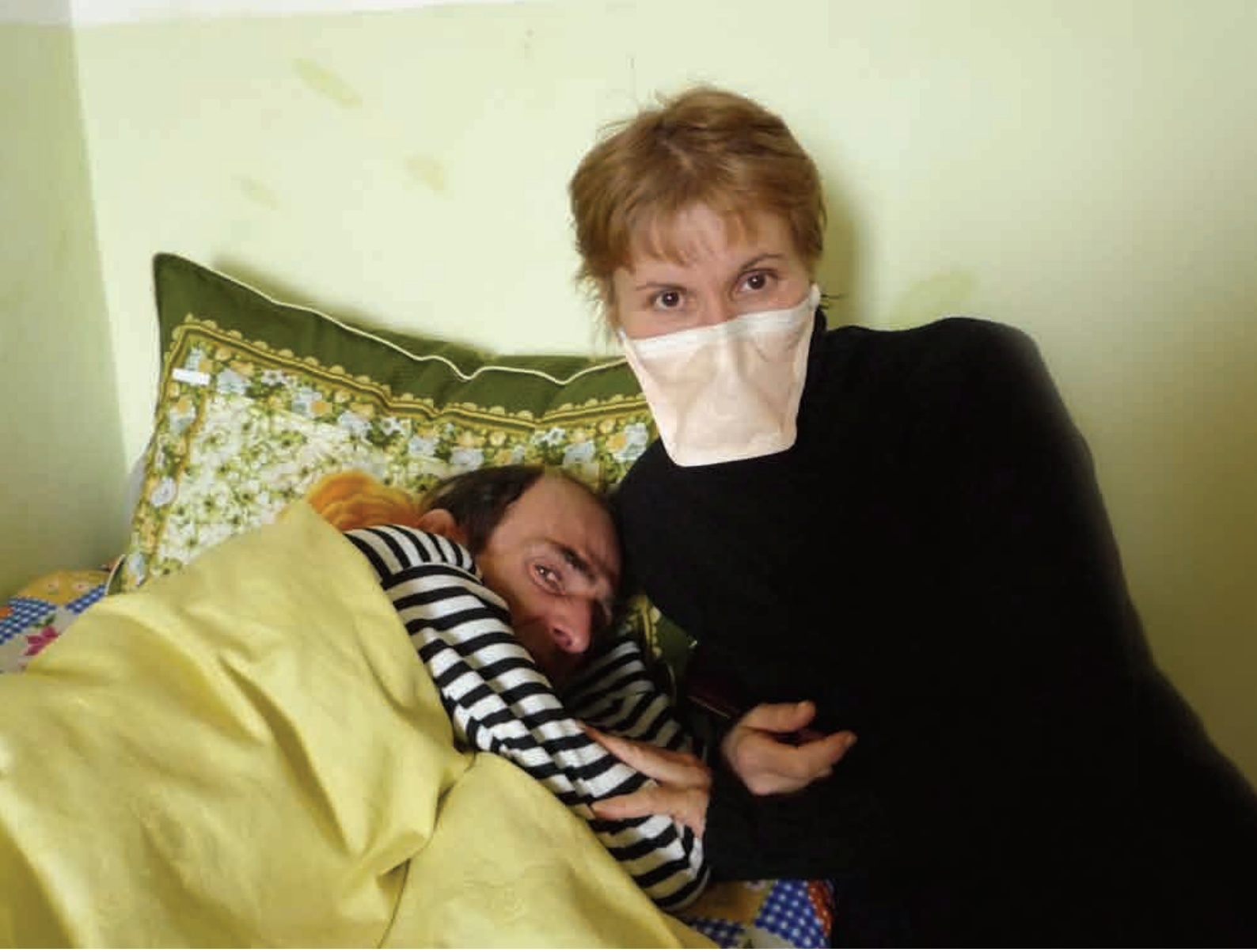


THE UNDERFUNDING OF TB RESEARCH ACROSS EUROPE

EU member states are not contributing their fair share to research and development for tuberculosis (TB). Médecins Sans Frontières (MSF) set out to analyse selected countries in greater detail and the results of funds spent in 2007 are summarised here. MSF sees research and development of new tools for neglected diseases such as TB as a major priority. This is because its field teams are losing too many battles in the fight for the lives of their patients due to the lack of adequate medical tools. Therefore, MSF is calling for a significant scale-up of research and development for TB and increased commitment by European governments.

CAMPAIGN FOR ACCESS TO ESSENTIAL MEDICINES

MEDECINS SANS FRONTIERES

The problem

The World Health Organization (WHO) estimates there are nine million new cases of tuberculosis every year, and almost 1.7 million people die from the disease annually[1]. Often considered a problem of the past, TB has returned with new faces and is affecting not only low- and middle income countries but rich nations as well. Globally, the emergence and spread of strains that are resistant to standard drugs, coupled with the rapid spread of TB among people living with HIV, have led to a situation where far from being contained, in some cases, TB is no longer a treatable disease.

The current medical tools to fight TB are inadequate. The most commonly used diagnostic test in resource-poor settings has essentially remained the same since it was developed almost 130 years ago. Known under the name of sputum smear microscopy, it misses about as many patients as it detects. Moreover, it is mostly ineffective in detecting TB in patients co-infected with HIV, who are most at-risk of dying.[2]

Similarly, the commonly used Calmette-Guerin Bacterium (BCG) vaccine was developed in the early part of the 20th century. This vaccine is highly ineffective: it can protect only small children, and only from the most severe forms of TB; furthermore, immunity is not long-lasting, and the vaccine has hardly any epidemiological impact as small children rarely transmit the disease.

Treatment of TB relies on antibiotics developed decades ago. TB treatment must be followed for at least six to eight months and can have significant side effects. Treatment of resistant strains of TB is even more difficult. It requires daily injections for up to six months and a total treatment time of 18 to 24 months. Patients take a number of different drugs each day, many of which have very significant side effects. What is more, only up to 70% of patients can be cured.[3]

MSF is not waiting for the development of new tools before treating more people with MDR-TB. In some projects we are introducing community-based treatment that makes treatment more accessible and potentially less burdensome for patients, and thus increases effectiveness.

Development of drug resistance over time is a well known, predictable problem for all antibiotics, even when drugs are used as they should be. There are now around half a million new cases of multidrug-resistant (MDR) TB every year[4]. Worse still, in 2006 TB strains known as extensively drug-resistant (XDR) were identified, and for these treatment options are severely limited.

Providing access to diagnosis and treatment for individuals with M/XDR-TB was established as an international health priority by the 2009 World Health Assembly.[5]

TB in Europe

In Europe, TB is still an important public health issue. In 2006, European Union countries reported 81,600 TB cases. In the whole WHO Europe region 55 cases are diagnosed every hour, amounting to almost 500,000 cases annually. The overall treatment success rate among new TB cases, including drug-resistant and drug-sensitive cases, remains relatively low at only 73%[6].

1 Global Tuberculosis Control - Surveillance, Planning, Financing. 2008. World Health Organization, Geneva. http://www.who.int/tb/publications/global_report/2008/en/index.html
2 Running out of Breath: TB Care in the 21st Century. 2005. MSF publication. http://www.msfaccess.org/fileadmin/user_upload/diseases/tuberculosis/FINAL%20RUNNING%20OUT%20OF%20BREATH%20210305.pdf
3 Cobelens et al. 2008. Scaling Up Programmatic Management of Drug-Resistant Tuberculosis: A Prioritized Research Agenda, PLoS Med. 2008 July; 5(7): e150.
4 Anti-Tuberculosis Drug Resistance in the World. Report 4. 2008. World Health Organization, Geneva. http://www.who.int/tb/publications/2008/drs_report4_26feb08.pdf
5 Prevention and control of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis. 62nd World Health Assembly, WHA62.15, May 2009
6 http://www.euro.who.int/tuberculosis

Treatment of multi-drug-resistant tuberculosis in Uzbekistan

Uzbekistan has one of the world's highest rates of multidrug-resistant TB. MSF has been working in the autonomous republic of Karakalpakstan, where the economic situation is particularly grim, since 1998. The cure rate for patients with MDR-TB in MSF's project in Nukus, the region's capital, is 60%. The rate in European countries often is not much better, or may even be worse such as in Germany, where only 52.1% of MDR-TB patients are cured[7]. For success rates to improve, both new diagnostics and new medicines must urgently be developed. They must be more effective, have fewer side effects and drastically reduce treatment times compared to the ones that are currently used.

Long treatment regimens for TB are accompanied by heavy side effects and, traditionally, long periods of isolation. "In this programme, those who enter therapy must come to terms with the fact that they can no longer go to work, or have sex with their partner, or play with their children as long as they remain infectious. The intensive therapy in hospital lasts at least six months. The patient receives a cocktail of five medicines, which includes a painful daily injection, and a handful of pills both mornings and afternoons. The side effects are not only unpleasant, they are often unbearable. The therapy is as brutal and as poisonous as cancer chemotherapy."
Dr. Cathy Hewison, MSF doctor, on MDR-TB

"The hardest thing was the side effects of the medicines. I constantly had to vomit, and saw things that weren't there. But I never thought of giving up. I had to live for my little daughters. I cannot tell you how happy I am to be cured."
MSF patient in Nukus

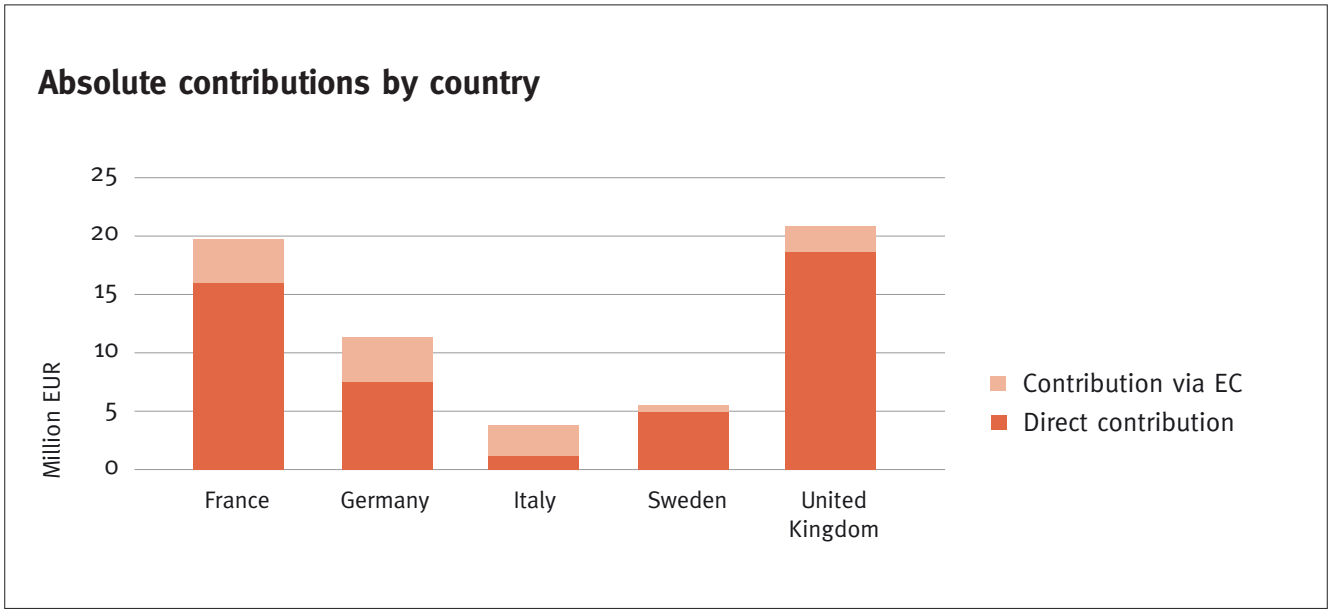
7 Robert Koch Institut (2007). Bericht zur Epidemiologie der Tuberkulose in Deutschland für 2007. http://www.rki.de/cln_100/nn_274324/DE/Content/InfAZ/T/Tuberkulose/Download/TB2007,templateId=raw,property=publicationFile.pdf/TB2007.pdf

The causes

Global funding is insufficient

Today's dismal situation is due mostly to the neglect of TB research over previous decades by the public and private sectors. Pharmaceutical companies have preferred to invest in more profitable markets. Through chronic underfunding of research the world has allowed TB to turn into a public health emergency in some countries. Despite widespread recognition of the problem research continues to fall short of needs. Of the estimated 1.45 billion Euro (US$ 2 billion) required annually to tackle TB, only roughly 350 million Euro (US$ 482 million) is currently invested globally.[8] This constitutes a deficit of over 75%.[9]

MSF analysed public contributions made to TB research and development in five European countries in 2007. These are France, Germany, Italy, Sweden and the United Kingdom. These five countries represent two thirds (67.7 %) of the European Union's income (Gross National Income or GNI). In absolute terms, the UK is leading with 21 million Euro spent on TB research and development, closely followed by France with 20 million. Germany contributes 11 million, Sweden close to 6 million and Italy only 3.5 million Euro. These figures include indirect contributions made via the European Commission (EC), whose contributions overall amount to nearly 19 million Euro. The chart below presents absolute contributions per country, with direct contributions and indirection contributions through the EC shown separately:



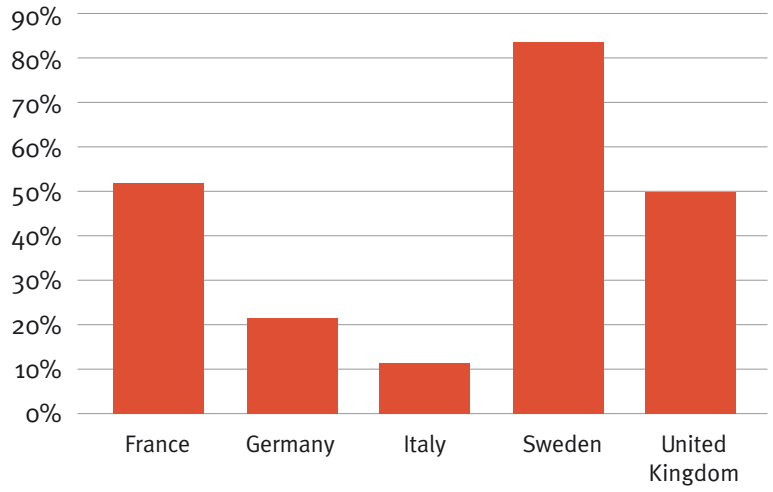
8 This amount includes all efforts to tackle TB.
9 It should be noted that cost estimates provided here are very conservative. New estimates are currently being prepared for the Global Plan to Stop TB, and it is likely that they will be substantially higher.

Fair share not being met

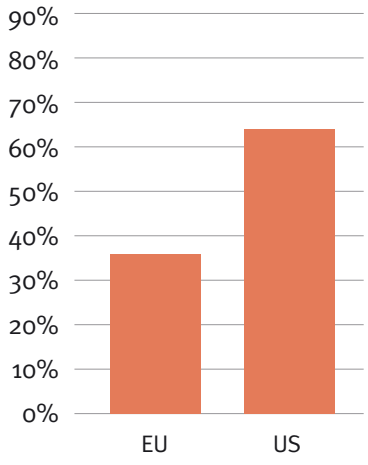
Assuming that countries' contributions to addressing the Global TB challenge should be commiserate with their wealth, it is possible to calculate fair share contributions for each country based on national income. This analysis therefore considers the principle of 'the richer you are, the more you should contribute'. All countries should be required to contribute - even the smallest or least developed - but in proportion to their abilities to pay as measured by GNI.

Except for Sweden who contributes 84%, all European countries MSF analysed are far from contributing their fair share, with France and the UK still doing significantly better (at 52 and 50% respectively) than Germany (22.5%) and Italy (11%). It should be noted that the fair share estimates for government provided here are on the conservative side as a growing contribution by the private sector, keeping its share constant, is assumed. Furthermore, richer countries are assumed to be paying the same share of their GNI as poorer ones while one may argue that poorer countries should actually pay less.

Absolute contributions by country



EU vs US



As a weighted average, these five countries contribute 36.5% of their fair share. This compares very poorly to US funding, which stands at 136.8 million Euro in absolute terms and represents 63.5% of the country's fair share. In other words, while the US contributes almost two thirds of its fair share, Europe only provides a third.

TB missing from the antibiotics resistance debate

Under the Swedish presidency, the EU has targeted antimicrobial resistance as a major priority with a focus on innovative incentives for effective antibacterials against hospital acquired infections. Tuberculosis, and the need to develop new antibiotics to treat TB, is not part of the current debate. However, the links between the need for TB tools and the wider need for new antibiotics are clear. The number of drug-resistant TB cases is on the rise and represents a public health emergency. It will not be possible to reverse this tendency without the development of more effective and less toxic antibiotics against drug-resistant strains of TB.

Potential gains from the antibiotics initiative should also be used to explore innovative incentives for R&D for TB. EU measures would also be justified by the significance of TB in Europe. For example, the UK's capital London has TB incidence rates that are similar to those in Eastern Europe and South America[10].

New financing mechanisms not getting needed support

Research and development for TB is neglected because most people it affects are poor and hence unable to afford expensive health products; therefore they do not represent a commercially viable market for high-priced medicines. Pharmaceutical companies focus on responding to more 'lucrative' diseases in rich countries[11].

Since TB is not generating sufficient interest and funding from the pharmaceutical industry, public actors have a responsibility to step in[12]. However, governments must not only fill the gaps by funding research and development of drugs, vaccines and diagnostics but they must look at new mechanisms that can harness the potential of both the public and private sectors. Mechanisms are necessary that do not rely on high prices secured through patent monopolies and other intellectual property rights which limit access and do not incentivise R&D for resource poor settings. The challenge is to delink the costs of research and development from the price of the product in poor countries. Therefore, besides strengthening support for more traditional mechanisms such as grants for basic research the following mechanisms should be considered:

Product Development Partnerships

Product Development Partnerships (PDPs) are not-for-profit organisations that usually have diverse members such as public research facilities, pharmaceutical companies, NGOs, etc. PDPs function by funding multiple projects in parallel. This is necessary due to the high failure rate among potential candidates. Rather than conducting research themselves, PDPs tend to take on a coordination and portfolio management function to integrate the work of their partners.

In the area of TB, AERAS (Global TB Vaccine Foundation), FIND (Foundation for Innovative New Diagnostics) and the Global Alliance for TB Drug Development (TB Alliance) are the three key PDPs working on vaccines, diagnostics and treatment respectively. However, they have not always enjoyed cooperation from industry and are not funded at levels which allow them to maximise their potential, in particular to afford the costly clinical trials that will be necessary in the coming years. Furthermore, PDPs, like any other mechanism, cannot be the only solution as research needs a diversity of approaches if success prospects are to be optimised.

10 Health Protection Agency 2008. Tuberculosis in the UK - Annual report on tuberculosis surveillance in the UK. http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1225268885969

11 See for example the Report of the WHO Commission on Intellectual Property, Innovation and Public Health. http://www.who.int/intellectualproperty/en/

12 The World Trade Organization attempted to devise a global system that would encourage innovation, including for diseases of the poor, by protecting patents on a global scale in the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). However, this has not worked and the rate of innovation has actually fallen while the number of patented 'me-too drugs' of little or no therapeutic value has been increasing. The Commission on Intellectual Property, Innovation and Health (CIPIH) sums this up by stating 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 the market".

Prize funds

Prize funds can stimulate innovation by offering large cash prize rewards for successful development instead of relying, as in the current model, on high sales prices protected by patent monopolies. In other words, they remove the need to recoup R&D costs through high prices as R&D would already have been paid for. Prize funds also allow governments to prioritise R&D paying only for successful results and direct it toward areas of greatest medical need.

For example, a proposed prize for a TB diagnostic test could be set at 50 million Euro. Setting clear specifications, for example relating to final product cost, effectiveness and sensitivity as a test, as well as adaptability to resource-poor settings, could help to ensure that only the 'right' products qualify. The prize fund model could be tailored to suit different objectives. For instance, in order to encourage both incremental innovation and provide funds to researchers in the years before a product is developed, a percentage of the fund could be reserved for researchers who have made a significant contribution to a solution.

Prizes could also be flexibly awarded in other ways to reward sharing or transfer of technology and know-how. For instance, rewarding scientists to be open about the results of their research could help stimulate information sharing. There already are organisations that can run prizes, and a successful prize has already been run by the TB Alliance to develop simpler and safer methods of developing a TB drug. So far the limiting factor is funding to further exploit this mechanism.

Short-trip to selected R&D landscapes

Germany's high potential is not being used. Some major institutions are dormant on TB and do not sufficiently prioritise 'poor-country diseases'. This Germano-centrism may be one reason why funding to non HIV-related PDPs in 2007 was at a shocking zero. Turf wars between ministries further complicate the situation. As the third-largest economy, and a self-proclaimed centre of excellence for research and development, Germany is clearly disappointing. It remains to be seen whether recent motions passed by the Bundestag on the issue and a new government give hope for improvement of the situation.

In **France**, research and development for tuberculosis is highly concentrated in the area of basic research. While the country's contributions in this area are considerable, the French TB R&D community is fragmented and shies away from taking a multidisciplinary approach. Furthermore, a chronic lack of translational research prevents findings from basic research to be applied and deliver concrete outputs.

Italy is the big laggard among MSF's study countries, contributing only one tenth of its fair share to TB research; only one third of the country's overall contribution is spent directly with two thirds spent indirectly via the EC. Moreover, even major institutions' funding allocations are not transparent, and in many cases detailed breakdowns of allocations by disease or project do not seem to exist. At any rate, it is clear that the Italian government all but neglects research and development affecting poor countries.

Sweden stands out for contributing more than 80% of its fair share to TB R&D. This is encouraging, even if there is considerable room for improvement in terms of supporting alternative and innovative funding mechanisms. Furthermore, Sweden has recently announced a significant decrease of its budget for research cooperation with developing countries, which is even disproportionally higher than overall aid budget cuts. This is certainly cause for concern.

The **United Kingdom**, despite struggling with a TB problem inside its borders, contributes only half of its fair share to TB research. Furthermore, while being slightly more creative and innovative than other EU countries in supporting new funding mechanisms, UK institutions still lack equitable licensing policies; moreover, the UK's choices of funding mechanisms to support, such as the Advanced Market Commitment, are questionable.

Recommendations

1. Increase funding

- MSF calls on all European governments to take TB seriously and demonstrate that in their R&D funding allocations. Specifically, this means that all European countries contribute at least their fair share, i.e., the amount of funding that is appropriate given their economy's size. Current contributions, shortfalls (based on conservative need estimates), as well as total requirements per country per year (all in million Euro) are as follows:

	Current contribution	Shortfall/additional contribution needed	Total contribution required per year
France	19.7	18.5	38.2
Germany	11.2	38.6	49.8
Italy	3.5	27.4	30.9
Sweden	5.7	1.1	6.8
United Kingdom	20.7	20.5	41.2

2. Support innovative funding mechanisms and sustainable R&D strategies

- EU governments must use their money wisely. Besides continuing to support traditional funding mechanisms such as grants, they should consider setting up prize funds or other innovative mechanisms. In addition, they must support product development partnerships and ensure they are adequately funded. As global leaders in health policy, European governments must also use their political weight to encourage other governments to follow suit.

- European governments must prioritise poor-country diseases such as TB and neglected tropical diseases. This needs to be reflected in comprehensive, research and development strategies. These must acknowledge that R&D is a long-term and high-risk endeavour that is of little interest to industry in these disease areas and hence needs governments to step in. There is also a critical need to support clinical trials for drug-resistant TB, an area that is not currently being funded.

- Furthermore, medical innovation alone is not enough. Funding mechanisms must also ensure that the products of research and development are made available, affordable and accessible to those who need them. Such mechanisms must also include specific provisions to overcome any patent or other barriers to low cost access. EU member states as well as the EC must implement the WHO Global Strategy on Public Health, Innovation and Intellectual Property.

- The European Union, led by the Swedish presidency, must extend its ambitions to tackle the problem of antimicrobial resistance to tuberculosis and other poor-country diseases where relevant.

- MSF calls on both the EC and the EU, and particularly on the upcoming presidencies, to consider the recommendations above in the Communication on Global Health that will be adopted in the next EU presidency period.

CAMPAIGN FOR ACCESS TO ESSENTIAL MEDICINES
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