis revealed by smear-positive microscopy. Of these, 52 cases were in families and 72 were isolated cases. Various parameters were studied: parental consanguinity, socioeconomic conditions, the severity of radiological lesions and the extent of tuberculin intradermoreaction (IDR).

Despite the small sample size, the results of the study demonstrated that exposure to the disease was higher in families with parental consanguinity.

These findings have prompted us to pursue the matter by recruiting a larger sample of tuberculosis patients from among the population of the health sectors of Bab El Oued and Bologhine in Algiers. The objectives of this project will be:

Primary objective:

To compare the HLA groups of isolated patients presenting with pulmonary tuberculosis with those of patients from families in which at least two cases of tuberculosis (pulmonary and/or extrapulmonary) have been diagnosed with a view to detecting a possible genetic predisposition.

Secondary objectives:

- Identify by microbiological study the genetic profile of acid-fast tuberculosis bacilli (AFB) isolated from index cases in the two groups of patients (isolated and family cases) to study the BK transmission pathways in the community;
- Identify environmentally predisposing factors (overcrowding, socioeconomic conditions), and immunodepressive factors (HIV serology) that could be conducive to the onset of tuberculosis in an urban health district in Algiers.

Expected outcomes

The outcomes of this study could have direct implications for our procedures, because early detection of family cases, which normally constitute chronic reservoirs of microorganisms conducive to transmission of the disease, could provide opportunities for targeted health interventions (chemoprophylaxis).

Fuller knowledge of the genetic profile of tuberculosis patients could help to identify individuals at risk and thus contribute to possible prevention efforts.

Molecular biology could complement conventional epidemiology when analysing the chain of transmission of the disease.

METHODOLOGY

Population studied :

.Index case : the study would include all patients over 15, of either sex, resident in the districts of Bab El Oued or Bologhine, presenting with previously untreated pulmonary tuberculosis demonstrated by microscopy or positive culture, or from any other district of Algiers if they accept the terms of the family study;

. Family study : the study includes first- and second-degree family members: grandparents, parents, brothers, sisters and children;

. Contact individuals : any individual who has shared accommodation with the index case for at least 3 months; professional or school contacts will not be included for ethical reasons.

Measurement instruments:

- 1- Scale of gravity of the disease (radiography to assess severity of radiological tuberculosis lesions carried out by an independent specialist according to the method used by the British Medical Research Council (BMRC) and bacterial load in sputum expressed in terms of AFB/fields;
- 2- Scale for assessing socioeconomic conditions (i.e. socioprofessional categories using the classification of the National Statistics Office and the

scale for evaluating socioeconomic conditions proposed by the British Register 30-91) ;

- 3- Transmission of BK : molecular genetic study of the DNA of the bacillus using the RFLP (Restriction fragment length polymorphism) reference method and/or spoligotyping;
- 4- Study of patient immunocompetence using tuberculin intradermoreaction and HIV serology;
- 5- Detection of an HLA group genetic susceptibility factor in family and isolated cases, in addition to their families and household contacts.

SUMMARY

Tuberculosis has emerged as a public-health priority in Algeria since independence. Measures taken early on by the political authorities (free diagnosis and treatment, free mandatory BCG vaccination at birth, and health sectorization) have been remarkably successful. Thus the annual risk of tuberculosis infection fell from 4% in 1966 to 0.22% in 1987 and the incidence of new smear-positive pulmonary tuberculosis (PTB+) cases fell from 250-300 cases per 100 000 of population in 1964 to 22 cases in 1990.

Concurrently, rates of resistance of BK to antibiotics have fallen steadily. However, since 1992, centralized reporting of cases has shown an increase in the overall number of cases and new PTB+ cases, whereas rates of primary resistance have continued to fall and rates of MDR-TB have remained low.

This situation requires re-evaluation and further action.

The actions to be taken are:

1. **Quality control** focusing on improving upstream and downstream information gathering and consolidating and improving culture microscopy laboratories. Informing and raising the awareness of staff is an essential component.

2. **Epidemiological surveys:** a tuberculin survey should be conducted on a national representative sample.

3. **Research**

- **Diagnostic techniques** : a research project on the value of gamma interferon in diagnosing tuberculous pleurisy (ongoing doctoral thesis).

- **Directed basic research** : BK molecular biology techniques supplementing conventional epidemiology, prompting a proposed study entitled « *Long-term survey of tuberculosis in families : the respective roles of socioeconomic conditions, genetic factors and histocompatibility* ».

This study will focus on smear-positive pulmonary tuberculosis patients at health facilities in Bab El Oued and Bologhine in Algiers.

Two patient categories will be singled out:

- «Isolated» cases with family members unaffected by tuberculosis;

- «Family» cases in which at least one other close family member has pulmonary or extrapulmonary tuberculosis.

The personal and socioeconomic background of the patients, the molecular epidemiology findings and the results of HLA gene analysis will be compared.

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