Breathing new life into the fight against tuberculosis

The think tank Santé mondiale 2030 has been in existence since October 2016. It brings together personalities involved in global health, such as Françoise Barré-Sinoussi, Paul Benkimoun, Michel Cot, Sana de Courcelles, François Dabis, Annabel Desgrées du Lou, Jean-François Delfraissy, Frédéric Goyet, Mathieu Lamiaux, Michel Kazatchkine, Marie-Paule Kieny, Lélio Marmora, Benoît Miribel, Olivier Nay, Louis Pizarro, Anna-Laura Ross, Benoît Vallet. Stéphanie Tchiombiano is the coordinator.

This document is the fruit of a collective work within the group. It does not commit in any way, nor does it reflect the individual opinion of each member.

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Summary of recommendations

For the first time, a high-level meeting of the General Assembly of the United Nations[1] will be dedicated to tuberculosis at the end of September 2018 in New York. It is undoubtedly the most important political meeting ever held on the subject. The health issues at stake are crucial, and the international community's expectations on the matter are high. Our recommendations focus on four main themes:

1. **Tuberculosis as an issue of leadership and influence**. France must reinvest financially and politically in the multilateral spaces for global health, especially those dedicated to the fight against tuberculosis. The latter is organised in a vertical way, with few synergies between players. Our recommendations:
   - ❖ Call for a clarification of roles and for a greater integration of the fight against tuberculosis with the framework of the Sustainable Development Goals (SDGs);
   - ❖ Encourage the BRICS (Brazil, India, China, the Russian Federation and South Africa) to strengthen their commitment;
   - ❖ Take the initiative to define a European position on these issues.

2. **Tuberculosis, a disease of poverty.** Tuberculosis hits the poorest and the most vulnerable around the world. It exacerbates inequalities and reinforces vulnerability of the most disadvantaged. France must promote the fight against tuberculosis as a symbol and indicator of progress in universal health coverage. Our recommendations:
   - ❖ Impulse a more proactive policy towards the most vulnerable and marginalized groups in society;
   - ❖ Advocate for a free access to quality screening and treatment for all, including for multidrug-resistant tuberculosis.

3. **Operational strategies to be reinvented**. Despite the international mobilization, progress on tuberculosis is not as significant as it should be. The strategies put in place in the countries of the South are totally standardized and not very creative. We need to "dust off" the way we fight against tuberculosis and find new, innovative and adapted approaches to a problem that isn't just medical. Our recommendations:
   - ❖ Stimulate the community approach and associative partners;
   - ❖ To think about the medical care of patients in terms of the overall burden and not only in terms of drugs;
   - ❖ De-compartmentalize tuberculosis services by pushing for the institutional integration of programmes in countries.

4. **Putting research at the heart of the agenda**. The tools currently available for the control of tuberculosis are sub-optimal and will not permit to achieve the objectives set at the international level. Our recommendations:
   - ❖ Drive a new global research and innovation strategy, further integrating operational research and social sciences;
   - ❖ To support institutionally and financially the establishment of a French research platform on tuberculosis.

A unique opportunity to remobilize the international community

The health stakes of the New York conference are crucial: tuberculosis is now the world's leading cause of infectious death (1.7 million people died in 2016, which approximately means 4,000 deaths per day[2]). Indeed, even if antibiotic treatments have been available for decades, the outbreak has still not been contained. Tuberculosis is both one of the top 10 most common causes of death for the world's population and the leading cause of death among people living with HIV[3]. This situation is not only alarming for the most vulnerable populations: the emergence of multidrug-resistant tuberculosis is a security threat for the world, and France is not spared by the disease[4].

Significant progress has been made in recent years, notably thanks to the investments of the Global Fund (which alone accounts for 80% of the financing of the fight against tuberculosis) and Unitaid (which has tripled its investments in tuberculosis in the last three years[5], and which has led to decisive advances in paediatric treatment, rapid screening and new treatments for multi-drug-resistant tuberculosis). The Stop TB Alliance aims to coordinate the fight against TB globally.

The fight against tuberculosis is based on three complementary axes: diagnosing the earliest possible stage of the disease, putting patients on treatment, and preventing the disease in the general population with a vaccine. If the latest WHO strategy (adopted in 2014) aims to eliminate the tuberculosis epidemic by 2035[6], this target now appears to be impossible to achieve without new approaches to prevention and treatment, and without a real collective boost. In the era of the SDGs, this action must also be multisectoral.

Why does France have a special role to play?

Country of origin of BCG, an anti-tuberculosis vaccine administered for the first time in Paris in 1921, France has always played an important role in the fight against tuberculosis.

In particular, France is very involved in research. Several studies carried out by French research teams have contributed to the evolution of screening or treatment strategies at the international level, whether it is to evaluate the benefits of intensive, systematic and continuous screening for tuberculosis in severely immunocompromised HIV-infected persons[7] , to improve screening and access to treatment of children[8], to study resistance to treatment[9], to shorten the time to treatment, to reduce the duration of treatment for multidrug-resistant tuberculosis[10] or to develop new generation molecular diagnostic tests[11]. In France, research on candidate vaccines are currently underway in Lille, Paris and Toulouse[12].

France is currently the world's **second largest financier** in the fight against tuberculosis, through two complementary mechanisms: the Global Fund to Fight AIDS, Tuberculosis and Malaria and Unitaid. In addition, Expertise France's 5% initiative finances projects and mobilizes technical experts to support 25 countries in Africa, Asia and Eastern Europe on tuberculosis at their request.

Finally, the next replenishment conference of the Global Fund will take place in Paris in 2019. The New York meeting on tuberculosis in September 2018 will therefore be an important milestone to build global momentum and make the Replenishment conference a success in 2019.

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Tuberculosis, an issue of leadership and influence

The New York meeting must generate renewed political commitment at the highest level to combat and end tuberculosis. France, which is particularly committed to the fight against major pandemics, must seize this opportunity to reaffirm its leadership in global health.

The institutions involved in the fight against tuberculosis are governance is fragmented and insufficiently coordinated: a vertical programme within the WHO, the Stop TB Partnership, the International Union for the Prevention of AIDS and Tuberculosis (IUAT), the International against Tuberculosis and Lung Disease" (based in Paris) and the Global Fund against AIDS, tuberculosis and malaria. In addition, synergies with efforts to combat antimicrobial resistance are still insufficient.
France could call for a clarification of the roles of the different actors in order to appease the spirit of competition that exists between some of them and to **call for a greater integration of TB control with the other SDGs**.

The BRICS undeniably have a stronger political and financial role to play in the fight against tuberculosis. They alone account for 46% of all cases of tuberculosis and 40% of tuberculosis-related deaths worldwide. While the Global Fund's contribution, which is the world's largest source of international funding for tuberculosis [ii], is essential for low income countries or in the lower income groups of middle-income countries, the funds devoted to tuberculosis control at the national level are mainly due to domestic financial commitments, particularly in the BRICS and other emerging economies ... Three countries bear most of the burden of this disease: India, China and the Russian Federation together account for almost half of the registered cases of multidrug-resistant tuberculosis (MDR-TB) worldwide. The Russian President spoke for the first time on global health at the Moscow conference in November 2017[i]. The Indian Prime Minister, Narendra Modi has established himself as a champion of the fight against tuberculosis a few months before the General Health Assembly in May 2018. Maintaining financial commitments at a constant level will not be enough to eliminate tuberculosis, and there is a lack of 2 billion dollars annually according to the WHO[iii] to implement the strategy to eliminate tuberculosis, not to mention the necessary investment in research and development (estimated at US$1 billion). **France must support this dynamic and encourage the BRICS to strengthen their commitment.**

France should take the lead in defining a European position on these issues. Europe's political place is to be found. On the one hand, Europe is doing well, with a decrease in new cases of tuberculosis, but on the other hand, Eastern Europe is a major source of resistant tuberculosis. Tuberculosis, as well as the fight against antimicrobial resistance, are priority issues for the German Chancellor. Angela Merkel, and there is a real opportunity for Franco-German co-responsibility, that should be seized in the run-up to the September 2018 meeting, but also, more largely for the global health debates of the next two years.

Tuberculosis, the disease of the poor

Despite the fact that diagnosis and treatment is virtually free of charge worldwide, tuberculosis is. fundamentally indicative of a country's social / economic inequalities. Wherever it is rampant, tuberculosis affects the poorest people. In low-resource countries, it affects the most vulnerable, the malnourished, people infected with HIV, displaced persons and drug users. In France, it mainly affects the homeless, persons of foreign origin, the elderly, migrants and incarcerated people. Because they are rejected or marginalized, too

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many infected people are "missing in action" and do not have access to quality services: only two-thirds of new cases are detected every year according to WHO[13], allowing the epidemic to spread to other countries. Tuberculosis exacerbates inequalities and increases the vulnerability of the most vulnerable by inhibiting their ability to work throughout the treatment period (six months for drug-sensitive tuberculosis, and many more for multi-resistant tuberculosis).

France must take these issues on board politically and make the fight against tuberculosis a symbol and an indicator of progress in universal health coverage[14]. The goal of universal health coverage is to ensure that all individuals have access to the health services they need without causing them financial hardship[15]. This approach is consistent with the values of equity and solidarity put forward by France to meet the major health challenges in the world[16].

Thinking about the evolution of tuberculosis care in the context of universal health coverage implies both a more **voluntary policy towards the most vulnerable and marginalized groups and a completely free access to screening and care.** In particular, it is time to stop confining ourselves to the traditional direct examination of sputum, which has shown its limitations in terms of sensitivity and specificity[17], in order to finally offer to the greatest number of people a diagnosis by molecular biology or culture of tuberculosis. Beyond first-line drugs and quality screening, the free TB package should include follow-up consultations, the patient transportation, hospitalization costs, nutritional support and medicines for the treatment of multidrug-resistant tuberculosis, where appropriate.

Dusting off TB control strategies

Despite international mobilization, progress on tuberculosis is not as important as they could be. From 2000 to 2016, the overall number of deaths by tuberculosis in the general population (excluding HIV), has for example decreased by only 30% at the global level. The mortality rate from tuberculosis is declining by about 3% per year globally and the incidence (i.e. the number of new cases) is declining by only 2% per year according to the WHO. These decreases are far too slow if our goal is really to eliminate tuberculosis by 2035.

The strategies put in place in the countries of the South remain standardised and not very creative. They have not been renewed for decades. The WHO has been advocating since the in the early 1990s for the implementation of a so-called "control" strategy called DOTS (Directly Observed Therapy Short-Term)[18]. 25 years after the WHO declared the tuberculosis a "global health emergency", the epidemic remains a global scourge. How to explain the fact that this strategy[19] has not evolved for several decades, while AIDS strategies today call for a spacing of several months between medical appointments for well-observing patients, with results that demonstrate that this does not affect their good compliance? National tuberculosis control programmes, inherited from old systems, are also vertical, and in most cases disconnected from public health systems.

We need to "dust off" our approach to TB control and find ways to new, innovative and more adapted approaches:

- **By stimulating a community approach and associative partners**, hitherto too little invested in the fight against tuberculosis: expert patients, quality of care observatory, representation within the bodies of the Global Fund coordination, etc.

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Tuberculosis patients or former patients speak little and their voice is hardly ever heard / defended.

- **Placing NGOs and infected people at the heart of the response**, by adapting existing community mobilization tools[20], could truly accelerate the fight. Associative actors are certainly the only ones that will enable us to create links with the 40% of infected people who are "missing" or to reach HIV-infected people and children under 5 years of age more easily, in order to facilitate their access to preventive treatment for tuberculosis[21]. A call for projects from the 5% Initiative could, for example, encourage associations to become more involved in the fight against tuberculosis and enable them to have access to funding.

- **By de-compartmentalizing and pushing for the institutional integration of programmes**, at the country level. Three-quarters of newly co-infected patients by the two diseases (tuberculosis and HIV) are in Africa and it is now important to bring together the teams fighting against these two pandemics on this continent so that they work in perfect cohesion. The Global Fund could play a major role in this dynamic, by further stimulating these connections.

- **In thinking about the medical management of patients in terms of overall coverage and not just in terms of drugs**. The concept of "global coverage" hitherto essentially mobilized in the fight against HIV-AIDS, can be declined for tuberculosis, which remains a disease of poverty, of marginality. The socio-economic determinants of the disease are and its concrete consequences on the lives of patients must be more further taken into consideration in the development of national control strategies. Therapeutic education, setting up of discussion groups, psychological or nutritional support can be some interesting leads.

Putting research at the heart of the agenda

Investment in research must be considered a sine qua non condition for the elimination of tuberculosis. While we regularly hear that the "tools" are available to eliminate HIV/AIDS as a public health problem[22] , tuberculosis clearly is not.

The current strategy is based on the simple principle of identifying and treating patients to reduce the reservoir and the transmission of infection. One might have imagined that this strategy, supported by significant financial resources, would bear fruit quickly. However, despite the identification of the infectious agent responsible for the disease for more than a century, despite the perfect knowledge of the mode of transmission of the disease - by air - and despite the existence of an effective curative treatment, available and free of charge for patients, tuberculosis still exists and kills 1.7 million people worldwide every year.

It is therefore necessary to face the facts: the failure of the strategy put in place over the past 40 years demonstrates the need to develop new diagnostic strategies and methods[23], new drugs, with shorter and more effective protocols[24], and/or new vaccines[25] to effectively interfere with the transmission chain. Challenges are numerous and include the difficult inclusion of vulnerable populations (children, pregnant women, the elderly) and the challenges of combating multidrug-resistant tuberculosis. Nearly 40% of people infected with the bacillus have not been detected/do not know they are carriers of the disease (and propagate it very quickly). It is no longer just a question of being interested in those who

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suffer from tuberculosis but also to those who are susceptible to be (carriers of latent tuberculosis or persons exposed to patients with latent tuberculosis). The WHO estimates that about a quarter of the world's population is infected with latent tuberculosis[26], which means that these people have been infected with the tuberculosis bacillus but are not (yet) sick and cannot transmit the disease. Over the course of their lifetime, infected individuals have a 5% lifetime risk of developing an illness. On the other hand, the risk is much higher for those who are immunodeficient, such as people living with HIV, that are malnourished or with diabetes. Research and innovation is a formidable response to these challenges[27]. Tuberculosis control must address issues of efficiency, while at the same time adapting to health systems and helping to strengthen them**. If new tools are to be available by 2025**, immediate investments must be made in research and development, while negotiating the terms of access to new treatments or cutting-edge technologies at an early stage.

Tuberculosis is neither a disease of the past nor a "disease with no future"[28]. It must be the subject of innovation, research, mobilization and hope. New research is needed today to ensure that tuberculosis is once again associated with technological innovations or medical advances, as was the case in the first half of the 20th century.

France and Europe must give impetus to a new global research strategy and innovation for tuberculosis[29]. They can be exemplary by intensifying considerably the effort and by supporting their research teams[30]. Two areas seem to us to be particularly important to support: (1) operational research so that "advances" in science can be more rapidly useful / translated into concrete interventions in the countries[31]; (2) social sciences to better understand the epidemic and its drivers (including barriers to screening and fear of hospitals). Research must not be solely biomedical: tuberculosis remains a disease of poverty, and popular representations of it are particularly negative. It is now necessary for social science researchers to reinvest in these complex issues.

More specifically, **the setting up of a French research platform on tuberculosis within the framework of the AVIESAN Alliance**, as did the ANRS for HIV-tuberculosis co-infections, would create a collective dynamic among researchers specializing in this disease.

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APPENDIX 1: Presentation of Santé mondiale 2030

Santé mondiale 2030 is an independent think tank that has been bringing together personalities with a long history of involvement in global health issues since 2016. It places its reflections within the framework of the Sustainable Development Goals.

OUR COMMITMENT

France is one of the largest providers of international health funding, but its influence in international bodies and health partnership platforms remains limited.

We are convinced that France can only be heard and listened to in the international arenas of global health when its actors succeed in conveying a strong and coherent message, structured around clear and stable objectives, supported by values that are attached to the history of health in France.

Our objective is to ***formulate recommendations*** *on France's global health policy and to* ***mobilize all stakeholders*** *so that health issues become a strategic focus of French international aid.*

OUR PREVIOUS NOTES

- 1- White Paper on Global Health
- 2- Our vision of Global Health
- 3- Heath is a priority for the Sahel

OUR MEMBERS

Santé mondiale 2030 brings together personalities who have long been involved in global health, such as Françoise Barré-Sinoussi, Paul Benkimoun, Michel Cot, Sana de Courcelles, François Dabis, Annabel Desgrées du Lou, Jean-François Delfraissy, Éric Fleutelot, Frédéric Goyet, Mathieu Lamiaux, Michel Kazatchkine, Marie-Paule Kieny, Lélio Marmora, Benoît Miribel, Olivier Nay, Louis Pizarro, Anna-Laura Ross, Benoît Vallet. Stéphanie Tchiombiano is the coordinator.

Our vision of Global health

Global health is a fundamental human right. It is **also a global common good. Universal access to health** and the construction of sustainable health systems are central to **human development,** the **economy** and **the fight against poverty**, as well as **security**. They therefore make a decisive contribution to the inclusive **development of societies and to peace**.

Health issues are complex and require **long-term strategic visions** to address the challenges posed by globalization, increased human trade, demographic transitions or climate change.

SANTÉ MONDIALE 2030

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[1] In November 2017, a global ministerial conference will be held on the fight against tuberculosis, which resulted in the "Moscow Declaration" that will serve as the basis for the meeting.
[2] Source Global Fund
[3] 35% of PLWHIV deaths are related to Tuberculosis according to WHO
[4] Nearly 5,000 cases of tuberculosis have been recorded in France according to Santé publique France, including a hundred patients with multidrug-resistant tuberculosis.
[5] Unitaid has, among other things, allowed to accelerate access to new antibiotics for multi-resistant tuberculosis. / To develop affordable and high quality paediatric formulations / To develop affordable and high quality paediatric formulations / To achieve a 40% price reduction for an innovative test for tuberculosis.
[6] The "end TB Strategy", http://www.who.int/tb/strategy/end-tb/fr/. The numerical targets of the strategy are as follows: (1) Reduce the number of deaths by 95% by 2035 compared to 2015. (2) Reduce by 90% by 2035 the incidence rate (i.e. new cases) of tuberculosis by 2035 and (3) By 2035, no more families will have to bear catastrophic costs related to tuberculosis.
[7] ANRS temprano trial: https://www.bordeaux-population-health.center/wpcontent/uploads/2017/10/2017-10-09_CP-Extended tracker-ANRS-TEMPRANO-1.pdf
[8] The TB-SPEED project aims to reduce childhood tuberculosis mortality with the development of a simplified and cost-effective approach to the diagnosis of paediatric tuberculosis in order to increase the case detection and improve access to treatment. This is a project implemented by the University of Bordeaux, IRD and the Chantal Biya Foundation, financed by UNITAID and the 5% initiative of Expertise France in 7 countries (Cambodia, Cameroon, Côte d'Ivoire, Mozambique, Sierra Leone, Uganda, and Zambia).
[9] Notably the team of the Pasteur Institute of Lille.
[10] Most cases of tuberculosis can be cured with standard antibiotics, but the strains of multi-drug resistant tuberculosis are much more difficult to treat. A study funded by the 5% initiative of Expertise France, and coordinated in 9 French-speaking African countries by the International Union against tuberculosis and respiratory diseases has shown that it is possible to reduce from 24 to 9 months the treatment of multi-resistant tuberculosis without major side effects. Unitaid invests 70 million in an MSF/Partners in Health/IRD project, which aims to develop a new generation of treatments for multi-drug resistant tuberculosis, over a shorter period of 6 months, replacing injectable treatments with oral treatments.
[11] A new-generation molecular diagnostic test called Deeplex-MycTB®, developed by the Pasteur Institute of Lille in collaboration with Genoscreen. In addition, researchers at the Pasteur Institute of Lille and Inserm, in collaboration with the Université Libre de Bruxelles, are currently developing a new test to diagnose people with tuberculosis and to identify among them those most at risk of developing active tuberculosis.
[12] Another example is the research of the Sanofi laboratory, which has developed a molecule to reduce the duration of treatment of latent TB: https://www.nih.gov/news-events/news-releases/onemonth-tuberculosis-prophylaxis-effective-nine-month-regimen-people-living-hiv.
[13] In 2015, 4.3 million cases of tuberculosis were undiagnosed, untreated and unreported. According to the 2016 Global Tuberculosis Control Report, these missing cases account for 40% of the 10.4 million people who develop active tuberculosis. Moreover, only 20% of 580,000 people diagnosed with drug-resistant tuberculosis have started a treatment.
[14]https://www.uhc2030.org/fr/nouvelles-et-evenements/nouvelles-uhc2030/article/sdg-indicator-3-8-1-measure-what-matters-465653/
[15] WHO, http://www.who.int/features/qa/universal_health_coverage/fr/
[16] *"The principles of equity and solidarity, particularly in the field of health, are strong values. carried by France. These are reflected in the promotion of health on a universal scale, including the fight against all forms of inequalities - social, and territorial - the promotion of access to all to health services and quality care, and by the provision of health coverage Universal (UHC)",* French strategy in global health, March 2017, p.16.
[17] Desikan P. Sputum smear microscopy in tuberculosis: Is it still relevant? The Indian Journal of Medical Research. 2013; 137(3):442-444.

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[18] The DOTS strategy is based on a pilot experiment conducted in Tanzania by public health physicians at Harvard Medical School, which was later transposed to the homeless outreach program in New York City, according to Jean-Paul Gaudillière in "2. From international public health to global health. WHO, the World Bank and the Government of Chemical Therapies", The Government of Technosciences. Governing progress and its damage since 1945. The Discovery, 2014, pp. 65-96.

[19] Throughout the course of treatment, patients should take their medication under the supervision of a physician or trusted third party. This system, which is now in place in 180 countries, makes it possible to "monitor" patients and ensuring compliance, to avoid resistance to antibiotics that would make the treatment ineffective. This strategy, infantilizing and costly for the patient, is it adapted to today's challenges? If it has demonstrated its curative effectiveness, is it adapted to reduce the incidence of the disease? Reducing tuberculosis control to a biomedical problem, it does not consider the social and anthropological realities of the illness.

[20] Tuberculosis is not a chronic disease, so community dynamics cannot, of course, be comparable with that of the fight against HIV/AIDS.

[21] Preventive treatment with isoniazid (an anti-tuberculosis drug) is recommended by WHO for people infected with HIV in so-called southern countries. This recommendation is unevenly applied even though scientific evidence of the benefits of this preventive treatment has been widely demonstrated, notably through the ANRS Temprano trial.

[22] Asserting that "the tools to eliminate HIV as a public health problem exist" is also questionable, but this is not the purpose of this paper.

[23] There is now a need to go beyond patients presenting at health centres, to develop new strategies to make testing available at the community level and to find more appropriate diagnostic tests, especially for children who cannot spit.

[24] Research will have to develop new molecules and new, more effective treatments, especially for patients who have developed resistance to treatment. If the durations of treatment have been considerably reduced in recent years, the drugs available for treatment have been are to be taken for periods that are still far too long for patients (6 months), and with very important adverse effects.

[25] If BCG is very useful in preventing severe disease in young children (near 90% effectiveness), it is not fully effective and only protects adults in about every other case. The search for a new vaccine is necessary if we really want to eliminate the illness within 20 years.

[26] http://www.who.int/fr/news-room/fact-sheets/detail/tuberculosis consulted on 18/07/2018.

[27] Unitaid, for example, is funding the world's largest initiative for innovation in latent tuberculosis treatment: the IMPAACT4TB project (Aurum Institute/PATH/John Hopkins University), dedicated to a short-term treatment (12 weeks), with better adhesion and an improved efficiency. The project is taking place in 12 countries in Africa, Asia and South America. It will be implemented at scale by several countries, with financial support from the Global Fund and USAID.

[28] Expression used by anthropologist Janina Kehr, highlighting the despised and marginalized status of tuberculosis, in his doctoral thesis in anthropology, under the direction of Didier Fassin, Paris, EHESS, November 2012.

[29] The Global Framework for Action on Tuberculosis Research 2016-2025 developed by WHO and its partners are a great roadmap for research.

[30] AVIESAN sud organized a workshop bringing together the main French and Francophone researchers working on tuberculosis in January 2018 (TB concerted action) to define research priorities http://www.infectiologie.com/UserFiles/File/reunion/2018-preprogramme-research-priorities-tb.pdf

[31] The example of Isoniazid prophylaxis of tuberculosis is typical: while the efficacy of Isoniazid prophylaxis for tuberculosis of this intervention has been largely scientifically demonstrated, it has still not been implemented optimally.

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