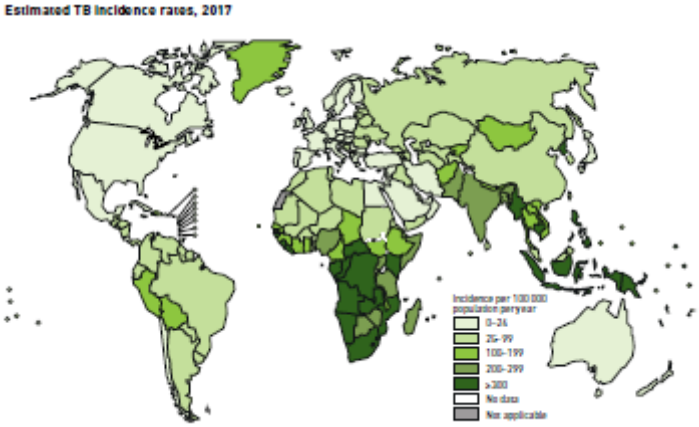
FIGHTING TUBERCULOSIS

I. BACKGROUND

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 2017, there were:

- 10 million new cases, eight countries gathering 68 % of TB cases
- 1.6 million deaths, the vast majority of them in low- and middle-income countries[1]

Figure 1 : Estimated TB Incidence Rates, 2017



SOURCE WHO : GLOBAL TUBERCULOSIS REPORT 2018, FIG. 3.4, PAGE 37 HTTPS://WWW.WHO.INT/TB/PUBLICATIONS/GLOBAL_REPORT/EN/

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 95% and decreasing new cases by 90% between 2015 and 2035. 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 the 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 was a tremendous and unprecedented step forward by governments and all partners engaged in the fight against TB, it endorsed an ambitious and powerful political declaration to accelerate progress towards End TB targets. This declaration was subsequently adopted by the General Assembly on 10 October 2018 (Resolution document A/73/L.4).

In the declaration it is stated : Preventing TB for those most at risk of falling ill, through the rapid scaling up of access to testing and the provision of preventive treatment, so that at least 30 million people receive preventive treatment by 2022, with specific targets for children, household contacts and people living with HIV;

[1] WHO, Fact sheet No.104, last updated October 2017: http://www.who.int/mediacentre/factsheets/fs104/en/

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 strategy relies on having healthcare personnel who can support and monitor patients, to ensure that they take their entire course of treatment. This approach is costly, however, and efforts are needed to simplify TB treatment by reducing the treatment duration.
Strains of *Mycobacterium tuberculosis* that are resistant to conventional treatments have begun to appear in the 80's. In 2017 they caused 55890,000 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/

II. POLICY

Sanofi was the very first company to manufacture rifampicin, a key antibiotic for the treatment of TB 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 basic 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.
Building on the strength of the company's experience, Sanofi introduced a program of industrial optimization and development designed to expand its product range and offer products that are better adapted, at lower cost. This is expected to improve access to treatment for as many patients as possible. The program is based essentially on existing production capacities in South Africa.
In 2011 rifapentine, a member of the rifamycin family, was shown by teams of scientists led 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.

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.

[2] WHO, Fact sheet No.104, last updated October 2017: http://www.who.int/mediacentre/factsheets/fs104/en/
[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.

III. ACTIONS

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

- **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, our 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 and Hong-Kong. 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.
  In order to further improve compliance, Sanofi is developing fixed-dose combinations (adult and pediatric formulations) for the 3HP regimen.

  In the Unites States, the PHS 340B[4] 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.

- **Finding solutions with our collaborators**
  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 first patients were recruited in January 2016, last patient in October 2018, results are expected in Q12020.

  In South Africa we are working with the Ministry of Health and the Nelson Mandela Foundation through the TB Free initiative to organize DOTS centers and train supporters.

  We are also active member of STOP TB partnership Private Sector delegation,

[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