

FIGHTING TUBERCULOSIS

GRI Standards:

N/A

EXECUTIVE SUMMARY

Along with HIV/AIDS and malaria, tuberculosis (TB) is one of the most widespread infectious diseases in the world and is one of the top 10 causes of death. To achieve the strategic objectives of tuberculosis elimination, the new WHO recommendations aim to accelerate the detection and to improve the results of tuberculosis treatment by using a new rapid diagnostic test and a shorter and less costly treatment regimen. Sanofi is a key historical partner as it is the first company to manufacture rifampicin, the cornerstone of tuberculosis treatment. Today, Sanofi remains at the forefront by developing new treatment options for tuberculosis. Sanofi is working with external partners to shorten the duration of treatment for latent and active tuberculosis. Besides, one of the main areas of intervention is prevention, particularly through the treatment of latent tuberculosis.

TABLE OF CONTENTS

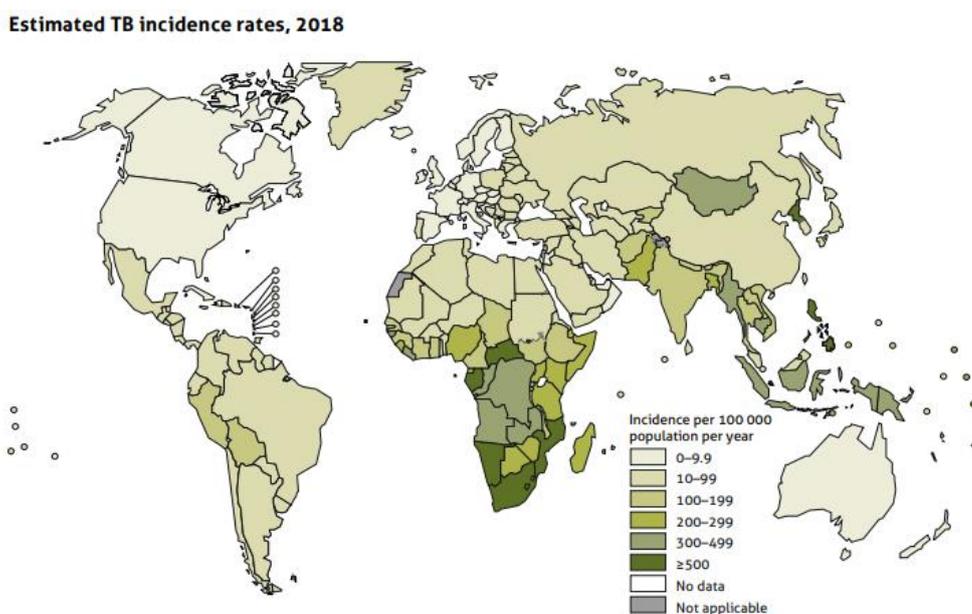
1. CONTEXT	3
1.1. The End TB Strategy : A global strategy to end the global TB epidemic	3
1.2. Major challenges to simplify treatment and fight resistant strains	4
2. POLICY	5
3. ACTIONS	5
3.1. Tuberculosis treatment solutions	5
3.2. Simplifying tuberculosis treatment	5
3.3. Optimizing access to tuberculosis treatment	6
3.4. Finding solutions with our partners	6
3.5. Improving educational efforts on Latent Tuberculosis infection	7

1. CONTEXT

Along with HIV/AIDS and malaria, tuberculosis (TB) is one of the most widespread infectious diseases in the world. This contagious disease, caused by the bacterium *Mycobacterium tuberculosis*, is spread through respiratory droplets. In 2018, there were :

- 10 million new cases, with eight countries gathering 67 % of TB cases.
- 1.45 million deaths, the vast majority of them in low- and middle-income countries¹.

Figure 1: Estimated TB Incidence Rates, 2018



SOURCE WHO : GLOBAL TUBERCULOSIS REPORT 2019, FIG. 3.4, PAGE 38 https://www.who.int/tb/publications/global_report/en/

In addition, a quarter of the world's population - currently estimated to affect 1.7 billion people worldwide - is infected with latent TB: they have no symptoms, are not contagious and most do not know they are infected. Without treatment, 5 % to 15 % of these people – 85 million to 170 million people globally – will develop active TB, the form which makes people sick and can be transmitted from person to person.

HIV infection makes people up to 37 times more likely to fall ill with the active disease.

Close to 1.5 million people die of TB every year.

1.1. The End TB Strategy : A global strategy to end the global TB epidemic

In May 2014, the World Health Assembly adopted a resolution on a post-2015 strategy aiming to end TB. The End TB Strategy sets ambitious targets, i.e., reducing TB deaths by 90 % and decreasing new cases by 80 % between 2015 and 2030.

¹ WHO, Global Tuberculosis Report 2019: https://www.who.int/tb/publications/global_report/en/

The Strategy is composed of three pillars : A first pillar focuses on integrated patient care and prevention, the second pillar focuses on the mobilization of all actors and the transformation of healthcare systems, and the third pillar focuses on the need for intensified research and innovation. Sanofi supports this Strategy and takes action to contribute to reaching its ambitious targets.

In September 2018 was the first United Nations High Level meeting (UN-HLM) on tuberculosis. This meeting was a tremendous and unprecedented step forward by governments and all partners engaged in the fight against TB. The outcome was a political declaration agreed by all United Nations Member States, in which existing commitments to the Sustainable Development Goals (SDGs) and WHO's End TB Strategy were reaffirmed, and new ones added.

The political declaration included four new global targets :

1. Treat 40 million people for Tuberculosis disease in the 5-year period from 2018 to 2022 ;
2. Reach at least 30 million people with TB preventive treatment for a latent TB infection in the 5-year period from 2018 to 2022 ;
3. Mobilize at least US\$ 13 billion annually for universal access to TB diagnosis, treatment and care by 2022 ; and
4. Mobilize at least US\$ 2 billion annually for TB research.

1.2. Major challenges to simplify treatment and fight resistant strains

Standard treatment for TB consists of a combination of antibiotics taken daily, usually for six months: two months of treatment with four antibiotics, followed by four months with two antibiotics.

When administered properly, the treatment for TB is generally highly effective. However, for many patients it is difficult to comply with six months of treatment. Poor compliance not only puts the patients at risk of treatment failure, it also creates conditions that encourage the development of antibiotic-resistant bacteria.

Since the early 1990s, the World Health Organization (WHO) has recommended a strategy known as Directly Observed Treatment, Short course (DOTS). This costly strategy relies on having healthcare personnel who can support and monitor patients, to ensure that they take their entire course of treatment. However, efforts are needed to simplify TB treatment by reducing the treatment duration.

Preventive TB therapy take 6 to 36 months and uptake is low. Research shows that patients are far more likely to complete shorter treatment courses.

Strains of *Mycobacterium tuberculosis* that are resistant to conventional treatments have begun to appear in the 80's. In 2017 they caused 377,520 new cases of multidrug-resistant tuberculosis (MDR-TB).² It is therefore crucial to stop the progression of resistance and to develop new treatments.

For more information, see : https://www.who.int/tb/publications/global_report/en/

² WHO, Fact sheet on Tuberculosis, last updated October 2019: <https://www.who.int/news-room/fact-sheets/detail/tuberculosis>

2. POLICY

Sanofi aims to contribute to the objective to end the epidemics of tuberculosis by 2030, as per Goal 3, target 3.3 of the Sustainable Development Goals.

Sanofi was the first company to manufacture rifampicin, a key antibiotic for the treatment of Tuberculosis that was isolated in 1957 by scientists at Lepetit Research Laboratories in Milan (Italy), now part of Sanofi.

The Company remains one of the key producers of this component in all drug-susceptible tuberculosis (DS-TB) treatments. Several of the company's manufacturing facilities have developed and are currently producing a range of antibiotics to treat TB, which are distributed in many countries.



In 2011 rifapentine, a member of the rifamycin family, was shown by the US Centers for Disease Control and Prevention (CDC) to have the ability to simplify considerably the treatment of latent TB (LTBI).³ The proposed development of rifapentine offers the prospect of simpler and shorter latent TB treatments, with the aim of improving patient compliance. A rifapentine-based regimen shortens treatment to 12 weekly doses in combination with another medicine, isoniazid. The World Health Organization (WHO) recommends the use of this regimen for treatment of latent TB infection in people living with HIV and contacts of TB cases of any age.

3. ACTIONS

3.1. Tuberculosis treatment solutions

Sanofi is one of the world's primary producers of rifampicin and manufactures rifampicin based fixed-dose combinations of antibiotics used to treat DS-TB ; the company is also manufacturing rifapentine, an antibiotic of the rifamycin family.

3.2. Simplifying tuberculosis treatment

Fixed-dose combinations of drugs are recommended by WHO and greatly simplify TB treatments by reducing the number of pills to be ingested. In addition to developing such combinations, Sanofi's current efforts are focused on endeavoring to simplify and shorten the course of treatment for non-resistant TB, both for LTBI and DS-TB.

In November 2014, the US Food and Drug Administration approved the indication of treatment of LTBI for rifapentine in combination with isoniazid, with a regimen of weekly rifapentine+isoniazid for three months (12 doses).

Since then, Rifapentine is also approved for LTBI indication in South Africa, Indonesia, The Philippines, Taiwan, Thailand, Hong-Kong, India, Mongolia, Singapore, Myanmar and Democratic Republic of the Congo.

³ T.R. Sterling, M.E. Villarino, A.S. Borisov, et al. (2011). "Three Months of Once-Weekly Rifapentine and Isoniazid for M. tuberculosis Infection." *New England Journal of Medicine*, 365, pp.2155-66.

This new regimen, the 3HP regimen, is recommended in the WHO Guidelines on the Management of Latent Tuberculosis Infection released in October 2014. Rifapentine has been included on the Essential Medicines List since April 2015. Moreover, in January 2017, rifapentine was granted WHO prequalification.

3.3. Optimizing access to tuberculosis treatment

In the United States, the PHS 340B⁴ has been decreased from U.S.\$52.5 per 32-tablet pack to U.S.\$24 per 24-tablet pack, helping PHS 340B-qualified entities to meet the needs of low-income patients.

End of October 2019 at the UNION conference, Sanofi and their partners announced a landmark agreement signed with Unitaid, the Global Fund to Fight AIDS, Tuberculosis and Malaria and involving a number of other funders and programs. Thanks to this innovative deal, Sanofi will offer a significant discount on the price of rifapentine, a critically important drug used to prevent tuberculosis.

The volume-based agreement is discounting the price of a three-month treatment course of rifapentine by nearly 70 %, from approximately US\$45 to US\$15 in the public sectors of 100 low- and middle-income countries burdened by TB and TB/HIV co-infection. The deal should bolster efforts to treat latent TB infection by broadening access to better preventive therapy.

All stakeholders warmly welcomed this new agreement as effective TB prevention will be a game-changer in the global fight to eliminate tuberculosis. Sanofi is very pleased to have concluded this innovative agreement. We believe that this sustainable commercial approach will widen access to the new standard of care for latent tuberculosis infection. Through this Global Health initiative, Sanofi remains at the forefront of the fight against Tuberculosis.

The substantially lower cost of rifapentine allows the main development partners supporting TB prevention, such as the Global Fund, PEPFAR, USAID and the Stop TB Partnership's Global Drug Facility, to make it much more widely available through their programs with governments in low- and middle-income countries.

This approach has already shown its effectiveness with a marked ramp up of the demand in the few months since the agreement took effect. South Africa's National Department of Health, for instance, which carries a high burden of TB for people living with HIV has taken the opportunity to switch patients to this shorter regimen.

3.4. Finding solutions with our partners

The development of rifapentine is carried out in close collaboration with the CDC in Atlanta (United States), which coordinates an international group of researchers and clinicians.

A clinical study aiming to shorten DS-TB treatment duration to four months started in 2015. The results at 12 months are expected for the UNION conference in October 2020. Final outcome at 18 months will be known after an additional 6 months. In addition, a pivotal and long-awaited trial on short-course treatment for the prevention of tuberculosis (TB) in children has opened in South Africa in 2019. The goals of this phase I/II trial are to evaluate the safety of giving rifapentine in combination with isoniazid to prevent TB in children, and to establish the dose at which rifapentine should be administered. The United States Centers for Disease Control and Prevention (CDC) execute the

⁴ Section 340B of the US Public Health Service Act requires drug manufacturers to provide outpatient drugs to eligible health care centers, clinics and hospitals at a reduced price

study with financial support provided by both CDC and UNITAID. Sanofi donates the medicines used in the study. Early data is expected by mid-2020.

3.5. Improving educational efforts on Latent Tuberculosis infection

Treatment of TB infection and preventing the development of active disease is essential to TB elimination worldwide.

Detecting and treating TB infection, however, presents unique challenges for those working to end TB. Recognizing this, Sanofi and The Union have developed a new open-access online training course to help clinicians, healthcare workers and national TB program managers to better identify and successfully treat LTBI.

This new online training program is designed to meet the needs of National TB Program (NTP) staff; National AIDS Program (NAP) staff ; clinicians (specialists, pediatricians, pneumologists, general practitioners, nurses) working with TB and/or HIV patients and other high-risk groups; and health care workers at all levels.

<https://courses.theunion.org/prevent-tuberculosis-management-tb-infection>

In parallel, Sanofi developed and launched a new global website fully dedicated to latent tuberculosis infection. Because information and adherence are essential to combat the disease, the key objectives of this website are to raise awareness on tuberculosis prevention and to educate patients, their families and more largely the general public on this huge public health issue.

Patients will find simple information to understand the importance of treating LTBI, and at the end eliminate TB.

<https://www.ltbi.com/>