

Cough up for TB!

The Underfunding of Research for Tuberculosis and Other Neglected Diseases
by the Italian Government





Introduction

In recent months, the public opinion and the media all over the world have highlighted what is being defined as a new health emergency. It is the H1N1 form of influenza that, according to the World Health Organisation's data, has infected over 30,000 people in 74 countries, for a total of 145 certain deaths; the WHO, again, has warned of the risk of a world-wide pandemic.

But alongside a problem like this, widely discussed and in relation to which governments all over the world are taking action, there are dozens of fatal and silent diseases. Silent because they don't make the news, there is nothing new about them. Silent because the public opinion doesn't know about them and because, all too often, politics keeps them out of its radius of action.

Médecins sans Frontières's report on Tuberculosis gives voice to one of these situations. Every year TB causes 1,7 million deaths in the world and about 9 million new infections. Far from being defeated, therefore, TB is still a widespread and dangerous disease.

What is the task of politics and what role can Italy have in the fight against such a persistent disease?

Clearly, as stressed in the report, a first step would be to bring its contributions towards research and development of new drugs in line with European and world standards.

Tackling these ills at their roots, however, means not only fighting specific diseases but also, and above all, eliminating the economic and social conditions that provide a fertile terrain in which they can spread. Defeating forgotten diseases such as TB therefore means working actively in order to improve the living, hygienic, sanitary and nutritional conditions in countries with a high rate of contagion. It is also necessary to start to recognise the innovative steps made by the International community over the last ten years in building new tools such as, first and foremost, the Global Fund for fighting pandemics. But politics can and must also move on other levels, from international organisations to the programmes funded by the European Union up to support, not only of an economic nature, for all those players, starting from Non-Government Organisations, that work in the field, in close contact with the population and with local organisations.

In a few weeks time a G8 summit will be held in Italy.

It is on that occasion that our country can renew its commitment and demand the attention of the great nations of the earth so that certain tragedies stop being "silent", attract the attention of all and sundry and inspire everyone to take responsibility.

Naturally the condition for this to be a legitimate ambition is that, unlike today, once a commitment has been entered into it should be fulfilled and once one's word has been given it should be kept.

It should not happen, a sit does nowadays, that resources intended for the development of the poorest countries, in particular of Sub-Saharan Africa, decrease instead of increasing.

Senator Pietro Marcenaro

Rome, 16th June 2009

Research in Italy for fighting a global disease

As the Italian President has stressed more than once, research is an essential aspect for Italy that cannot be mortified and constantly under-appreciated. In recent years the research projects of the European Union have seen Italian research making a name for itself, not in absolute terms, but considering the limited number of researchers that is a typical feature of our country. Indeed, Italy has secured about half the average European number of projects corrected by the number of researchers in each country. Last year, a process of promotion of young researchers was started, in that it was decided that a certain percentage, for the moment small, of the funds earmarked for research should be allocated by means of competitions in which only researchers under the age of forty can take part. The regulations for distributing the funds for biomedical research managed by the Ministry of Health are being revised, with a view to applying merit-based criteria (also following the protests voiced by researchers in many disciplines demanding a more transparent and more methodologically appropriate distribution of public funds for research). For the fourth year running, the Agenzia Italiana del Farmaco (AIFA – Italian Drug Agency) will complete the funding of independent clinical research projects concerning the effectiveness and toxicity of drugs. The conditions for applying for funds will be indicated precisely in the announcement, and the applicants will be judged on their merits. For the first time, the chairperson of the Research & Development Commission was chosen by a committee of experts who submitted the names of three top-level manager-researchers to the Ministry of Research. We have recalled some recent episodes constituting “innovations” in the management of research in Italy. It is hoped that they are not the result of chance but a stable approach. It must also be recalled, however, that much remains to be done, since the situation is hardly reassuring when compared with that of other European countries. We have too many universities but they do not reach acceptable levels of training of the new professionals; the cultural level of our young people is, on the average, very low. Our industrial research is among the most wanting at European level, with a consequent low number of patents. We are definitely not in the lead in the fields that drive the economy such as electronics, telecommunications and biotechnology. The good intentions of single politicians and administrators are unfortunately not followed by the facts, as one is often forced to admit. It must also be stressed that worries about the situation in Italy should not let us forget the problems of European research. Compared with the United States and above all compared with the vitality of Asia, we are unfortunately the last coach of a train that is unable to work up enough “speed” to compete with other continents. European countries cannot go on each taking care autarchically of their own little garden. European funds for research account for less than 5 percent of Member States expenditure for research. We continue to have the same redundant programmes rather than placing most of our resources in the same “basket” and then redistributing them according to merit and avoiding too many duplications. In the United States the public has spent about 0.40 percent of its GDP to support Research & Development in the biomedical field. European Union countries have only spent 0.17 percent. It is therefore necessary for the single countries to increase the amounts allocated by them, above all, to basic research. The per-head contribution for medical research as a whole should rise gradually from the current 40 Euros to 80 Euros.

It is of course not enough simply to increase the funds. Above all it is necessary to spend them well and to improve co-operation among the various research groups, as well as to share the results promptly. The current academic tendency aimed at exploiting each little step forward commercially does not go exactly in the same direction, as it tends to increase secrecy and to defer publication of the results.

In this context, the principles of fairness and of the global right to health must govern the choice of priorities that need not always (and necessarily) privilege the prevalence of universal needs (burden of diseases). Indeed, it is only with these principles that it is possible to remedy the fact that some diseases are “forgotten”, not only rare diseases but also those that prevail in countries with poor resources. The increase in knowledge acquired along the pathways that, for example, lead to the development and rational use of a drug are not always associated with the frequency of the disease they are meant to treat, but with the molecular, biological and clinical problem, and with the complexity that they are able to clarify and solve. Thus, it may be possible to generalise new knowledge, making it useful also for treating other diseases, in which case it is an investment for better future health of a vaster population. The principles and aims of fairness and health for everyone underlying the initiative launched in 1978 by the WHO for a rational use of drugs, also with an essential list of drugs, are unfortunately still widely disregarded. This includes the treatment of tuberculosis, an “ancient” disease that, in spite of the fact that it still causes two million deaths a year (five thousand deaths every day) has little visibility by comparison with the new influenza pandemic, with bird flu and with SARS; the consequences of which are luckily less serious than those of tuberculosis. Unhappily, tuberculosis represents “normality”, an “expected” disease, with which we have been living for centuries. Tuberculosis is one of the diseases of poverty and sadly is still present among us, threatening us all.

Indeed, according to the WHO there are over nine million new cases of tuberculosis in the world every year (85,000 in the European Union, 5000 in Italy in 2007). The two most effective drugs are still isoniazid and rifampicin. These are two “old” drugs that characterised the history of Italian research in the nineteen-fifties and sixties and this country’s contribution towards global health.

They are two front-line drugs for treating tuberculosis, which kills more people than any other disease caused by a single organism after HIV infection, which is often also combined with tuberculosis. Unhappily, nowadays many cases of tuberculosis are resistant to these two drugs, and it is necessary to use others that are less effective, more toxic and more expensive.

It is therefore from research aimed at developing new and more effective and safe drugs and vaccines that one of the greatest contributions to the fight against tuberculosis should come. This is also a struggle for solidarity, to which Italy can contribute in terms of skills and goodwill.

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Abstract

The World Health Organisation (WHO) has estimated that every year there are over nine million new cases of tuberculosis and 1.7 million deaths¹ deaths (Global tuberculosis control – surveillance, planning, financing). Tuberculosis (TB), often thought to be a scourge of the past, is still present, even in new forms, and strikes not only low to medium-income countries but rich countries, too. The healthcare tools at disposal for tackling this crisis are extremely inadequate. In countries with limited resources, the disease is still diagnosed mainly by examining the expectorate under a microscope. This is a technique developed about 130 years ago by Robert Koch, who discovered the TB mycobacterium. To treat it, we still resort to antibiotics developed decades ago, that generally have serious side effects and require a period of treatment of six to eight months.

Médecins sans Frontières (MSF) has therefore decided to define tuberculosis a “neglected disease” since, in spite of its high morbidity and mortality world-wide, the funding for research & development of new drugs, vaccines and diagnostic tests continues to be drastically insufficient. Tuberculosis, malaria and the other neglected diseases account for 12 percent of the total number of deaths in developing countries, however only 1.3 percent of the new active ingredients placed on the market between 1975 and 2004 (21 out of 1,556) is intended for treating these diseases.

The purpose of this report, drafted by MSF jointly with the Centro di ricerche sulla gestione dell’assistenza sanitaria sociale (CERGAS – Centre for Research into Management of Healthcare and Social Services), is therefore to “map” Italian commitment to research & development for TB and other neglected diseases by analysing Italian funds **allocated to tuberculosis, as well as those allocated to malaria and to other neglected diseases that have a world-wide incidence**. MSF also proposes to stress the crucial role that the Italian Government should take on, in order to close the existing gaps.

In 2007, the World Health Organisation (WHO)’s Stop TB Partnership launched a Global Plan to Stop TB quantifying at 8.5 billion Euros the funds needed, over a period of ten years, for R&D of drugs, vaccines and diagnostic tools for TB.¹¹ This figure is equal to 850 million Euros a year. Many, however, feel that this estimate is incomplete. For this reason, MSF refers to a more recent estimate (2009) supplied by the Treatment Action Group (TAG). In its document “Analysis of TB funding trends”, this organisation quantifies the funds needed for TBC R&D at about 1.45 billion Euros (1.8 billion dollars) a year.¹¹¹

In Italy, the main sources of public funding of research consist of the Ministry of Labour, Health and Social Policies, the Ministry

for Universities and Scientific Research (MIUR) and the Regional Councils. Furthermore, starting in 2006, the Agenzia Italiana del Farmaco (AIFA – Italian Drug Agency) has initiated a project for funding independent clinical research on the subject of the efficacy and toxicity of drugs. Also starting in 2006 (Act of Law n° 266 of 23rd December 2005, Article 1, sub-section 337), a new funding mechanism was introduced based on the possibility given to citizens to earmark 5 per thousand of their personal income tax to non-profit-making organisations, including research organisations.

1. In 2007 the Ministry of Labour, Health and Social Policies funded biomedical research activities for an amount of about 301 million euros.

2. As already mentioned, the AIFA has set up a fund for independent clinical research, into which 5 percent of the promotional expenses of pharmaceutical companies is paid. In 2006 about 35.5 million euros were assigned by AIFA to independent clinical research, while only 173,150 euros were allocated to neglected diseases.

3. The information concerning direct funding by the MIUR is limited and only available with a delay of several years. 70 to 80 per cent of the research activity carried on by the Consiglio Nazionale delle Ricerche (CNR – National Research Council) through its Centres scattered throughout Italy also depends on the MIUR. In this case, the only estimate of the available funding, originating from the CNR’s financial statements made available by the State Audit Court amounts to about 86 million euros for the year 2005, and is approximate.

As far as concerns in particular research activities referred to neglected diseases, in the three-year period 2007 – 2010 the CNR received funds amounting to € 406,330 from the MIUR for creating a “multi-parameter nanotechnological diagnostic platform for transferring innovative molecular markers to a clinical framework” targeting a number of infectious tropical diseases (dengue, Chagas disease, etc). To this amount we must add € 57,000 for a “Strategic study for the construction of a therapeutic anti-tuberculosis vaccine of the regional type, in-vivo monitoring and analysis of the clinical strains of Mycobacterium tuberculosis and study of the innate mechanisms of immunity to tuberculosis”. The last funds supplied in 2006 by the MIUR to the CNR for research correlated with neglected diseases, amounting to € 24,000, referred to the detection of “Micro-RNA in clinical samples of Mycobacterium tuberculosis isolated from patients with drug-resistant TBC, and analysis of their possible role in the onset of drug resistance”.

The analysis carried out by MSF jointly with CERGAS revealed that the Italian funding for research into neglected diseases is far

to low. Through the Ministry of Labour, Health and Social Policies and the Ministry of Education, Universities and Research, in 2007 the Italian government assigned 381 million euros to biomedical research. To these funds we must add the 46.8 million euros allocated to biomedical research organisations originating from the “5X1000” system, giving a total budget of 427.8 million euros allocated to R&D activities in the biomedical field in Italy.

The public budget allocated by Italy to biomedical research in 2006 is paltry if compared to the investments in research by private enterprises, whether philanthropic or industrial.

We should consider, for example, the 171 million euros placed at disposal by bank-owned foundations and the 1.07 billion euros invested by the pharmaceutical companies (figure provided by Farindustria 2005) in Research & Development. Based on the data acquired by MSF and CERGAS, it appears that in Italy, in 2007, 31,131 million euros were allocated to research into tuberculosis and other neglected diseases, that is to say a mere 7.27 percent of the public funds earmarked for biomedical research.

Italian public funding of Research & Development for tuberculosis and neglected diseases is therefore seriously insufficient. What is more, the complexity of the structure through which this funding is provided does not enable a precise evaluation of the proportion of the total annual budget for biomedical research actually assigned to that field.

Italy should therefore make an effort to give these diseases priority, when allocating funds, so as to create and support a research agenda inspired truly by global public health needs. Furthermore, Italy should make a commitment towards working out alternative mechanisms other than patents to encourage research into tuberculosis and neglected diseases. One example of an alternative mechanism is the *prize fund*, a mechanism of financial rewards that would separate remuneration for the innovation from market returns. Another is *Advanced Market Commitment* (AMC), according to which a financial commitment is made while new drugs and vaccines are still in the development stage to purchase them in future. The Italian Government has undertaken in 2009 to contribute towards the AMC for a pneumococcus vaccine with the amount of 635 million dollars, that is to say a considerable portion of the 1.5 billion dollars placed at disposal world-wide for this initiative. Although this Italian investment in the fight against one of the main killers active in developing countries is acknowledged and welcome, it is important to stress that the AMC system has significant limits. It does not encourage the initial stages of research and, in the case of the AMC for the pneumococcus vaccine, it does not guarantee access to the end product in medium-income countries.

Recommendations:

- It is necessary to increase transparency with regard to Italian public funding of biomedical research in general, and specifically to research into tuberculosis and neglected diseases. The process of collecting these data by MSF and CERGAS, proceeded extremely slowly, unlike similar activities in other European Union countries.

- It was not always possible to determine precisely the amount of public funds actually allocated to tuberculosis and to neglected diseases since, often, the organisations concerned found it quite difficult to monitor the thematic destinations of the funds.

- It is also recommended that the Italian Government should promote other mechanisms as alternatives to patents for R&D, to encourage research into tuberculosis and neglected diseases, separating the reward for the innovation from market returns. Italy could, for example, contribute towards the creation of a prize fund for developing an effective tuberculosis test easy to use at decentralised health facilities.

Introduction

The purpose of this study, conducted by MSF jointly with the CERGAS, is to map the Italian commitment in terms of Research & Development into TBC and neglected diseases by analysing Italian funding in detail.

Thus, after mapping the sources of funds for biomedical research in Italy in general, public funding (through the Ministry of Labour, Health and Social Policies, the MIUR, Istituto Superiore di Sanità and the AIFA) for Research & Development into new drugs or diagnostic tools for tuberculosis (TB), malaria and neglected diseases (as defined by the World Health Organisation) is then examined in greater detail.

Chapter One describes the reasons that led Médecins sans Frontières (MSF) to monitor at International level public funding of Research & Development (R&D) of drugs, diagnostic tools and vaccines for TB, malaria and other neglected tropical diseases by the European Union and some European governments. This report is part of that cycle of studies, conducted in 2008 and 2009.

Chapter Two describes the methodology used in drafting this report. The study was conducted by means of:

- a)** analysis of documents and of the databases available care of the Ministry of Labour, Health and Social Policies, the Ministry for Universities and Research, ISTAT, the Regional Councils and the Organisation for Economic Co-operation and Development (OECD);
- b)** several semi-structured key informant interviews;
- c)** for the part concerning international comparisons, analysis of reports drafted in the framework of MSF's Campaign for Access to Essential Medicines.

The documentary analysis and the interviews were carried out by a research group of the CERGAS of Luigi Bocconi University in Milan.

Chapter Three analyses at a general level Italian government funding of health research, focusing on dimensional but also sectorial distribution, both at the level of in-house activities and at regional level.

Chapter Four describes the sources of funding of health research in Italy and the beneficiaries of the funds, analysing the problems that make a complete quantitative analysis of the data obtained from public sources very difficult.

Chapter Five analyses the funds allocated to health research by the Ministry of Labour, Health and Social Policies, describing the decision-making processes and the stakeholders involved, as well

as any bodies entrusted with co-ordinating the various funding initiatives. This part also examines the necessary financial needs and the criteria actually used in allocating the resources, by:

- a)** analysing the formal criteria stated by the financial backers in the official documents;
- b)** analysing the funding actually provided and the assessments of the results of the health research in recent years in relation, specifically, to the funds provided by the Ministry of Labour, Health and Social Policies, by the AIFA and by the Istituto Superiore di Sanità.

Possible alternative mechanisms for encouraging Research & Development of new drugs, vaccines and diagnostic tools for tuberculosis and neglected diseases are also briefly mentioned.

The report ends with a number of recommendations and operational proposals for the Italian Government, for the purpose of finding an adequate response, through the allocation of funds for research and development, in the struggle against tuberculosis, malaria and other neglected tropical diseases.

Médecins sans Frontières has full responsibility for the contents of this report

1.

The reasons for this report

The healthcare needs of the poorest continue to be ignored

Médecins sans Frontières (MSF) personnel often experience in the field a situation of profound frustration due to the lack of suitable therapeutic tools for treating patients with tuberculosis or so-called neglected diseases such as Chagas disease. The main reason for this situation is that research for the purpose of developing new drugs, vaccines and diagnostic tests for neglected diseases (see below) is seriously insufficient.

Tuberculosis: obsolete tools

The World Health Organisation (WHO) has estimated that every year there are over nine million new cases of tuberculosis and 1.7 million deaths^{iv} (Global tuberculosis control – surveillance, planning, financing). Tuberculosis (TB), often thought to be a scourge of the past, is still present, also in new shapes and strikes not only medium to low-income countries but rich nations as well.

The appearance and spreading of strains resistant to the drugs most commonly used to treat TB, as well as the rapid spreading of the disease among HIV-positive people, have increased exponentially the difficulty of diagnosing and treating it. With regard to therapy, we still use antibiotics developed decades ago, which generally have serious side effects and require a treatment period of six to eight months.

The healthcare tools at disposal for tackling this crisis are extremely inadequate. In countries with limited resources TB is still **diagnosed** mainly by examining patients' expectorate under a microscope. This technique was developed about 130 years ago by Robert Koch, who was responsible for discovering the TB mycobacterium, and consists of searching for TB bacilli in patients' expectorate under the microscope. In actual fact, only half the cases of TB can be detected by examining the expectorate, and in particular it is not possible to diagnose TB in this way in patients with a HIV-TB co-infection, who are those at the greatest risk of death.^v Similarly, we continue to resort to the BCG (Bacillus Calmette-Guérin) **vaccine**, developed by the Pasteur Institute in the early 20th century. This vaccine is effective only in very small children, who rarely transmit the disease, and therefore has hardly any epidemiological impact at all.

As for **treatment** of TB, we still rely on antibiotics developed decades ago. The treatment is very hard-going for patients, as it causes considerable side effects and has to be followed for at least six to eight months. Every year however, there are about half a million new cases of multi-drug resistant TB (MDR-TB), treatment of which is even more unpleasant, entailing daily injections for six months and a treatment period of at least 18 to 24 months, during which a number of different drugs are administered, some

of which have debilitating and serious side effects. What is more, not more than 70 percent of patients with MDR-TB manage to recover.^{vi}

To make things worse, starting in 2006, some extensively drug resistant strains of TB (XDR-TB) strains have been identified.^{vii} Unfortunately, these patients have very little likelihood of being cured. HIV-TB co-infections are also an enormous problem, as far as concerns both diagnosis and treatment. The number of cases of TB in countries with a high prevalence of HIV have tripled over the last 15 years and there are at present 11 million people with both diseases.^{viii}

The current situation with regard to TB at global level is due to a great extent to the fact that research has been neglected for decades. By way of example, while 8.5 billion Euros would be needed to deal with TB, at present a total of only about 344 million euros are invested. Thus, the International community has enabled TB to become a world-wide health emergency.

Malaria: half the world is at risk

Roughly half the world population is at risk of catching malaria, in particular the populations of low-income countries. Every year there are about 250 million cases of malaria, and approximately 880,000 deaths. Pregnant women and children under the age of five are the two groups exposed to the greatest risk of complications, and every 30 seconds a child dies of malaria. Yet malaria can be treated, and therefore all these deaths could be prevented.^{ix}

As far as concerns treatment, the traditional anti-malaria drugs, such as chloroquine and sulphadoxine/pyrimethamine, have become ineffective in most contexts characterised by high morbidity and mortality rates, and have been gradually replaced (sometimes with considerable delay) by treatment based on derivatives of artemisinin. It is, however, not possible to exclude the future development of resistance to the new drugs in the long term, if only because resistance to antimalaria drugs has occurred in the past with almost every drug used to treat this disease. Since all the latest generation of antimalaria drugs belong to the same pharmacological category, if resistance to the derivatives of artemisinin develops, there will be no alternative drugs for treating malaria. It is therefore essential not to repeat the mistake made with tuberculosis: research into new treatments must not be neglected. Lastly, research into a vaccine for malaria is proceeding. However, the first vaccine will presumably not be available on the market for several years yet, and might have a low level of effectiveness.^x

The other neglected diseases: an alarming picture

The typical feature of so-called “neglected diseases” is that they affect populations living in conditions of poverty. According to the World Health Organisation (WHO), over one billion people (one sixth of the world population) have one or more neglected diseases.^{xi}

The following are considered neglected diseases by the WHO:

Buruli ulcer;
Chagas disease (trypanosomiasis americana);
Dengue/ Dengue haemorrhagic fever;
Dracunculiasis (Guinea worm infection);
Fascioliasis;
African human trypanosomiasis (also known as sleeping sickness);
Leishmaniasis;
Leprosy;
Lymphatic filariasis;
Forgotten zoonoses;
Onchocercosis;
Schistosomiasis;
Helminthiasis transmitted by orofecal microbes;
Trachoma;
Framboesia (yaws).

Potentially, some of these diseases, as in the case of Guinea worm infection, could be eradicated. For some, in particular, such as leishmaniasis, Chagas disease or sleeping sickness, there are no effective and safe drugs because Research & Development has been completely neglected by the private sector due to the fact that these patients (who live in areas of extreme poverty and often in war zones) do not constitute interesting “markets”.

It should be remembered, lastly, that the definition “neglected disease” is used in different ways by different organisations, and even within one and the same organisation. While there is a general consensus as to the fact that the diseases classed as “neglected diseases” by the WHO are indeed such, some maintain that TB, malaria and AIDS are also neglected diseases.

MSF has decided to define tuberculosis and malaria as “neglected diseases”, together with the others, since in spite of their high morbidity and mortality, funding for Research & Development of new therapeutic tools remains insufficient. Matters are different for HIV/AIDS, a disease for which there is no lack of investments in Research & Development – although what is lacking is a mechanism able to ensure universal access to treatment: almost 70% of those who require antiretroviral therapy are not receiving it yet. Furthermore, paediatric HIV, which is prevalent only in developing countries, could be considered a neglected disease since investments aimed at developing effective tests for babies under the age of 18 months and suitable paediatric formulations are insufficient.

An inadequate global Research & Development system

Although tuberculosis, malaria and neglected diseases account for 12 percent of the total number of deaths in developing countries (DC’S), only 1.3% of the new active ingredients put onto the market between 1975 and 2004 (24 out of 1,556) were meant for treating these diseases, and only three were for TB.^{xii}

There is a very simple explanation for the serious shortage of tools for fighting tuberculosis, malaria and the other neglected diseases: since the people with these diseases are poor and therefore unable to buy expensive drugs, they are not an interesting market from the commercial point of view. For this reason, most drug companies, in which investments are normally guided by profit, have concentrated their activities on more “profitable” diseases that affect mostly patients in rich countries.^{xiii}

The World Trade Organisation (WTO) has attempted to identify a global system for stimulating innovation by applying patent protection on a world-wide basis, also in the pharmaceutical field. The TRIPS (Trade-Related Aspects of Intellectual Property Rights) agreement was signed in 1994. Notwithstanding, in the pharmaceutical industry the TRIPS agreement never really stimulated innovation. Indeed, over the years the number of so-called “me-too” drugs (introducing very minor or negligible innovations as compared to existing drugs in the same category) seems to have multiplied.^{xiv}

Tuberculosis in Italy

The epidemiological situation in Italy (defined by the Ministry of Health’s system for notifying cases) features a low incidence in the population at large, a concentration of cases in some specific risk groups and in some specific age groups and the emergence of multi-drug-resistant strains of tuberculosis. Between 1995 and 2006 the incidence of tuberculosis in Italy decreased slightly, from 10 cases per 100,000 inhabitants (1995) to 7.47 cases per 100,000 inhabitants in 2006, which is slightly higher than in 2005 (7.1). This places Italy below the limit defining countries with a low prevalence (10 per 100,000). Overall, in 2006 4,387 cases of tuberculosis were reported in Italy, of which, however, 46.2 percent in non-Italian citizens. There are, however, doubts as to the reliability of this information.

In Lombardy, a capture-recapture study based on notifications, lab reports and hospital discharge sheets indicated that the figures were underestimated by 32 percent. Serious problems, therefore, persist in Italy with reference mainly to the following: **a)** failure to comply with the obligation to notify cases; **b)** frequent delays in diagnosing or failure to diagnose the disease due to the sometimes non-specific symptoms and the low level of perception of the problem on the part of the new generation of clinicians; **c)** microbiological diagnosis, services being sometimes not very reliable and not evenly distributed throughout the country; **d)** failure to monitor the outcome of the disease; **e)** lack of national epidemiological data on drug resistance.

The Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH), created by the WHO in 2006, has stated that for "... diseases affecting millions of poor people in developing countries, patents are not a relevant factor or effective in stimulating R&D and bringing new products to market".^{xv}

The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), too, maintains that "Greater funding is required in the field of R&D of drugs for neglected diseases. (...) Since these diseases affect the poorest developing countries, there is a lack of the opportunities to develop profit able to attract investments in R&D activities for so-called "normal" diseases, or such opportunities are connected with higher levels of risk that do not encourage investments".^{xvi}

Public responsibility

The role of the public sector is essential. After all, it is governments that are responsible for promoting an R&D agenda addressing the needs of global public health. Although research into neglected diseases, including malaria and tuberculosis, has received considerable thrust in recent years thanks to support from the private philanthropic sector, it must be remembered that this funding is not necessarily sustainable in the long term, and there is a risk that it will turn out to be insufficient for meeting global needs.

Public players should therefore take direct responsibility for funding the Research & Development of drugs, vaccines and diagnostic tools meeting the needs of the populations of developing countries; and should create suitable mechanisms for encouraging the private sector to invest in this type of research.

European states, including Italy, have stated on various occasions their will to take on this commitment. In 2000, in particular, the European Union's agenda in Lisbon set the "Barcelona target": to increase R&D investments to 3 percent of the GDP within 2010.^{xvii}

Furthermore, the two years of proceedings of the WHO's Intergovernmental Working Group (IGWG) ended with the approval of the Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property, adopted in May 2008 as Resolution 61.21 by the World Health Assembly (WHA).^{xviii}

With this motion, the Member States commissioned the Director General of the WHO to:

"establish urgently a results-oriented and time-limited expert working group to examine current financing and coordination of research and development, as well as proposals for new and innovative sources of funding to stimulate research and development related to Type II and Type III diseases and the specific research and development needs of developing countries in relation to Type I diseases".¹

Médecins sans Frontières and tuberculosis

Médecins sans Frontières (MSF) has been dealing with tuberculosis ever since it first started its activities over 35 years ago. Up to now, MSF – often jointly with National health authorities, has treated TB patients in 31 countries and in a broad variety of contexts, from shanty towns to rural areas, from prisons to refugee camps. In many of its projects MSF has tried to supply

patients with HIV and TB with integrated treatment. The number of patients with multi-drug resistant TB has also increased: from the 11 patients treated by MSF in 2001 to the 574 of 2007, in Uzbekistan, Georgia, Armenia, Kenya and South Africa.

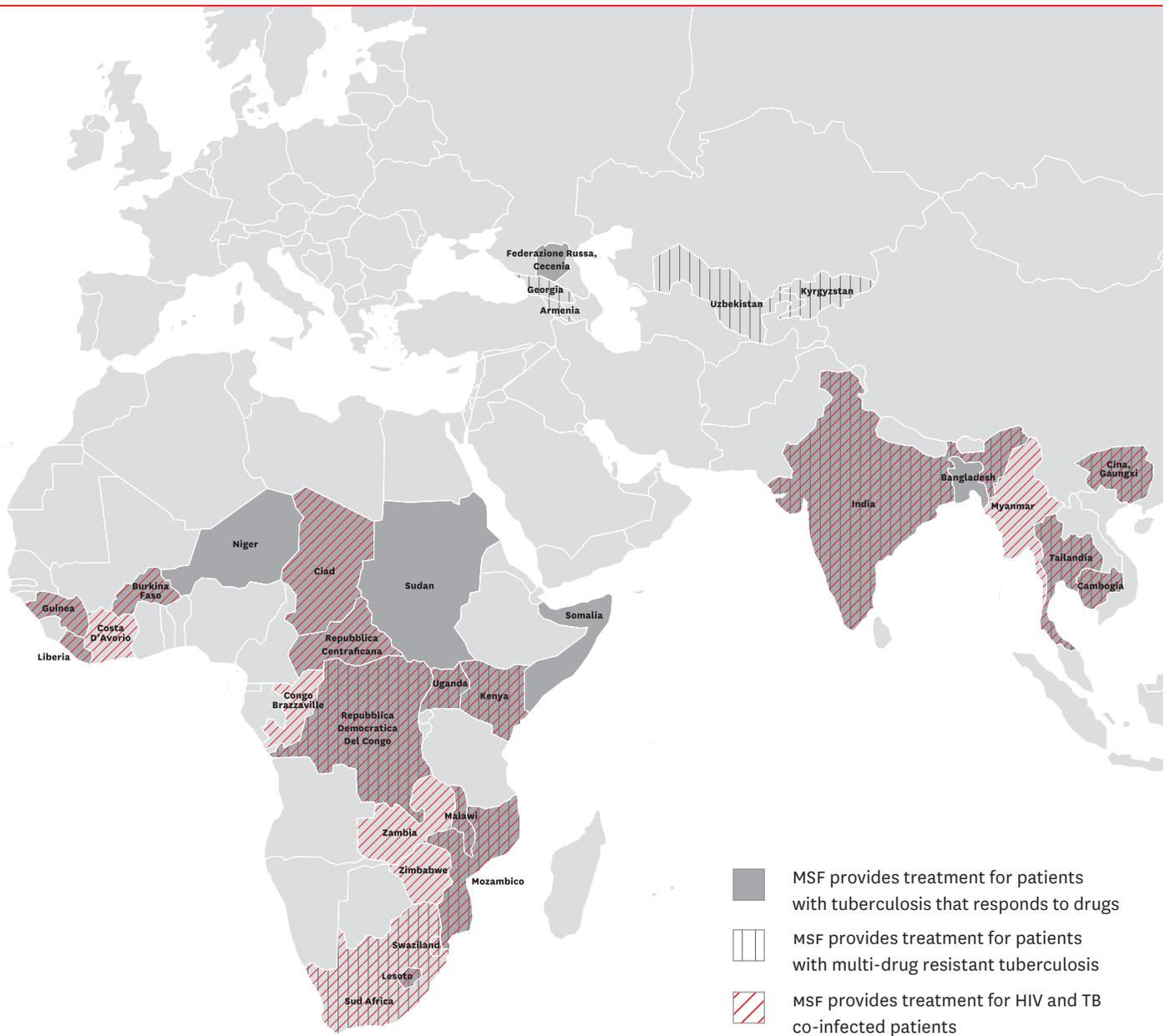
In 2007 MSF treated over 26,000 people with TB.

Tuberculosis in Italy

The Italian epidemiological situation (defined by the Ministry of Health's system for reporting cases) is characterised by a low incidence in the population at large, a concentration of cases in some specific risk groups and in some specific age groups and the emergence of multi-drug-resistant strains of tuberculosis.

Between 1995 and 2006 the incidence of tuberculosis in Italy recorded a slight drop, from 10 cases per 100,000 inhabitants (1995) to 7.47 cases per 100,000 inhabitants in 2006, which was slightly higher than in 2005 (7.1), although it did, in any case, place Italy below the limit classing it as a country with a low prevalence (10 per 100,000). Overall, in 2006, 4,387 cases of tuberculosis were reported in Italy, of which 46.2 percent in non-Italian citizens. There are, however, doubts as to the reliability of this information since in Lombardy, a capture-recapture study based on notifications, lab reports and hospital discharge sheets indicated that the figures were probably underestimated by 32 percent. Serious problems, therefore, persist in Italy with reference mainly to the following:

- a) failure to comply with the obligation to notify cases;
- b) frequent delays in diagnosing or failure to diagnose the disease due to the sometimes non-specific symptoms and to a lack of experience on the part of the new generation of clinicians;
- c) microbiological diagnosis, services being sometimes not very reliable and not evenly distributed throughout the country;
- d) failure to monitor the outcome of the disease;
- e) lack of national epidemiological data on drug resistance.



¹ Type I diseases are present both in developed and in developing countries with high levels of vulnerable population. Examples of contagious diseases such as measles, hepatitis B and *Haemophilus influenzae* type b (Hib) abound, as well as various non-contagious diseases (e.g. diabetes, cardiovascular diseases and tobacco-related diseases). Type II diseases are present both in developed and in developing countries, but with a substantial proportion of cases in the latter. Examples are HIV/AIDS and tuberculosis: they are present in both rich and poor countries, however developing countries account for over 90% of cases. Type III diseases are present, overwhelmingly or solely,

in developing countries, like sleeping sickness (trypanosomiasis) and river blindness (onchocerciasis) in Africa. Very little R&D is carried out for these diseases and practically none for commercial purposes. New technology for these diseases is often discovered by chance, as when a veterinary medicine developed by Merck (ivermectin) proved to be effective in controlling human onchocerciasis.

Type II diseases are often defined *neglected diseases* and Type III diseases *very neglected diseases* (definitions taken from the CIPIH Report, page 26).

2.

About this report and its underlying methodology

This is the fourth of a series of reports published by MSF, aimed at monitoring public funding on the part of some European governments and of the European Union of Research & Development of drugs, diagnostic tools and vaccines for tuberculosis (TB), malaria and other neglected diseases. These reports propose to assess the extent to which European countries are facing up to their responsibilities in developing a research agenda (basic, translational and clinical research) addressing global public health needs. This report illustrates and analyses Italian government funding of Research & Development (R&D) for neglected diseases, in terms both of the amount of funds and of the manner in which they are disbursed.

Methodology

The report is focused on the years 2007 and 2008. All the departments of the Italian Ministry for Foreign Affairs concerned with development co-operation and Italian government agencies have been considered, as well as the intermediate funding organisations and the beneficiaries of financial support for R&D. We interviewed about 35 key informants from the same number of government institutions and organisations, of society, of the academic world and of companies.

In defining the amounts invested in research, the following parameters were set:

The reference year is 2007, however the 2008 data were also considered when the funding had effects on more than one year;

- only the amounts of money actually disbursed were entered, not those that were merely earmarked;
- for multi-year projects it was assumed that the funds were disbursed in a linear fashion for the whole duration of the project;
- basic research was included when it was referred specifically to one of the diseases considered;
- the quality and the value of the research was not evaluated; rather, it was assumed that the available funding tools were functional to supporting research meeting scientific standards;
- the purpose of the study was to identify the proportion of R&D in Italy that was financed by the Italian Government;
- the data used in the report were submitted to all the key informants for comments and corrections before publications. Any and all such comments and corrections have been incorporated into or highlighted in the report.

The following limitations and difficulties were encountered:

- while some interviewees placed the requested data at disposal in real time, others found it difficult and in some cases impossible to find the exact data;

- some interviewees were unable, due to internal policies or regulations, to share the data freely with MSF, and therefore provided only general data or estimates;
- many of the fund providers interviewed allocate funds on the basis of the financial period rather than on the solar year; for this reason the report combined the 2006/07 data and 2007/08 data so as to cover the solar year. In one case the interviewees were not in a position to supply data for the financial period 2006/07 and the total expenditure for 2007/08 was therefore used as a value for the solar year 2007.

3.

Health research in Italy

Health research funded by the Ministry of Labour, Health and Social Policies

The resources for health research funded by the Ministry of Labour, Health and Social Policies are defined by the Italian Parliament every year in the Budget Law.

The total amount should be, in accordance with Legislative Decree 502 of 1992, equal to 1 percent of the funding for the Italian National Health System (Sistema Sanitario Nazionale – SSN) (funds allocated to the National Health Fund). The Ministry of Labour, Health and Social Policies finances the health research activities that fall within the definition of so-called current research and targeted research. Current research has the aim of “developing in time essential knowledge in specific fields of biomedicine and public health”, while targeted research should implement the goals of health research defined by the strategic lines of the National Health Plan (Legislative Decree 502/1922, Article 12, and subsequent amendments).

In addition to this, specific initiatives can be indicated at political level that the Ministry of Labour, Health and Social Policies is obliged to finance. For example, 5 percent of the Ministry of Labour, Health and Social Policies’ health research funds (equal to over 15 million euros for 2007 and 28 million euros for 2008) was earmarked, with a decree issued by the Prime Minister and the Ministries of Health and for Universities and Research, for researchers under the age of 40. Similarly, in 2006 resources (amounting to 100 million euros) were earmarked for an extraordinary country-wide oncological research programme. Lastly, the Ministry of Labour, Health and Social Policies also manages the resources supplied to research organisations originating from the mechanism known as “5 per thousand” by which citizens can donate 5 per thousand of their personal income tax to such organisations.

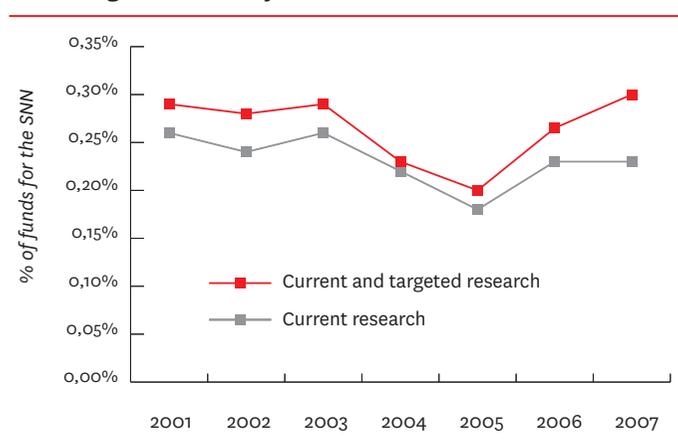
Funding trends of current and targeted research in recent years

In recent years the funds assigned to health research by the Ministry of Labour, Health and Social Policies rose from the approximately 220 million euros of 2000 to about 301 euros in 2007, with an annual growth rate of about 5.8 percent. This average is the result of years in which funding grew considerably, as, for example, in 2006 (+31.8 percent), and others in which it grew little, or even decreased, as in 2004 (-21.8 percent). Funding of health research in the period from 2000 to 2007 accounted for a share variable from 0.21 percent to 0.34 percent of the funds for the SSN, and in these years it always has grown less than funding of the SSN, except for the last two years (2006 and 2007). Indeed, while funding for the SSN grew in nominal values by an average of about 5.5 percent a year, funding of health research went up and down somewhat (Figures 1 and 2). In recent years, therefore,

funds for health research were always less than was called for in Decree 502 of 1992. It is also obvious that the decisions referred to allocations for health research are not correlated with funding of the SSN but are the result of ad hoc political decisions.

The trends followed by funding of current research and that of targeted research were very different. While funding of current research grew on the average by 3.9 percent a year, and in two years, 2004 and 2005, it dropped by almost 10 percent, funding of targeted research grew on the average by 20.2 percent a year with peaks of growth of about 60 percent in 2006 and of 74.8 percent in 2007. The share of the total funds allocated to targeted research rose from 23.2 percent in 2000 to 34.6 percent in 2007. Thus, there was a tendency towards an increase in the proportion of funds allocated to targeted research.

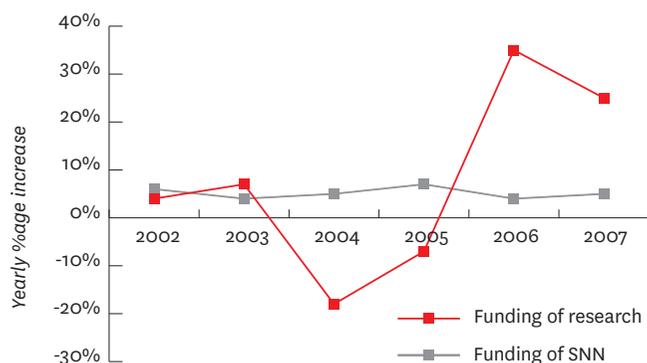
Figura 1
Funding of current and targeted research as a percentage of funding of the SSN – years 2001-2007



The allocation of funds to current and targeted research

Through the National Research Programme (PNR), agreed to with the National Health Research Commission (CNRS), the Ministry of Labour, Health and Social Policies indicates the research priorities for the SSN on the basis of three-year periods. The programme is adopted with the agreement of the State-Regions Conference within six months from the date on which the National Health Plan comes into effect. The National Research Programme provides guidance for the institutional recipients of the funds of the Health Research Fund (Table 3). These are the 43 IRCCS’s (Istituti di ricovero e cura a carattere scientifico – Scientific Research Hospitals), the Regional Councils and Autonomous Provincial Councils, the ISS (Istituto superiore di sanità – Higher Health Institute), the ISPESL (Istituto Superiore

Figure 2
Yearly increase in funding of the SSN and of current and targeted research – years 2002-2007



per la Prevenzione e la Sicurezza sul Lavoro – Higher Institute for Prevention and Safety at the Workplace), the National Agency for Regional Health Services (AgeNaS) and the 10 IZS’s (Istituti Zooprofilattici Sperimentali – Experimental Institutes for the Prevention of Diseases in Animals).

Funding for current research goes almost entirely to the IRCCS’s (Scientific Research Hospitals). In recent years, however, the IZS’s, the ISS, the AgeNaS and the ISPESL, too, have also become beneficiaries of these funds. The proportion of the total funds assigned to these organisations was about 10 percent, except in 2007, in which it rose to a share of 15 percent (Tables 3 and 4). The funds for targeted research, on the other hand, were more uniformly distributed among the beneficiaries.

In the period from 2000 to 2007, on the average, the IRCCS’s received 48 percent of this funding. In those years, the proportion remained more or less the same, except in 2006, when only 29 percent of the total funding was allocated to the IRCCS’s.

In recent years, also, there has been a tendency of the Regional Councils to obtain higher shares of funds for targeted research, up from 19 percent of the total in 2000 to peaks of 40 percent in 2004 and in 2006.

Governance of health research funded by the Ministry of Labour, Health and Social Policies

Decisions referred to health research funded by the Ministry of Labour, Health and Social Policies are taken by the General Management for Scientific and Technological Research of the Ministry of Labour, Health and Social Policies and by the National Commission for Health Research (CNRS). This Commission consists

of experts appointed partly by the Ministry of Labour, Health and Social Policies and partly by the Permanent Conference for relations between the State, the Regional Councils and the Provincial Councils of the Autonomous Regions of Trento and Bolzano (State-Regions Conference). Most of the members of the Commission are academics from the Italian universities of greatest prestige, others are members of the technical staff of the regional councils or representatives of non-profit organisations that provide financial backing for health research (e.g. AIRC – the Italian Cancer Research Association).

The CNRS was created in 2007 and its members, apart from the Chairperson and Deputy Chairperson, have remained unchanged even after the recent change in government. The Undersecretary for Health (in the newly re-organised Ministry of Labour, Health and Social Policies) chairs the CNRS. Its meetings are also attended by several permanent guests, including the head of the National Agency for Regional Health Services (AgeNaS), the head of the National Centre for Disease Prevention and Control (CCM), the head of ISPESL and those of other ministry agencies concerned with this type of issue.

The Steering Committee consists of the Deputy Chairperson, two members appointed by the Ministry, two appointed at regional level from among the CNRS committee members and Ministry of Labour, Health and Social Policies. Some of the programmatic decisions concerning health research and its funding are taken by the Steering Committee, which therefore plays a very important role.

Apart from its regular plenary meetings, the CNRS also works in the form of sub-groups that focus on specific issues. One sub-group, for instance, is currently busy revising the criteria according to which the Ministry allocates funds to current research, another is drafting the call for applications for specific topics (e.g. stem cells), yet another is working on monitoring systems for targeted research. All the sub-groups report back to the CNRS for drafting the final decisions.

As announced by the Undersecretary for Health at a press conference on 1st October 2008, the Ministry of Labour, Health and Social Policies is redefining the systems for judging the research projects and the criteria for allocating resources for “biomedical research”, to be applied both by the Ministry of Labour, Health and Social Policies and by the Ministry of Education and Universities (MIUR).

Table 3
Organisations receiving funding for current and targeted research

Provider	Flow	Beneficiaries
Ministry of Health	Current	IRCCS (criteria-based system) Age.Na.S, ISS, ISPESL, IZS (system based on single balance-sheet items and projects)
	Targeted	IRCCS’s, Regional and Autonomous Provincial Councils, ISS, ISPESL, Age.Na.S, IZS’s <i>NB: Universities can apply for funds for targeted research only for supporting the institutional beneficiaries mentioned above</i>

Table 4

Beneficiaries of funding for current research (in millions of Euros) – years 2000-2007

Beneficiaries	2000	2001	2002	2003	2004	2005	2006	2007
IRCCS's	178,1	183,3	185,4	179,0	161,6	150,0	186,0	189,9
IZS's	-	-	-	10,4	10,2	10,0	10,0	15,0
ISS	-	-	-	6,0	5,0	5,0	10,0	10,0
ISPESL	-	-	-	6,0	5,0	1,0	2,0	2,0
Age.Na.S	-	-	-	0,6	0,4	0,4	2,3	1,5
Research Bulletin	-	-	-	0,1	-	-	1,2	2,1
MscI. to be shared out	-	-	-	-	-	-	-	3,3
TotaoI	178,1	183,3	185,4	202,1	182,2	166,4	211,5	223,8
% IRCCS	100,0%	100,0%	100,0%	88,6%	88,7%	90,1%	87,9%	84,8%
Subsidies	-	-	-	3,6	-	-	20,0	-

Source: Ministry of Labour, Health and Social Policies

The new criteria call for the creation of a single scientific assessment committee that will identify, every two years, one or more groups of experts at International level who will, in turn, entrust the appraisal to independent referees. This method should guarantee both greater co-ordination of the decisions between the Ministry of Labour, Health and Social Policies and MIUR as well as greater transparency and international standards for judging the merits of the projects.

Current research

According to the indications of the Ministry of Labour, Health and Social Policies, current research has the very broad aim of “developing in time essential knowledge in specific fields of biomedicine and public health”. Scheduling of current research is defined by means of a call for applications containing the proposed programmes for a three-year period. The IRCCS's take part in the process of assignment of the funds for current research by sending the CNRS the necessary documentation in the form of a letter of intent, describing their lines of research for the following three-year period (and which must be consistent both with the ministry strategy and with their own thematic interests).

The system of criteria for allocating funds to current research

In the framework of its three-year planning, every year the Ministry of Labour, Health and Social Policies assigns resources using a system of evaluation based on five categories of indicators concerning:

1. scientific production;
2. productivity, capacity to attract resources and transferrability of the research;
3. healthcare activity;
4. promotion/adoption of excellence in care;
5. training activities.

Each category of criteria is weighted. In principle, all the criteria indicated are considered valid for determining allocation of funds, but according to the Ministry Decree, the Working Group can choose a minimum of three indicators for each typology of criterion. What is more, in the three-year period 2006-2008 the single criteria no longer had a pre-established weight, as had been the case in the previous three-year period. The choice of indicators became more flexible, and enabled greater use of discretionary powers on the part of the Ministry of Labour, Health and Social Policies.

With regard to the decision-making process, in February of each year the IRCCS's send the Ministry of Labour, Health and Social Policies their financial and scientific statements covering the activities of the previous years by means of an electronic platform (workflow), and receive 20 percent of the funds constituting the balance for the previous year. Monitoring and assessment of all the activity indicators of the IRCCS's continue, generally speaking, until April, when the CNRS receives all the statements covering the activities, needed in order to authorise advances on the funding for the new year (40 percent of the available total). The CNRS accesses the workflow to revise the data submitted by each IRCCS. In the event of incongruities or inexact or missing information, the CNRS may request further investigation before deciding whether to authorise disbursement of the funds. The Working Group has the task of providing the Commission with a technical report illustrating the criteria used in the process of allocation of the resources and explaining the exclusion of any institutions from the assignment procedure. Final approval is up to the CNRS. The remaining 40% of the funds decided upon is handed out in September.

Research & Development activities: data and trends

In 2007 in Italy, drug companies invested 1,170 million Euros (+4.9 %) in Research & Development (R&D), with an increase

Key Research & Development data for Italy

Millions of euros	Pharmacology	Hi-tech sectors	Manufacturing industries	Total Companies
R&D Investments	1.170,0	7.109,4	8.304,8	11.282,1
% of company total	10,4	63,0	73,6	100,0
% of domestic sales	10,1	1,9	0,9	0,9
%age variation 2007/2006	4,9	5,7	5,7	5,1

Units	Pharmacology	Hi-tech sectors	Manufacturing industries	Total Companies
R&D jobs	6.250	46.577	54.338	73.683
% of company total	8,5	63,2	73,7	100,0
% of Italian total	3,5	26,1	30,5	41,3
% of total jobs	8,7	3,2	1,2	1,1

Source: Istat data

grater than that of the total turnover (+ 1.4 percent, sales to chemists and hospitals). The number of jobs in R&D amounted to 6,250 (+1.4 percent), that is to say 8.7 percent of the total number of jobs in the Italian pharmaceutical industry. This percentage is higher than that referred to the total of all companies (1.1 percent) and to that of the economy (0.7 percent). Pharmaceutical research accounts for 6.6 percent of all research carried on in Italy.

Clinical trials in Italy

New medicines are the end result of a process that require 10 to 15 years of research and several stages of preclinical and clinical studies, governed by specific national and international standards and guidelines having the purpose of ensuring reliability of the data and the safety and well-being of the patients taking part in the studies.

Generally speaking, the stage concerned with investigating the effectiveness and tolerability of the drug in human beings, that is clinical trials, is carried out at university centres or hospitals and accredited and authorised public and/or private research institutes, and must comply with strict ethical, scientific and methodological criteria.

Clinical research accounts for a significant proportion of the total budget for research leading up to the marketing of a new drug. After a drug is placed on the market, clinical research continues, with so-called Phase IV or post-marketing clinical studies.

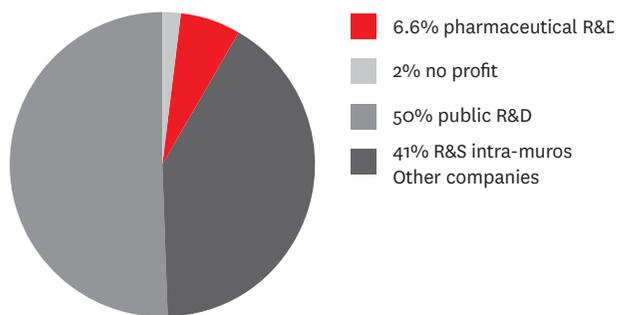
The distribution of the investments shows that the clinical, registration and post-marketing studies account for a significant share of the total investments in R&D (47.8 percent of the total according to EFPIA – European Federation of Pharmaceutical Industries and Associates - data). The data provided by the Italian National Observatory on Clinical Trials place various information about clinical studies in Italy at disposal.

4,669 clinical studies (total number for registration plus post-marketing) were conducted from 2000 to the end of the first half of 2007. In the period considered, the drug companies promoted

71.3 percent of the trials. 80 percent of trials were conducted in more than one centre, and one third of them were Italian and 2 thirds International (this trend has grown in the five-year period from 52.3 percent in 2000 to 76.3 percent in the first half of 2007). Italy was the co-ordinating country in only 6.9 percent of cases.

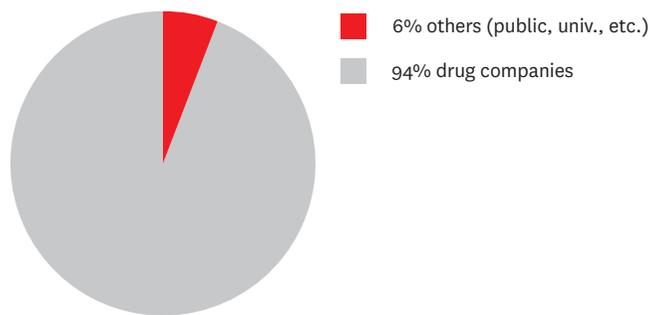
R&D investments per financial backer (% of total)

% of total, per backer



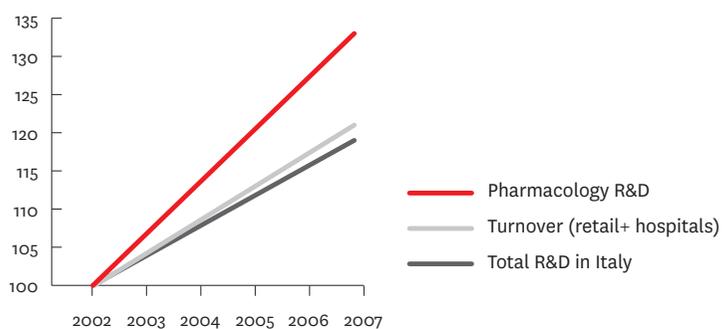
Italy - R&D expenditure in the field of pharmacology

% of total, per backer



Italy - Trend of R&D investments in the field of pharmacology

2002 Index = 100, constant growth rates



Source: Istat data

4.

Italian government funding of health research

Research & Development in Italy

The most up-to-date information is that supplied in November 2008 by Istat, concerning the results of its surveys on in-house Research & Development (R&D) in Italy, referred to companies, public institutions and private institutions.

For a more complete picture of the R&D activities, the data concerning R&D conducted at public and private universities are also presented. These were estimated by ISTAT on the basis of information supplied by the Ministry of Education, Universities and Research (MIUR).

Istat, 2006

Main results

In 2006 the expenditure for in-house health R&D on the part of companies, public institutions, non-profit institutions and universities amounted to a total of 16,835 million euros, with an increase over 2005 of 7.9 percent in nominal terms and of 6.1 percent in real terms. The percentage incidence on the Gross Domestic Product also rose, to about 1.14 percent. The main contribution towards the total expense for R&D activities came from companies, with an increase of 4.5 percent as compared with 2005. The amounts spent for in-house health R&D by universities (+8.2 percent), by public institutions (+7.3 percent) and by private non-profit institutions (+90.9 percent) also rose. These changes, however, must be interpreted also in the light of the transition of some important research institutions from the private to the public sector and from the public to the non-profit sector (which now accounts for 3.7 percent of the national health R&D spending).

The forecasts for 2007 and 2008 (not available for universities) indicated further expectations of growth for in-house R&D (+5.4 percent in 2007 and +6.3 percent in 2008). In every field the increase in the number of people employed in R&D is quite significant: from the +1.1 percent of the universities to the +10.6 percent of public institutions, to the +13.2 percent referred to companies, and to the +65.9 percent of non-profit institutions. In the last two fields, the shift of resources towards the remuneration of personnel, whether internal or external, employed for in-house R&D activities is encouraged by the presence of tax incentives that enable such expenses to be deducted from the amount subject to IRAP (Regional Tax on Production Activities).

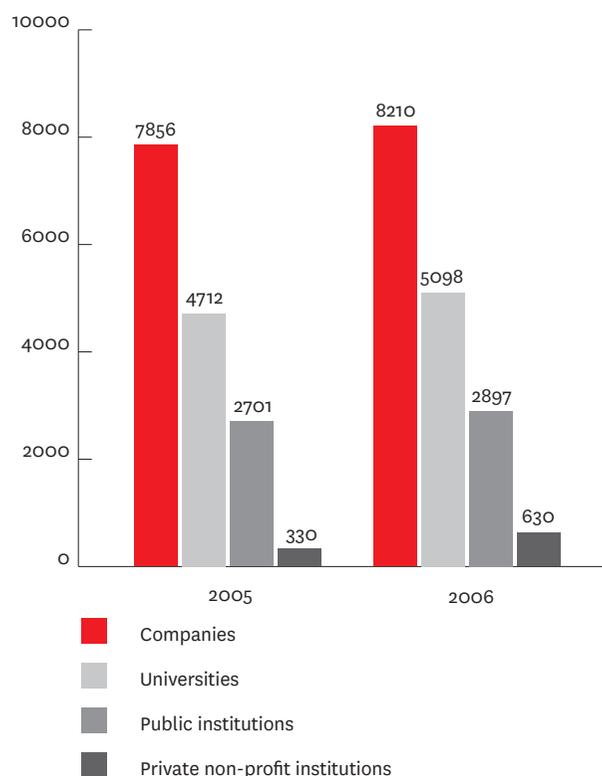
Expenditure for In-house Research & Development

During the course of 2006 the companies sector carried on in-house health R&D for a total expenditure of 8,210 million euros, equal to 48.8 percent of the Italian total (Figure 1). Universities spent 5,098 million euros (30.3 percent of the total expenditure) in R&D, public institutions 2,897 million euros (17.2 percent) and, lastly, private non-profit institutions contributed with 630 million euros (3.7 percent).

The 2006 data confirmed the basic stability in time of the relative contributions of the different sectors to total R&D spending, while the proportions of public and private spending in R&D remained both in the region of 50 percent.

Private expenditure for R&D remained, therefore, considerably below the 66 percent level recommended by the European Commission (DG6 – bis).

Expenditure for in-house R&D in different institutional fields Years 2005-2006 (millions of euros)



In 2006 an increase was seen in the percentage increase of expenditure for basic research (28.7 percent, versus the 27.7 percent of 2005), while the share allocated to applied research remained more or less unchanged (44.7 versus 44.4 percent) and that allocated to experimental research dropped (26.6 versus 27.9 percent). The increase in the relative impact of basic research was the result of an increasing investment in basic or pre-competitive research by public institutions (+8.8 percent) and, above all, by companies (+34.7 percent).

Overall, 59.5 percent of national spending in basic research was concentrated in the universities and 24.0 percent in public

institutions, while the contribution of companies and of non-profit institutions remained considerably lower (12.3 and 4.2 percent respectively).

51.6 percent of the expenditure for applied research and 83.3 percent of that for experimental development is concentrated, on the other hand, in companies, while the contribution of universities and public institutions to spending for applied research amounted to 22.8 and 20.2 percent of the total respectively. The investments in experimental development were seen, in any case, to grow in public institutions (+20.6 percent in the comparison between 2005 and 2006) and in universities (+8,5 percent). With reference to 2006, the contribution of public institutions to total spending for experimental development amounted to 4.8 percent and that of universities to 11.3 percent (in 2005 it was only 9.9 percent).

Extent and distribution per sector of Research & Development activities by enterprises

The expenditure for R&D on the part of companies was characterised by the fact that it was concentrated among the largest production units: in 2006 companies providing at least 500 jobs invested in R&D a share equal to 70.7 percent of the overall expenditure of all companies. Compared with 2005, however, the percentage contribution of large enterprises was seen to drop slightly, while there was some growth of the proportions accounted for by enterprises providing up to 49 jobs (from 6.0 to 7,3 percent), by those providing between 50 and 99 jobs (from 4.1 to 6.2 percent) and by those providing between 100 and 249 jobs (from 8.5 to 8,8 percent).

Research personnel

In 2006 the number of people employed in R&D activities (expressed as equivalent full-time jobs) was 192,002, with an increase over 2005 of 9.6 percent (higher, then, than the 7.9 increase in expenditure). The increase involved all fields, although the most significant variations occurred among private non-profit institutions, in companies and in public institutions.

The field with the highest number of jobs in R&D (expressed as equivalent full-time jobs) is that of companies (80.081, reaching 41.7 percent of the total), followed by universities (67,688 jobs or 35.3 percent of the total), public institutions (36,165 jobs or 18.8 percent) and private non-profit institutions (8,068 jobs or 4.2 percent).

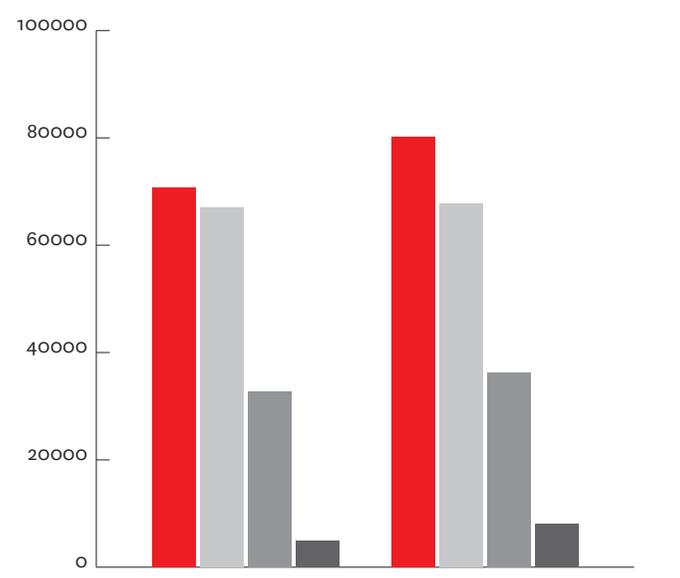
Research & Development activities at regional level

The regional distribution of spending for in-house R&D confirmed the driving role of the Northwest in 2006, this being the part of Italy accounting for 37.4 percent of the expenditure, followed by central Italy (25.1 percent), the northeast (19 percent) and the south (18.5 percent). North-eastern and southern Italy grew by about one percent each as compared with 2005, eroding the position of central Italy which, conversely, lost two percentage points.

The total expenditure for R&D continues to be heavily concentrated in three regions – Lombardy, Lazio and Piedmont – which account for 59.1 percent of the R&D expenditure of private enterprises, 54.1 percent of that of public institutions and 31.7 percent of the spending incurred by universities. Overall, 50.5 percent of the national R&D expenditure is concentrated in these regions.

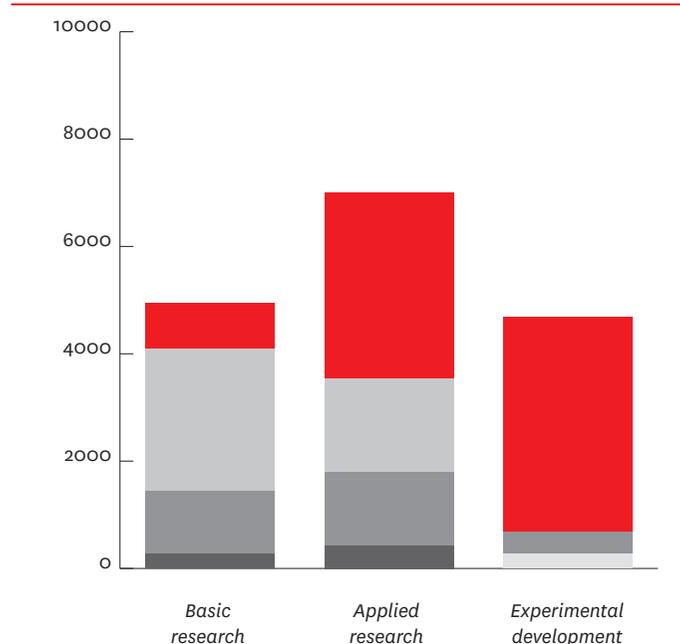
Jobs in in-house R&D according to institutional field Years 2005-2006

(number of jobs expressed as full-time equivalent jobs)

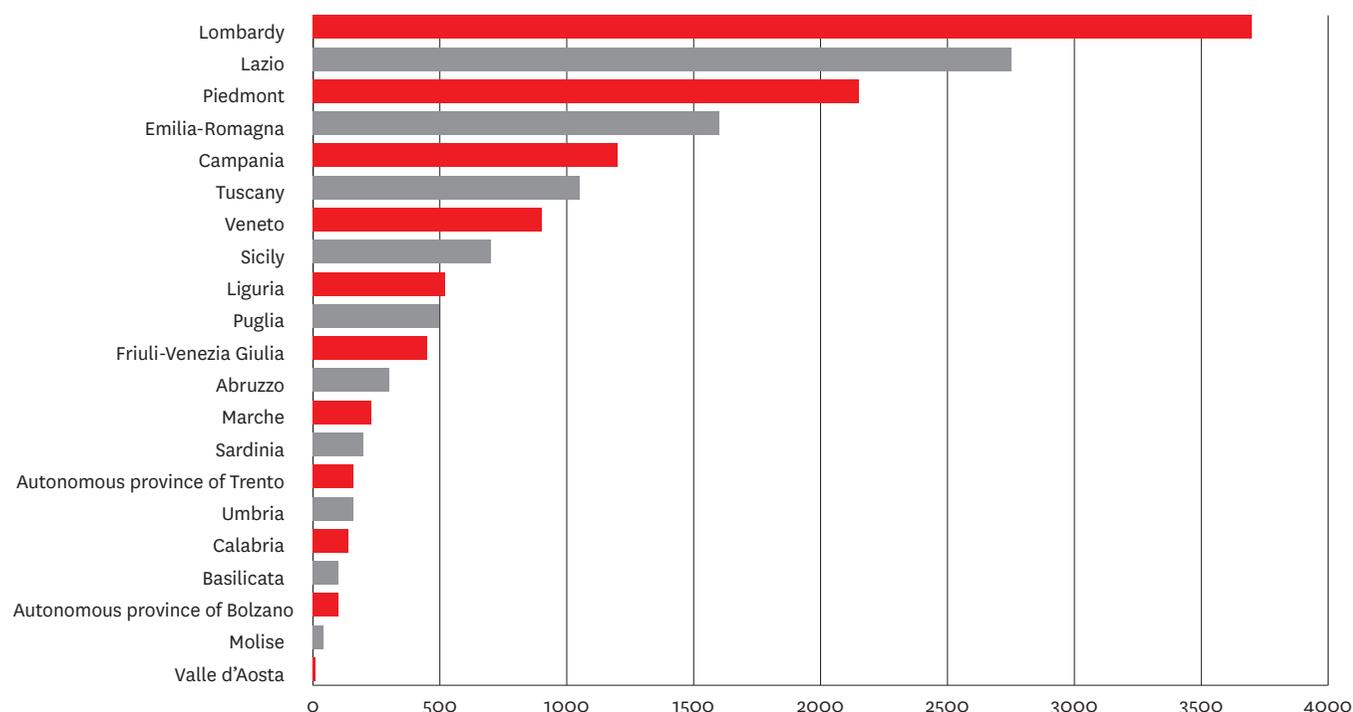


Expenditure for in-house R&D according to type of research and institutional field – Year 2006

(millions of euros)



Expenditure for in-house R&D in each region and autonomous province – Year 2006 (millions of euros)



Health research in Italy

National research programme

Health research should meet the cognitive and operational needs of the National Health Service and its health targets, identified in the form of a specific research programme, envisaged in the National Health Plan.

The National Health Plan defines the goals and main fields of research of the National Health Service, with reference to the needs of the service. The national scientific community contributes towards consistent achievement of these goals.

After consulting the National Health Research Commission, the Minister drafts the health research programme and proposes initiatives to be included in the programme of national scientific research and in those of international and Community research. The programme is then adopted by the Ministry, with the agreement of the Permanent Conference for Relations between the State, the Regions and the Autonomous Provinces of Trento and Bolzano, within six months from the date of coming into effect of the National Health Plan. It covers a three-year period and is funded by the contributions called for in Legislative Decree 502 of 1992.

The health research programme:

- identifies priority goals for improving the state of health of the population;
- promotes experimenting with ways of operating, managing and organising health services, as well as of clinical and care practices and identifies tools for investigating their impact on the state of health of the population and of the users of the services;
- identifies the tools for assessing the effectiveness, appropriateness and financial congruity of procedures and activities, also in consideration of similar trials initiated by international agencies, and with particular reference to activities and procedures with

which adequate assessment of their effectiveness is lacking;

- promotes research and experimenting aimed at improving multi-professional integration and continuity of care, with special reference to social and health services with a high health-care component;
- promotes research and experimenting aimed at improving communication with citizens and with the users of health services, and at promoting correct and systematic information for users and their participation in improvement of the services;
- promotes research and experimenting with appropriate activities for implementing guidelines and the relevant diagnostic and therapeutic paths, and for self-appraisal of the activity of staff, investigation and monitoring of the results achieved.

The health research programme is broken down into Current Research and Targeted Research activities.

Current research is implemented by means of the institutional projects of national research organisations (regional councils, Istituto Superiore di Sanità, Istituto Superiore per la Prevenzione e la Sicurezza sul Lavoro, the Agency for Regional Health Services, public and private scientific research hospitals, experimental institutes for the prevention of diseases in animals) in the framework of the guidelines of the national programme approved by the Ministry of Education and Research.

Targeted research implements the priority biomedical and healthcare goals of the National Health Plan. The targeted biomedical research projects are approved by the Ministry of Labour, Health and Social Policies, in concert with the Ministry for Universities and Scientific and Technological Research, in order to facilitate co-ordination between them.

Current and targeted research activities are carried on by the regional councils, by the Istituto Superiore di Sanità, by the Istituto Superiore per la Prevenzione e la Sicurezza sul Lavoro, by the Agency for Regional Health Services, by public and private scientific research hospitals and by the experimental institutes for the prevention of diseases in animals. Universities, the CNR and other public and private research organisations as well as public and private companies can contribute towards implementing the projects, on the basis of specific agreements, contracts or conventions.

To implement the programme, the Ministry of Labour, Health and Social Policies – also acting on the initiative of national research organisations – proposes to the Ministry of Education, Universities and Research and to the other ministries concerned, the areas of biomedical and health research of common interest, agreeing to the subjects, the funding procedures and the criteria for evaluating the results of the research.

In exercising its function of monitoring implementation of the National plan, the Ministry of Labour, Health and Social Policies has the technical and scientific help of the National Health Research Commission and of the technical and scientific bodies of the National Health Service and of the regions.

The regional councils formulate proposals for preparing the health research programme. They can take responsibility for implementing single targeted projects, and ensure monitoring application of the ensuing results in the framework of the Regional Health Services.

Targeted research implements the priority biomedical and health goals identified in the National Health Plan (**articles 12 and 12 bis** of Legislative Decree 502/92, as amended and supplemented by Legislative Decree n.229/99).

Targeted health research projects are approved by the Minister of Labour, Health and Social Policies, in concert with the Minister for Universities and Research, for the purpose of facilitating co-ordination between them.

Targeted research activities are carried on by the Regional Councils, by the ISS, by the ISPESL, by the Agency for Regional Health Services, by public and private scientific research hospitals and by the experimental institutes for the prevention of diseases in animals.

Universities, the CNR and other public and private research organisations as well as public and private companies can contribute towards implementing the projects, on the basis of specific agreements, contracts or conventions. In exercising its function of monitoring the progress of research projects and the achievement of the planned results, the Ministry of Labour, Health and Social Policies has the technical and scientific help of the National Health Research Commission.

The funds allocated to targeted research for the years 2007-2008 were:

2007 Funds	Research projects	2008 Funds
10.000.000	Extraordinary oncology programme	
5.000.000	Targeted food safety research	5.000.000
3.000.000	Rare diseases	3.000.000
3.000.000	Stem cell research	3.000.000
3.000.000	Targeted research into health and safety at the workplace	3.000.000
15.256.500	Young researchers	28.827.409
77.000.000	Ordinary targeted research	10.000.000

Current research is scientific research aimed at developing in time fundamental knowledge in specific fields of biomedicine and of public health.

Research is implemented through the three-year scheduling of the institutional projects of the national research organisations and public and private institutional bodies, the research activity of which has been recognised by the state as pursuing goals of public interest (ISS, ISPESL, the Agency for Regional Health Services, scientific research hospitals, experimental institutes for the prevention of diseases in animals).

According to Legislative Decree 288 of 16th October 2003, in order to achieve scientific recognition, organisations must have specific economic, structural, human and scientific requisites that must be demonstrated for the three years prior to recognition.

With regard to funding of current research (contribution to in-house research), the goal achieved was to guarantee financial continuity of public organisations as far as concerned the cost of personnel, by covering 70 percent of the funding provided in the previous year. In order to avoid not having sufficient financial resources at disposal, the amount of earnings that an organisation that has obtained excellent scientific results can accumulate each year has been limited to 20 per cent. The decree concerning programming covers a three-year period, and therefore the “positive trend” of an organisation could reach 60 percent in the three-year period 2006-2008.

Organisations that have a “negative trend”, on the other hand, can even lose up to 90 percent of their funding in the three-year period.

5.

Should we respond to needs or pay a fair contribution? Italy is not doing either

Impartiality and global solidarity

In a spirit of global solidarity, the governments of rich countries should fund a biomedical Research & Development agenda catering for the needs of global public health, contributing towards funding this agenda fairly and in proportion to their financial capacity.

With this approach, the governments of rich countries would fund research concerning tuberculosis, malaria and other neglected diseases, even though these diseases do not affect their own populations, or affect them only to a very minor extent. Attributing a value to this “fair contribution” is, however, not an easy task.

Financial needs

Let us take the example of TB. In 2007, the WHO’s Stop TB Partnership launched the Global Plan to Stop TB, quantifying the funds needed for R&D, drugs, vaccines and diagnostic tools for tuberculosis (TB) at over 6 billion euros, over a period of ten years. This was equivalent to over 600 million euros a year.

Many, however, feel that this estimate is incomplete. For this reason, MSF refers to a more up-to-date estimate (2009) provided by the Treatment Action Group (TAG) that, in the document “Analysis of TB funding trends”, quantise the funds needed for R&D for TBC at about one and a half billion Euros.

In 2007, however, the total world-wide investment in R&D for TB amounted to only 292.67 million euros. According to G-Finder, the public sector contributed 57 percent, philanthropic institutions 31 percent and the private sector 12 percent. In its “Analysis of TB funding trends”, the TAG quantified the funds needed for R&D referred to TB at 1.45 billion Euros (two billion dollars) a year. In 2007, however, the total world-wide investment in R&D

for TB amounted only to 346 million euros (482 million dollars). According to the TAG’s analysis, the public sector contributed to the total investment with a share of 57% in 2007 and of 59.1% in 2006. In order to compare the data contained in this report with other reports published earlier, we shall assume that the proportion of funds provided by the public sector remained steady at the 2006 level, that is to say 59.1%. On the basis of this assumption, the public contribution to investments in R&D for TB should amount to 59.1% of the estimated required funding, which is 1.45 billion euros. Considering that in 2007 the Italian GNP was 3.8% of the world GNP, the Italian contribution towards R&D for TBC should amount to 32.6 million euros a year (equal to 3.8% of the estimated yearly public funding needed at global level).

Similar estimates of the funding needed are unfortunately not available for the other neglected diseases. This is yet another demonstration of just how neglected these diseases and these populations are.

Funds allocated and financial needs

Le fonti di finanziamento della ricerca sanitaria in Italia sono sThe sources of funding for health research in Italy are both public and private. According to the last report by the Global Forum for Health Research, in 2006 (the last year for which data are available), public investments in Research & Development activities referred to health amounted to 1.89 billion euros (2.50 billion dollars). Apart from these data, which are incomplete and available only as aggregate data, analysing the various flows of funds in Italy is problematic because of the lack of systematic monitoring covering all the sources of funding for health research.

G-Finder

The G-Finder Project, which published its first report early in 2009, provides extremely useful data concerning the manner in which funds are allocated to R&D. G-Finder, however, concentrates on analysing only the funds allocated, but does not analyse the needs in terms of global funding, and therefore does not highlight the current gap between global needs and actual funding. On reading the report thoroughly, in any case, it is possible to see the very large differences that exist between different diseases, in terms of funding. It can also be seen that most of the funding for diseases affecting mainly the populations of malaria.

This does not mean, however, that these funds are Developing Countries (77 percent) goes to HIV, TB and sufficient to cover real needs. It is therefore necessary to increase global funding of R&D for neglected diseases, in relation to the actual needs and to the priorities in the field, and without “discriminating” between the various diseases (this would be equivalent to discriminating between the various different patients). Lastly, but no less important, it appears to be necessary to revise the mechanisms for handing out the funds, reaching beyond the current models, often based on excessively cautious funding mechanisms or that are not innovative.

An analysis of the data bank of the Organisation for Economic Co-operation and Development (OECD) concerning Science, Technology and R&D statistics, for example, revealed significant gaps in the data referred to Italy (for example, the data are available only for a few years). The available data group together very broad research areas that do not enable data referred to health research into neglected diseases, and in particular tuberculosis, as defined in this study, to be identified.

Inside Italy, ISTAT collects data concerning R&D activities of public and private organisations, but not referred specifically to health research.

ISTAT's enquiry concerns only organisations that carry on in-house research, which excludes the large foundations and associations that provide funds, even substantial funds, for research, but that are themselves not research organisations as such. It is therefore difficult to extract a complete picture of public and private funding of health research on its own, as this would require targeted data acquisition.

In Italy, the main sources of public funding of health research consist of the Ministry of Labour, Health and Social Policies, the Ministry for Universities and Scientific Research (MIUR) and the Regional Councils. Furthermore, starting in 2006, the Agenzia Italiana del Farmaco (AIFA) has initiated a project for funding independent clinical research projects concerning the effectiveness and toxicity of drugs. Again, starting in 2006 (Act of Law n° 266 of 23rd December 2005, Article 1, sub-section 337), a new funding mechanism has been introduced, based on the possibility offered to citizens to earmark 5 per thousand of their personal income tax for non-profit bodies and organisations, including research organisations.

Of all the data collected by MSF and CERGAS, the most reliable concern the flows of funds provided by the Ministry of Labour, Health and Social Policies, those of the AIFA and those referred to the "5 per thousand".

Through the two main streams referred to current and targeted research, the Ministry of Labour, Health and Social Policies funds projects and research activities of several organisations known as institutional organisations, including the scientific research hospitals (IRCCS) and national agencies or organisations such as the ISS, the national Agency for Regional Health Services (now called AgeNAS) and the Regional Councils.

In 2007 the Ministry of Labour, Health and Social Policies funded health research activities for about 301 million euros.

With a resolution in 2003 (Act of Law 326/2003), the AIFA set up a fund for independent research into drugs, into which drug companies pay 5 percent of the amount spent by them for promotion. These funds, to be used for conducting clinical studies with a special focus on orphan drugs and rare diseases, are allocated annually, on the basis of assessments carried out by outside experts. Applications can be made by National Health Service (SSN) facilities, research organisations and universities, and the idea is to fund research and clinical studies in areas to which, generally speaking, the drug companies contribute little or nothing. In 2007 the AIFA assigned about 35.5 million euros to funding of such projects.

Thanks to the "5 per thousand" mechanism by which citizens can choose how to use part of their personal income tax, in 2007 health research projects were funded for a total amount of 46.8 million euros.

The information concerning funding by the MIUR is also rather limited and is made available with a delay of several years. A review of the research activity carried on by Italian universities conducted by the Comitato di indirizzo per la valutazione della ricerca (CIVR – Advisory Board for Assessing Research) for the three-year period 2000-2003, for example, found that the funds obtained by universities from the MIUR for activities in two important areas of health research – biology and medicine – amounted to about 80 million euros a year. It was, however, not possible to obtain either an estimate inclusive of other disciplines in which health research could be carried on, such as social sciences, or data subsequent to 2003. What is more, about 70 to 80 percent of the research activity of the CNR through its centres scattered all over Italy depend on the MIUR. Again in this case, the only estimate of the available funds is taken from the financial statements of the CNR as submitted to the Audit Court, and amounts to about 86 million euros for the year 2005.

Lastly, it was not possible to obtain any reliable data concerning funds provided by the Regional Councils for health research, partly because it was difficult to distinguish between directly allocated (own) funds and those received by the Regional Councils from the central government and paid out by the former to research organisations.

It should be remembered, lastly, that among the private organisations that supply funds for health research, a distinction must be made between profit-making and non-profit organisations. The latter include organisations that, among other activities, also fund health research, such as the large bank-owned foundations that collect funds from citizens and other donors in order to fund health research projects in a specific and targeted manner.

Alternative funding mechanisms

The current system for stimulating and rewarding research and development of drugs, diagnostic tools and vaccines does not meet the needs of poor countries and populations, which are not a profitable market.

The Intergovernmental Working Group on Public Health Innovation and Intellectual Property (IGWG), set up by the WHO, concluded its work in 2007 with the adoption by the World Health Assembly (WHA) of a Global Strategy and a Plan of Action for Innovation, Public Health and Intellectual Property.^{xxv}

The motion approved by the WHA opens up completely new prospects. For the first time, governments and the international community are called upon to tackle directly the consequences of the failure of the patent system for R&D into new diagnostic tools, drugs and vaccines meeting the needs of poor populations and accessible to them.

The key recommendations of the IGWG are based on the principle that the biomedical research agenda must be defined on the basis of global health needs. In order for this to happen it will be

Provider	Type	Funds	Year and source	Notes
Ministry of Health	Public	€ 301 million	2007, Ministry of Health	Includes current and targeted research and further projects such as “Young Researchers”, “Stem cells” etc.
AIFA	Public	€ 35,5 million	2006	Independent research into drugs
MIUR	Public	€ 80 million (a) + € 86 million (b)	(a) CIVR 2003 figure referred to funding of universities by MIUR (b) figure for 2005 taken from CNF financial statements and referred to funding of CNR by MIUR	(a) Very rough estimate as referred only to research in biology and medicine (b) Very rough estimate as referred only to research by CNR in medicine, life science and molecular design
Regional Councils	Public	-		Data non available
5‰	Citizens	€ 46,8 million (a) + € 37 million (b)	a) figure for 2006, Ministry of Health (b) figure for 2006	(a) Figure referred to “5 per thousand” donated to the Health Ministry (b) This figure must not be added to the total since it goes to the main associations and non-profit foundations that, in turn, provide funds for health research
Total public funds		~ € 586 million a year		
Bank and savings bank foundations	Private non-profit	€ 80 million	2006, Ital. Assoc. of Bank and Savings Bank Foundations	Estimate for research in medicine, natural sciences and technology
AIRC/FIRC	Private non-profit	€ 107 million	2006, Annual Report	Funding for Research Projects and study grants for researchers
Telethon	Private non-profit	€ 33,5 million	2008, Annual Report	For in-house research and external funding
LILT	Private non-profit	€ 3,2 million	2007, Annual Report	-
Fondazione italiana sclerosi multipla	Private non-profit	€ 3,2 million	2007, Annual Report	-
Total public funds		~ € 230 million a year		
Drug companies	Private for profit	€ 1,07 billion	2005, Farmindustria	The figures differ depending on the source. According to Farmindustria, 2/3 are spent for development and 1/3 for research
Total private profit-making		~ € 1,0 billion per year		
Overall total		~ € 1,88 billion per year		

necessary to explore a range of mechanism alternative to patents for encouraging this activity and able to separate the cost of R&D from the price of the end product.

Encouraging R&D requires a balanced mix of *push* and *pull* mechanisms. So-called pushing mechanisms encourage the R&D process “from the laboratory to the market”, and include, for example, conventional subsidies for single research projects. Pulling mechanism stimulate investments by the private sector in new areas, creating the possibility of making a profit in them. In other worlds, global public health needs are turned into “attractive” investments also for the private sector by means of suitable offsetting mechanisms (as we will analyse briefly below, by way of example).

Prize Funds

The prize fund mechanism has been proposed as a new way of rewarding investments in Research & Development of therapeutic tools meeting the needs of poor populations and accessible to them. It is a mechanism by means of which Research & Development are rewarded not directly by the market returns guaranteed by a monopoly but through a fund set up for this purpose. At a meeting organised by MSF in Geneva on 11th April 2008 on the subject of “Financing Medical Innovation Through Alternative Mechanisms” (available at [http://www.msfaccess.org/resources/key-publications/key-publicationdetail/?tx_ttnews\[tt_news\]=1442&cHash=babfee68ea](http://www.msfaccess.org/resources/key-publications/key-publicationdetail/?tx_ttnews[tt_news]=1442&cHash=babfee68ea)) and a subsequent meeting with the title “Designing Innovation - Inducement Prizes for Chagas and TB” (available at <http://www.keionline.org/content/view/204/1/>), a group of experts recommended the use of prize funds, in particular for encouraging the development of new diagnostic tests for tuberculosis and of new drugs and diagnostic tests for Chagas disease.

The Bolivian and Barbados governments, too, have supported the creation of a Prize Fund for developing a diagnostic test for tuberculosis, which should be both effective and easily used in peripheral healthcare facilities. The proposal was formulated during the meeting of the Working Group on Public Health, Innovation and Intellectual Property at the World Health Assembly in 2008 (available at www.who.int/phi/ewg/en/index.html).

The Bill & Melinda Gates Foundation has supplied funds to the X-Prize Foundation for developing a suitable prize fund strategy for encouraging Research & Development of a new diagnostic test for tuberculosis.

One fundamental aspect of *Prize Funds* is, as already explained, the fact that a significant financial reward is offered at the end of the R&D process, releasing it from market considerations and, thus, potentially attracting various different players, commercial and otherwise. It also provides better assurances that the product will be placed on the market at accessible prices for poor countries, and that competition with generic products of a suitable quality will not be hampered.

Italian AMC towards the pneumococcus vaccine

Another mechanism is the so-called *Advanced Market Commitment* (AMC), with which a financial commitment to purchase

the new drugs and vaccines in future is entered into when they are still in the development stage. An AMC pilot project has been launched recently for a new pneumococcal vaccine, pneumococcal disease being one of the main causes of child mortality in poor countries.

In 2009 the Italian Government undertook to contribute the amount of 635 million dollars under the AMC scheme for the pneumococcal vaccine. This amount is a considerable share of the 1.5 billion dollars placed at disposal globally for this initiative. Although this Italian investment in the fight against one of the main killers in the developing world is acknowledged and welcome, it is important to stress that AMC has significant limits: it does not encourage the initial stages of research and, in the case of the AMC for the pneumococcal vaccine, it does not guarantee access to the end product in medium-income countries.

Indeed, the AMC system is not very suitable for funding the early stages of Research & Development: it would turn out to be extremely expensive, since it is practically impossible to define accurately all the parameters determining the cost of research so far ahead of introduction of the end product onto the market. Applying the AMP system to a product in the early stages of R&D might be very expensive and ineffective and, at the same time, would entail the risk of discouraging other mechanisms and other partnership models.

The commitment towards the fight against pneumococcal infections, then, should be included in a global, structured and consistent framework of commitment, by the Italian Government, towards funding of R&D for new therapeutic tools for diseases prevailing in developing countries. The information acquired by MSF and CERGIS seems to show, instead, that the involvement of the Italian Government in the AMC for the pneumococcal vaccine is, for the moment, an isolated initiative.

Partnership models

PDPs (Product Development Partnerships)

Product Development Partnerships, or PDPs, are non-profit-making organisations created in order to promote and conduct Research & Development activities for tuberculosis, malaria and other neglected diseases, and funded, generally speaking, by private and institutional donors. As examples of PDPs involved with tuberculosis, malaria and neglected diseases we can recall the Global Alliance for TB Drug Development and the Drugs for Neglected Diseases Initiative (DNDi).

Some PDPs have already managed to develop new drugs. The DNDi, created in 2003, for example, has launched two products for fighting malaria: artesunate/amodiaquine (ASAQ) in 2007 and artesunate/mefloquine (ASMQ) in 2008. These are fixed-dose combinations of two pre-existing drugs, that make administration and compliance on the part of the patient considerably easier. The pharmaceutical technology used to create the co-formulation was not protected by a patent.

MSF maintains that these partnerships are useful – it is also one of the co-founders of the DNDi, and has worked together with other groups on specific research studies – but recognises that they are insufficient as such for meeting all the needs that still exist.

For example, on comparing the global response to tuberculosis

with the global response to cancer or to cardiovascular diseases, it can be seen that the number of drugs being developed is no match. In spite of the undeniable usefulness of PDPs and of funding of a philanthropic nature that often supports them, a strong commitment on the part of governments² is needed in order to increase the number of R&D projects and to make them sustainable in time. On their part, the leading drug companies maintain that greater commitment by them to the field of neglected diseases would depend on a significant revision of the system³.

It should be remembered, lastly, that the European Union, including Italy, has taken on an important role in funding clinical research for new drugs and vaccines for HIV, malaria and tuberculosis in Sub-Saharan Africa thanks to the European & Developing Countries Clinical Trials Partnership (EDCTP), as illustrated in the report published by MSF in 2008 on the “Gap in funding of TB and other neglected diseases by the European Union”. In 2007 Italy contributed 2.2 million euros to the EDCTP.

² Boosting innovation for neglected diseases – a call to governments; DNDi Research Appeal, www.researchappeal.org

³ Novartis chief in warning on cheap drugs, Financial Times, 30th September 2006, London

6.

Funding system for developing new tools

Following are the public bodies that actually or potentially fund Research & Development (R&D) in Italy in the field of tuberculosis (TB), malaria and other neglected diseases:

1. Ministry of Health
2. ISS
3. CNR
4. AIFA

Ministry of Health

In 2007 the Ministry of Health funded R&D projects for new tools for fighting TB and malaria, while no funds were provided – again referred to 2007 – for the other neglected diseases. The Ministry of Health's overall 2007 budget for infectious diseases (emerging and/or re-emerging diseases) amounted to 31,097,063 euros. The funding was definitely allocated as an item of the budget, however it is not possible to know whether the amount in question was actually spent.

Istituto superiore di sanità (ISS)

The Istituto superiore di sanità (ISS) is the government agency responsible for monitoring and public research in the field of health and of food and drug safety. The ISS has a particular vocation for basic and applied research in all those areas that constitute threats for public health. It employs 2,000 people and is organised in seven departments and four national centres.

The ISS is at the centre of a vast network of biomedical research that includes research institutes, and universities. It also co-operates with the most important public and private European biomedical research organisations, and has relations of strategic co-operation with international scientific organisations working in the field of protection of health.

Based on the information acquired, it appears that at the present time the ISS is following the projects indicated below:

1. “Sorveglianza della resistenza ai farmaci antitubercolari in Italia” (Monitoring of antitubercular drug-resistance in Italy), headed by Lanfranco Fattorini of the ISS, share of funding in 2006-2007: 100,000 euros (50,000 euros allocated in 2007).

2. “New mechanisms of Mtb immune evasion: impact on disease outcome and strategies of immune intervention”, project by Coccia-Nisini (81,000 euros allocated in 2007).

In 2007 the Ministry of Labour, Health and Social Policies gave the ISS 150,000,000 euros for research into malaria, tuberculosis and neglected diseases. Unfortunately we were not given more detailed information, and specifically not separately for each disease, and it was not possible to obtain this information in any other way.

Consiglio nazionale delle ricerche (CNR)

The Consiglio nazionale delle ricerche (CNR) is the largest public research organisation in Italy. Founded on 18th November 1923 and transformed in 1945 into a state-run agency, its activities consist mainly of training, promotion and co-ordination of research in every field of science and technology.

Department: Medicine

Project: Immunology and Infectivology

Job: Tropical diseases

Module: Tropical diseases

First year of activity: 2005

Expected year of closing: 2011

Funding received: Information not available

Among the CNR's research projects, the following can be mentioned: “Realizzazione di una piattaforma diagnostica nanotecnologica multiparametrica per la traslazione in ambito clinico di markers molecolari innovativi” (Creating of a “multi-parameter nanotechnological diagnostic platform for transferring innovative molecular markers to a clinical framework) presented in accordance with Article 11 of Ministry Decree 593/200 I.D.A. (Innovative Diagnostic Array), and which has the aim of devising and creating a platform for multi-parameter clinical tests.

Research Centre	Type of disease	Ministry of Health, Euros, 2007
Istituto per le malattie infettive Lazzaro Spallanzani IRCCS	Malattie infettive	2.976.810
Fondazione S.Raffaele del Monte Tabor	Malattie infettive (HIV/TBC)	17.460.250
Fondazione ospedale Maggiore Policlinico di Milano	Malattie infettive (HIV/TBC)	10.66.003
		31.097.063

The new system should combine the following: ease of performance, suitability for screening tests, flexibility in terms of customisable combinations and use for infectious tropical diseases (Dengue, Chagas disease, etc.).

MIUR Management Decree concerning admission for funding

N° 1083/Ric dated 30/07/2007

Estimated cost

€ 643.200,00

Total admitted cost

€ 623.200,00

Contribution towards total expense

€ 406.330,00

Duration of the project

36 months

Starting date of project

1st September 2007

End date of project

31st August 2010

Again in the framework of the CNR, the team headed by Dr. Francesca Mariani, CRN researcher and head of module ME P04.005.002, Host-pathogen interaction for a new anti-TB vaccine, has carried on the following research activities:

1. “Studio strategico per la costruzione di un vaccino terapeutico antitubercolare di tipo regionale, monitoraggio e analisi in vivo dei ceppi clinici di *Mycobacterium tuberculosis* e studio dei meccanismi innati di immunità antitubercolare” (Strategic study for the construction of a therapeutic antituberculosis vaccine of the regional type, monitoring and in vivo analysis of clinical strains of *Mycobacterium tuberculosis* and study of the innate mechanisms of immunity to tuberculosis), in the framework of the Italy-Morocco project of the Ministry for Foreign Affairs – General Management for cultural promotion and co-operation, which received funds amounting to € 57,000,00 – Year 2007;

2. “Ricerca di micro-RNA in isolati clinici di *Mycobacterium tuberculosis* di pazienti con TBC farmaco-resistente, e analisi del loro possibile ruolo nell’insorgenza di resistenza ai farmaci” (Detection of micro-RNA in clinical samples of *Mycobacterium tuberculosis* in patients with drug-resistant TBC, and analysis of their possible role in the onset of drug resistance), in the framework of the Research Project of National Interest, 2007. This project obtained funds amounting to € 24,000.00.

Agenzia italiana del farmaco (AIFA)

The Agenzia italiana del farmaco (AIFA) is an organisation according to public law operating in accordance with guidelines and under the surveillance of the Ministry of Health, according to criteria of independence, transparency and Cost-efficiency, and linking up with Regional Councils, the ISS, scientific research hospitals (IRCCS’s), Patient Associations, doctors and Scientific Societies and the production and distribution communities.

- San Raffaele del Monte Tabor Foundation: 35,850 euros.
- Istituto per le malattie infettive Lazzaro Spallanzani: 137,300 euros (for four projects).

Furthermore, the Department of Epidemiology of the “Istituto per le malattie infettive Lazzaro Spallanzani” was granted current

funds provided by the Ministry of Health, which could be used for diseases such as tuberculosis, malaria and other neglected diseases, but we were unable to find out in what proportions (the breakdown of this type of funding is not monitored).

On the basis of the data acquired, it was also found that other organisations contacted in the framework of this study did not receive any public funds in 2007 for research into malaria, TB and neglected diseases. Examples of these are:

- Pavia University, which did not receive any public funding in 2007;
- Naples II University, which did not receive any public funding in 2007;
- Cagliari University, which did not receive any public funding in 2007, only private funding (a small research project concerning cutaneous and visceral leishmaniasis received Sardinian regional funds (20,000 euros) and private funds (Banco di Sardegna, 20,000 euros).

The difficulty of acquiring data and the small number of grants allocated to research and development of new drugs and diagnostic products for tuberculosis, malaria and other neglected diseases show that in Italy the health research funding system is extremely fragmented. It is not placed in a structured framework of activities based on need, and the funds are in any case inadequate. There is also no information system grouping together the data concerning the many providers of public and private funding and the contents of all the projects funded. As far as concerns the public sector, the few complete data available are only for the funding provided by the Ministry of Labour, Health and Social Policies and the AIFA, while the information is incomplete and not up-to-date for all the funding provided by the Ministry of Education, Universities and Research (MIUR).

In view of these circumstances, it is difficult to co-ordinate and route public resources efficiently. It would therefore be desirable to set up a mechanism for co-ordinating all investments in public health research, as well as an information system covering the data referred to funds allocated both in the public and in the private sector. The initiative of the Ministry of Labour, Health and Social Policies, aimed at modifying the health research funding system and defining consistent criteria for funding by the Ministry of Labour, Health and Social Policies and by the MIUR, would, indeed, seem to meet the need for greater co-ordination. We have also noted that, in the public sector, the Ministry of Labour, Health and Social Policies has an important role in the area of health research in general. An analysis of the flows of funds, however, highlighted that the resources allocated in recent years were always lower than the target set in 1992 (1 percent of the funding of the National Health Service).

The amount of funds has also varied a great deal depending on conditions from time to time and on the political sensitivity of the moment, so that significant allocations have been decided in Parliament, and therefore beyond the control of the Ministry. Most of the funds allocated by the Ministry of Labour, Health and Social Policies as, furthermore, channelled through current research, without a process defining research priorities. For the ISS, for example, the allocation for current research is not even subject to the system of criteria adopted for IRCCS’s, and the

research priorities are defined even less explicitly. In this framework, which we could define as research commissioned by third parties, therefore, the Ministry of Labour, Health and Social Policies again has a fairly passive role.

Information concerning investments by the Regional Councils in health research per tuberculosis, malaria and neglected diseases is difficult to find and it is often difficult to understand how much has been actively allocated and how much is transferred from the central level.

Overall spending by the Italian Government at international level

In the period 2001-2008 Italy contributed the sum of 790 million euros to the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM). At the moment Italy is the sixth largest contributor to the GFATM, with amounts that in the years 2001 to 2005 reached 433 million dollars. Italy ranks fourth in terms of commitments made by donor countries but is the country with the largest debt to the fund (followed by the United States) as it still had 20 million euros of the 2005 share and the 260 million promised for the two-year period 2006-2007.

In spite of the political commitment on the part of the Senate Foreign Affairs Committee and the Budget Committee to raise these funds, they have not been found.

This means that in 2007 aid provided by Italy dropped in real terms by 3.6 percent, for a total of about 2.5 billion euros.

Indeed, Italy has reduced its funding at European level drastically, in spite of the fact that it has increased the net resources placed at disposal in the budget by 46.7 percent. This is certainly positive, but not sufficient for meeting the commitments entered into. Italy should increase its public contributions to Development Aid (which includes also the quota of Research & Development of drugs) by over 150 percent within 2010 in order to meet its commitments under international agreements.

In the last five years Italy has always been below the European average in providing contributions to aid. Its slow economic growth and its high indebtedness are some of the factors contributing towards explaining Italy's poor results, however the difficult domestic and international economic situation does not justify such low levels of aid.

If Italy, among other things, had acted like other donor countries did when they found themselves in similar conditions, it should have maintained a minimum level of aid equivalent to 0.29 percent of the GDP, net of its debt. Thus, as far as concerns political choices in terms of aid, Italy is close only to small economies or those in transition, such as Ireland, Latvia and Estonia, and the cut by over 400 million euros - more than halving the money available for development co-operation (of which 1.7 for targeted research into neglected diseases) - is actually far too small to be justified by the need to save on domestic expenditure, and therefore looks far more like a precise economic policy decision.

Conclusions

Italy is not contributing enough

In 2008, Médecins sans Frontières (MSF) decided to carry out a series of analyses of the amount of funding allocated to research into new therapeutic tools for treating tuberculosis (TB), malaria and neglected diseases in various different European countries. The spending commitments of the United Kingdom, Germany, Sweden and the European Union have been analysed in other reports published by MSF in 2008 and 2009.

In view of the Italian chairmanship of the forthcoming G8 Summit in July 2009, it was imperative for MSF to understand the extent of Italy's commitment and the mechanisms for funding research into neglected diseases in our country.

This analysis, conducted by MSF Italia jointly with the CERGAS, revealed that Italian funding for research into neglected diseases is definitely insufficient by comparison with the country's GDP.

In 2007 the Italian Government (through the Ministry of Labour, Health and Social Policies and the Ministry of Education, Universities and Research) allocated 380,000,000 million euros to biomedical research, to which the 46,800,000 euros (assigned to biomedical research organisations) originating from the "5 per thousand" system must be added, giving a total of 427,800,000 million euros.

The budget allocated by the Italian Government to biomedical research in general is paltry if compared, for example, to the investment made in 2007 by philanthropic organisations which finance – among other activities – biomedical research, such as bank-owned foundations (171 million euros), and the private commercial sector (1.07 billion euros – 2007 figure according to Farmaindustria, 2007- invested in Research & Development activities by the pharmaceutical industry in Italy).

As far as concerns more specifically biomedical research into tuberculosis and other neglected diseases, according to the information collected by MSF and CERGAS, in 2007 31,131,000 euros – that is to say only 7,27 % of public funds intended for research – were allocated but not always actually spent.

The share allocated by Italy to health research for the poor is therefore insufficient, and the structure through which the funding is provided also appears to be inadequate. Its complexity and lack of transparency make it very difficult to understand what proportion of the total annual biomedical research budget is allocated to that specific field. In order to make these diseases a priority, it would therefore be necessary to start monitoring accurately the allocation of funds to each disease.

MSF also hopes that Italy will undertake to develop and promote mechanisms for encouraging alternatives to the patent system, which has proved absolutely ineffective for promoting innovation in the field of neglected diseases. Alternative mechanisms already proposed at the World Health Assembly, such as Prize Funds, could make the field of neglected diseases "attractive" also for private industry, enable the cost of research to be separated from the price of the end product and make this product accessible to all those who need it (universal access).

Recommendations

Research & Development activities necessary in order to tackle the tuberculosis emergency

International funding of research

The lack of suitable tools makes diagnosis of tuberculosis very difficult in contexts featuring limited resources, above all in patients with extrapulmonary forms, in children and in those with a TB/HIV co-infection.

The lack of adequate tools makes it equally difficult to provide effective and well-tolerated pharmacological treatment able to cure all the patients. There is therefore an urgent need to develop a research agenda for responding to this global health emergency. At least two research paths seem to us to be priorities:

a) Developing more effective and better tolerated drugs for tuberculosis, and in particular for multi-drug resistant and “extensively drug-resistant” forms.

The new drugs should enable the treatment protocols to be simplified (for multi-resistant forms it is possible to reach 24 months of treatment). In view of the complexity of the research process and the shortage of funds, it is also essential to devise a plan for co-ordinating the various different projects, so as to use the existing resources and skills effectively. It is with this aim, for example, that a group of patients, doctors and researchers met in Cambridge, Massachusetts, in June 2008, to create RESIST-TB (<http://resisttb.org>), an organisation that proposes to promote and conduct research projects concerning multi-drug resistant forms of tuberculosis. RESIST-TB is currently drafting a detailed plan of the studies needed in order to develop new treatments for multi-drug resistant tuberculosis, but the future of this initiative is uncertain due to the shortage of funds.

In spite of the declarations of global commitment to improve the diagnosis and treatment of multi-drug resistant tuberculosis (World Health Assembly, 2007, Resolution 62.15), the gap between rhetoric and reality is still wide.

Recommendation:

Italy should invest in the funding of international projects aimed at developing new therapeutic tools against multi-drug resistant tuberculosis. In this framework, the Government should also determine which ministry (Ministry of Labour, Health and Social Policies, Ministry of Education, Universities and Research or Ministry for Foreign Affairs) should be responsible for funding the PDPs.

b) Sviluppo di un test diagnostico della tubercolosi facilmente utilizzabile in strutture sanitarie periferiche. Analysis of expectorate, developed by Robert Koch over a century ago, is still the most widely used diagnostic test in developing countries.

Although it is relatively quick and easy to use in contexts with limited resources, it has significant drawbacks, in particular with reference to extrapulmonary forms, paediatric cases and patients with HIV/TB co-infections. Cultures give rise to more accurate results, however this method has other limits, such as the time required to obtain the results, its complexity and its costs. To sum up, what is lacking is a test that can be easily used even at peripheral health facilities with a shortage of resources and as close as possible to the great majority of patients.

In this respect, in March 2009 Médecins sans Frontières (MSF), together with the Treatment Action Group (TAG) and Partners In Health (PIH), organised a meeting of experts and of representatives of patient communities in order to attempt to determine what the priorities of research in the field of diagnosis should be. The outcome of this meeting is available on the internet (<http://www.msfaccess.org/index.php?id=602>).

Recommendation:

At the time of allocating funds to biomedical research, Italy should give priority to international research projects aimed at developing new diagnostic tests for tuberculosis that meet the specific needs of developing countries, where 90% of deaths occur.

In this framework, the Government should also determine which ministry (Ministry of Labour, Health and Social Policies, Ministry of Education, Universities and Research or Ministry for Foreign Affairs) should be responsible to funding PDP's.

Amount of funding and organisation and clarity in allocating public funds

In the light of our analysis, it is clear that the Italian Government has disregarded the general goal of Barcelona (to increase investments in Research & Development).

On the basis of the data acquired for the year 2007, also, the funds allocated to research into infectious diseases (including tuberculosis, malaria and other forgotten diseases) by the Ministry of Labour, Health and Social Policies appear to amount to about 31 million euros, although it has not been possible to find out whether they were actually spent. The funds allocated to these diseases by the ISS in 2007 amounted to about 131,000 euros and those allocated by the AIFA to 173.150 euro. No information was made available by the CNR.

As far as concerns research into new molecules and diagnostic tools, it should be remembered, even if this initiative was later than 2007, that Italy is taking part in the AMC for developing a pneumococcal vaccine with a commitment amounting to 635 million euros.

Generally speaking it emerged from our enquiry that:

- The Italian Government and the organisations analysed are not sufficiently transparent: collecting the data for this report took MSF and CERGAS a very long time, unlike what happened in other European Union countries.
- It appears that there is no clear link between the ISS and Ministry of Labour, Health and Social Policies, and no clear separation of roles and responsibilities that would enable the efforts for research and development into new drugs and diagnostic tools for TB and the other neglected diseases to be optimised. Similarly, there seems to be no structured plan for research into these diseases based on an analysis of needs.
- It is not clear what funds are actually allocated in Italy since, often, it was found difficult in the organisations analysed to monitor the thematic use of the funds.

Recommendations:

- Generally speaking, Italy should increase funding of research projects for TB, malaria and other neglected diseases, so as to contribute towards global public health, with a view to global solidarity.
- The Ministry of Labour, Health and Social Policies should create a specific item of expense, subject to annual reporting, among the expenditure allocated to the ISS.
- The AIFA could increase the share of funds for independent research in the field of neglected diseases, including as priorities those that affect mainly developing countries (albeit with more than a few cases in Italy) and funding research groups working in partnerships with research groups operating in developing countries.
- The ISS could include research into tuberculosis, malaria and neglected tropical diseases among the priorities in its programme.
- Research centres such as the San Raffaele del Monte Tabor Foundation and the Istituto per le malattie infettive Lazzaro Spallanzani should engage in research into neglected diseases, as specified in their mandates.
- The centres of excellence in tropical medicine, such as – by way of example – the Ospedale Sacro Cuore di Negrar, should be the beneficiaries of public funding for targeted research.
- The CNR could play a fundamental role in the field of developing new diagnostic technology for TBC and forgotten diseases, as is the case currently for other diseases, including rare diseases.

Alternative funding mechanisms and incentives for research

The paper by the IGGW on Innovation, Intellectual Property and Public Health, and the subsequent motion approved by the World Health Assembly in 2009 oblige us to acknowledge the failure of the patent system for promoting new therapeutic tools suitable for meeting the health needs of poor countries, and to recommend promoting alternative mechanisms, such as *Prize Funds*, for encouraging R&D for TB, malaria and neglected diseases.

Recommendation:

The Italian Government should make a strong commitment for the promotion of alternative mechanisms for encouraging R&D for TB, malaria and neglected diseases. In particular, the Italian Government could promote the introduction of a *prize fund* for

a new diagnostic test for tuberculosis, that should be effective, accessible and easy to use in developing countries.

Up to the present time, the gap between the north and south of the world as far as concerns access to health is still enormous. Yet, “Health and dignity are undistinguishable in the human being” (Carlo Urbani, 1999). We hope that Italy will increase and strengthen its commitment by contributing towards filling this gap that is unacceptable from the ethical and human point of view.

Glossary

Compliance

A patient is fully compliant with a therapy if the drugs are taken at the correct dose, at the right times of day and for the whole cycle of treatment, if all the doses are taken, if the patient does not skip any follow-up appointments and if he/she feels joint responsibility for his/her therapy. In TB, one patient out of two finds it difficult to follow the treatment cycle. Poor compliance can cause the treatment to fail, drug-resistance to develop and the possibility of transmitting the disease to other people.

Pathogen

Any agent causing a disease (e.g. viruses, bacteria, fungi).

Culture

Bacterial culture is a laboratory method for reproducing bacteria in order to identify their presence in a patient's sample. This is done by letting the bacteria grow in a pre-established culture medium in controlled conditions, in a laboratory, away from the natural environment in which they normally grow (for example, in the case of TB, the human body).

DOT

Directly-Observed Treatment. Unlike Self-Administered Therapy (SAT), DOT calls for the patient to take the treatment in the presence of healthcare personnel or a volunteer from the community, in order to ensure that the patient takes all the drugs planned for the whole course of treatment.

DOTS

Directly-Observed Treatment Short-course è la strategia raccomandata dall'OMS per individuare e curare la TBC. La DOTS consiste di cinque elementi: impegno a livello politico, accesso agli esami per la diagnosi di TBC, affidabile approvvigionamento dei farmaci, sistemi di sorveglianza e monitoraggio e utilizzo di regimi terapeutici altamente efficaci con osservazione diretta del trattamento.

Front-line drugs

The drugs used in the first instance to treat a disease. In the case of TB, the following drugs are used: isoniazide (H), rifampicin (R), ethambutol (E), pirazinamide (Z) and streptomycin (S). These drugs are very effective against drug-sensitive TB and as a rule are well tolerated by patients.

Second-line drugs

Second-line drugs are used when front-line drugs are no longer effective for treating a patient. They are less effective against *Mycobacterium tuberculosis* and cause far more side effects than the front-line drugs.

Peripheral level

In the organisation of health systems, the peripheral level is the first point of contact between the sick person and the health services. In low-to-medium income countries, peripheral health facilities are often located in remote and rural areas.

“Push” and “pull” mechanisms

Funding mechanisms of the “push” type are those in which investments are made in research in order to stimulate the development of new products. “Push” programmes provide direct funding in the form, for example, of grants made to universities or state-owned laboratories. “Pull” mechanisms, on the other hand, are financial tools devised for creating or strengthening a market, thus increasing the probability of a return on financial investments and consequently making such investments more attractive.

Mycobacteria

Bacteria of the *Mycobacterium* genus, causing diseases such as tuberculosis and leprosy.

Microscopy

Microscopy is currently the most widely used technique for diagnosing TB. From two to five samples of the patient's expectorate are taken, stained and then examined under a microscope. If any bacilli are present, they will be seen as red rods while the rest of the sample is pale blue.

Point-of-care test

Carrying out the test at a “point-of-care” means that the diagnosis is carried out as close as possible to the place where the patient lives. The underlying concept of “point-of-care” is that of doing the test in the easiest way for the patient and having the result immediately, so that treatment can be started at once.

Drug-resistance

When a drug used to treat tuberculosis is actually ineffective against the *Mycobacterium tuberculosis* strain in question, the bacterium is defined as drug-resistant (differing from drug-sensitive).

TB negative or positive expectorate smears

TB is expectorate smear-positive when the *M. tuberculosis* bacteria are identified upon examining the patient's expectorate under a microscope. With smear-negative TB, no bacteria are identified in the patient's expectorate.

Extrapulmonary TB

A form of tuberculosis in which the *M. tuberculosis* bacteria do not infect the lungs but other parts of the body. The most commonly infected parts are the lymph nodes, the bones, the central nervous system, the cardiovascular system and the gastrointestinal system.

Latent TB

This is a form of tuberculosis characterised by the presence in the body of tubercular mycobacteria in a “dormant” state. In other words, they do not grow or reproduce actively. This form of infection is not contagious. It is the opposite of active TB.

Drug-sensitive TB

Bacteria are defined as sensitive to a drug when such drugs are capable of killing or of stopping reproduction of the bacteria in the body, and can therefore eliminate the infection. TB strains sensitive to all front-line drugs are defined as drug-sensitive.

Out-patient therapy

Out-patient therapy for TB is administered under the direct observation of an appointed person (see DOT) but without hospitalising the patient. Patients living close to a healthcare centre go there every day to take their treatment. Patients who live at a distance from the centre are visited at home by healthcare personnel in the community, who brings the treatment to them.

Combination therapy

Therapy characterised by the simultaneous administration of two or more drugs.

Drug Sensitivity Test or DST

This is also known as an antibiogram. It is a technique for determining which drugs are effective and which not. The TB bacilli are exposed to a culture medium enriched with an antibiotic. If the bacteria are capable of growing, then the antibiotic is ineffective and the bacteria are resistant to that drug. If there is no growth of the bacterial, the antibiotic proves itself effective and the bacteria are sensitive, or susceptible, to the drug.

Active tuberculosis

This is a form of tuberculosis characterised by the growth and active reproduction of the bacteria in the infected part(s) of the body, leading to destruction of the infected tissues and organs. Unlike latent TB, it requires immediate treatment.

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Notes

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Médecins sans Frontières (MSF) was founded in Paris in 1971 by a group of doctors and journalists, and is now the largest independent humanitarian organisation providing medical help.

At the present time, over 2300 humanitarian workers, of which 200 are Italian, and 23,000 local helpers are working in far-flung corners of the world, in 63 countries, on 365 projects.

In one year, the MSF teams have carried out over 8,500,000 consultations, treated 1,300,000 cases of malaria, vaccinated 2.5 million people against meningitis and 430,000 children against measles, carried out over 53,000 operations, assisted 12,000 female victims of sexual violence, helped over 100,000 babies to be born and supplied antiretroviral treatment to 112,000 HIV-positive people.

In 1999 MSF received the Nobel Peace Prize, using the funds for its Campaign for Access to Essential Medicines.

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