

Feature

Access to

Fight against Tuberculosis— An Old Disease with a New Face

Global public health improved thanks to *DELTYBA*, a tuberculosis drug

The United Nations (UN) Millennium Development Goals (MDGs) were adopted in 2000. Among the MDGs, the goal to combat HIV/AIDS has made great progress. Then, in 2015, the UN announced its Sustainable Development Goals (SDGs), which inherit the ideals of the MDGs, and embarked on new initiatives to achieve these goals. Deploying its tuberculosis drug, *DELTYBA*, the Otsuka group is seeking to eliminate tuberculosis, which is listed as target 3.3 in the SDGs, and also contribute to improvement of global public health.

What is tuberculosis?

It is an airborne infectious disease where tuberculosis mycobacteria enter the body and multiply, mainly in the lungs, resulting in symptoms such as coughing and production of sputum. In serious cases, the infection can cause breathing difficulties and affect other organs, potentially resulting in death. While highly contagious, the disease takes hold in 5–10% of cases, and may develop several years after infection due to a weakening immune system.



Feature: Access to Medicine

SDGs target 3.3

By 2030, end the epidemics of HIV/AIDS, tuberculosis, malaria, and neglected tropical diseases and combat hepatitis, water-borne infections, and other communicable diseases



Medicine

Number of individuals infected with mycobacterium tuberculosis

Approx. **1.7** billion

Annual deaths from tuberculosis

Approx. **1.3** million

Tuberculosis still spreading worldwide

Tuberculosis is still spreading worldwide. Tuberculosis is one of the world's top three infectious diseases, along with malaria and HIV/AIDS. Approximately 10 million people develop tuberculosis each year, of whom around 1.3 million die*, making it the leading cause of death among infectious diseases. Moreover, tuberculosis is highly contagious. About 1.7 billion people are said to be infected with mycobacterium tuberculosis (M.TB) bacteria out of a global population of 7 billion.

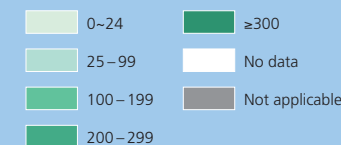
M.TB, which may develop into active tuberculosis disease, is a very "stubborn bacterium," and patients who have contracted the disease must continue taking multiple medications in combination, sometimes for six months or more due to drug-resistant strains. TB is prevalent in many low- and middle-income countries and low-resource settings. Because tuberculosis requires long-term treatment, it represents a major economic challenge in high-burden countries.

* WHO Global Tuberculosis Report 2018

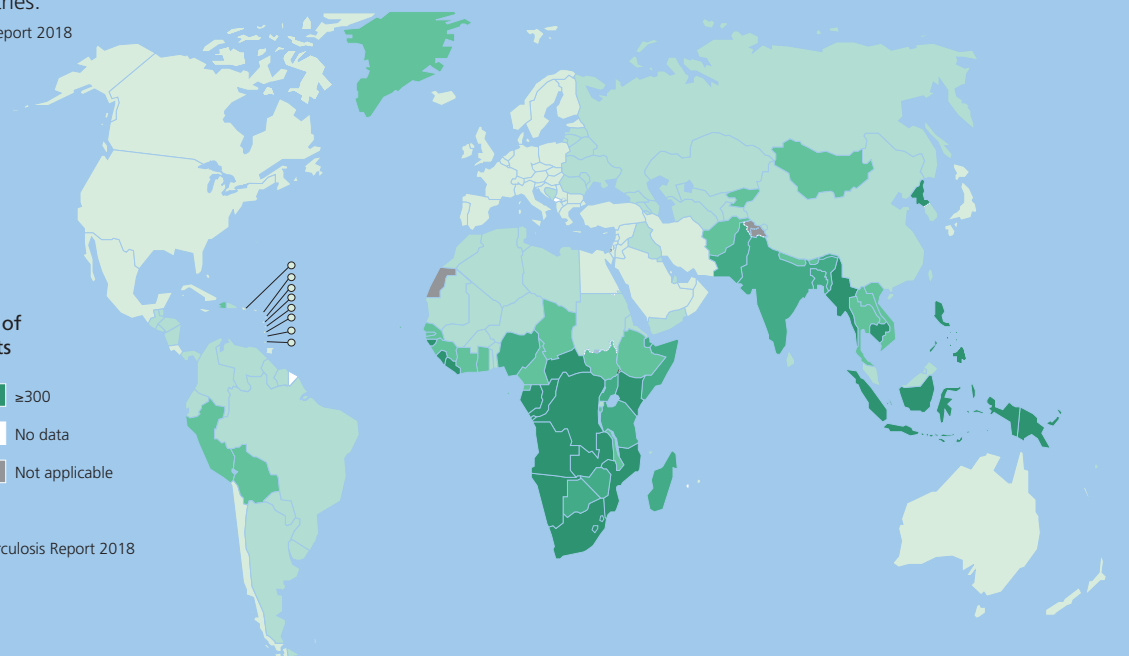
Limitations of conventional medicinal treatment.

Currently, multiple drugs are used to treat tuberculosis. If only one drug is administered, the bacteria become resistant to it, so treatment usually involves administering three to four drugs. In most cases, drug-sensitive tuberculosis can be successfully treated with first-line drugs and proper case management. In recent years, however, the emergence of resistance to tuberculosis drugs has become widespread. Discontinuation of medication for some reason, such as irregular doses or side effects, gives rise to bacteria that are resistant to the drugs that have been taken. Among these are multidrug-resistant tuberculosis (MDR-TB) bacteria that have become resistant to rifampicin and isoniazid, the two most potent first-line therapeutic agents. Extensively drug-resistant tuberculosis (XDR-TB) is resistant to an even greater number of drugs, representing a major global challenge in the campaign to control the disease.

Global Distribution of Tuberculosis Patients



Reference: WHO Global Tuberculosis Report 2018



DELTYBA is improving global health



One of the first new drugs in 50 years

Birth of DELTYBA

“If nobody does it, Otsuka must do it.”

DELTYBA received approval for the treatment of MDR-TB in 2014. It has a completely different mechanism of action compared with previous therapeutic agents, and is also effective against tuberculosis bacteria that have become resistant to existing drugs. Therefore, it is expected to play a role as a therapeutic drug for MDR-TB which is becoming more and more serious. In 2015, DELTYBA was included in the WHO Model List of Essential Medicines (list of priority drugs in any country).

DELTYBA is one of the newest tuberculosis drugs approved in the world in the last 50 years. Although MDR-TB is currently gaining prominent attention, tuberculosis research was regarded as “out of fashion” in the pharmaceutical industry until recently. That is because after rifampicin was discovered in 1964 it was thought that tuberculosis had become a treatable disease. In the 1970s, when many researchers and research institutes around the world stopped development, Otsuka was the only company to continue research, based on the belief that “Tuberculosis is a serious global health problem, and we must continue our research if nobody else does it.” DELTYBA was created after more than 30 years of such research activities. Otsuka Pharmaceutical remains actively engaged in R&D on new tuberculosis



drugs. According to a 2017 report published by the Treatment Action Group (TAG), a patient advocacy group for combating HIV/AIDS and tuberculosis, Otsuka Pharmaceutical was the largest private funder of TB research and development.

Top Ten Funders of TB Research in 2017

Funding Organization	Sector	Total (USD)	Percent of Total Funding
1 U.S. NIH	Public	245,461,895	32%
2 Bill & Melinda Gates Foundation	Philanthropic	127,953,459	17%
3 USAID	Public	33,989,472	4%
4 Unitaid	Multilateral	28,556,016	4%
5 Otsuka Pharmaceuticals	Private	22,773,887	3%
6 U.K. DFID	Public	20,642,634	3%
7 Company X	Private	20,550,920	3%
8 European Commission	Public	19,275,723	3%
9 U.S. CDC	Public	18,256,200	2%
10 EDCTP	Public	17,708,217	2%

DELTYBA Research History

1964	rifampicin was discovered as standard treatment for tuberculosis
1971	Otsuka Pharmaceutical commenced drug discovery research to work on infectious disease as one its key the themes
1982	Full-scale research into tuberculosis drugs was started
2004	Clinical trials were started for OPC-67683 (later DELTYBA) for the treatment of tuberculosis
2014	DELTYBA was approved and launched in Europe and Japan as a therapeutic drug for multidrug-resistant tuberculosis (MDR-TB)
2015	DELTYBA was added to WHO Model List of Essential Medicines
2016	Agreement was concluded with the Stop TB Partnership's Global Drug Facility (GDF).
2017	Licensing agreement was executed with R-Pharm of Russia for the manufacture and commercialization of DELTYBA in the Russian Federation and 12 surrounding countries
2017	Licensing agreement was executed with Mylan of India to expand DELTYBA approval and commercialization activities in high-burden countries



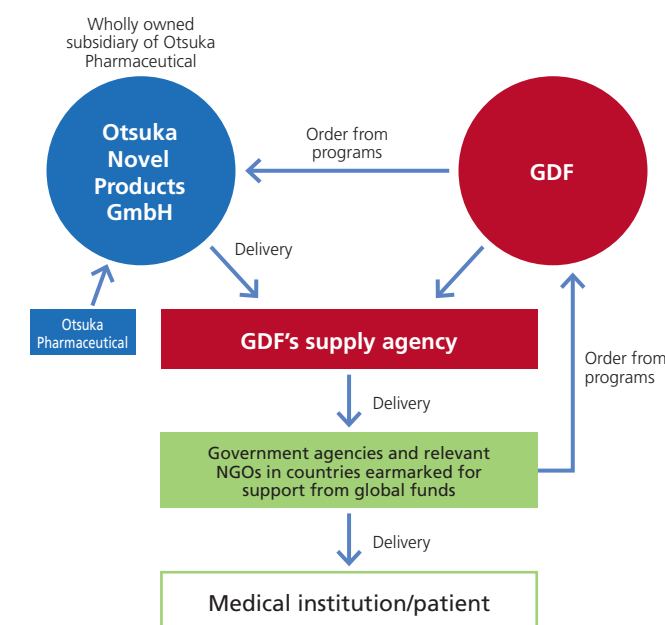
External Collaborations

Expanding access to tuberculosis drugs in low-income countries in collaboration with the Stop TB Partnership's Global Drug Facility (StopTB/GDF)*

DELTYBA is one of the first new tuberculosis drugs approved in the last 50 years, but this is meaningless if the drug is not accessible to patients. That said, there are many tuberculosis patients in developing countries of Africa, Asia, and other regions where the Otsuka Group does not have a business base. For this reason, we began working with the Stop TB Partnership's Global Drug Facility (StopTB/GDF), an organization dedicated to expanding access to quality-assured tuberculosis drugs and diagnostic agents and ensuring the sustainable procurement of those drugs in developing countries. StopTB/GDF now supplies DELTYBA to more than 80 countries, and more than 70% of patients currently taking this drug receive their medicines procured by StopTB/GDF, highlighting the organization's excellent contribution to expanding access.

* Founded in 2001, the Stop TB Partnership has a mission to serve every person who is vulnerable to tuberculosis and to ensure that high-quality diagnosis, treatment and care are available to all who need it. StopTB/GDF is the largest global provider of quality-assured anti-tuberculosis medicines, diagnostics, and laboratory supplies to the public sector while also providing technical assistance to TB programs and supporting wide use of innovative tools.

DELTYBA: Supply route via StopTB/GDF



Topics

Cooperation with Japanese government on DELTYBA

We also cooperate with and receive support from the Japanese government in various ways. These include support with access initiatives overseas to sharing educational information at international conferences and events.



One of the eight items in the economic cooperation plan agreed to by Japanese and Russian leaders is improving medical care and promoting healthy life spans. At the Eastern Economic Forum held in Vladivostok on September 7, 2017, Japan's Prime Minister, Shinzo Abe, made a speech about mutual cooperation aimed at getting swift approval for DELTYBA in Russia. In that speech, he said, "In the fight against tuberculosis, Japan and Russia have joined hands."



At a United Nations General Assembly High-Level Meeting on Tuberculosis held in New York City on September 26, 2018, Katsunobu Kato, Minister of Health, Labour and Welfare, gave a speech on developing treatments for multidrug-resistant tuberculosis in Japan and contributing to eradication of the disease worldwide, and at the same time adopted the political declaration toward eliminating tuberculosis.





Establishing a supply network which will save patients around the world

Expanding access to patients worldwide

Numerous collaborations have been formed to combat tuberculosis and other diseases that threaten global health, such as with the WHO, United Nations, and various national governments who provide active support. In addition to its aforementioned cooperation with GDF, Otsuka Pharmaceutical contributes to the health of people around the world through various collaborative initiatives with its many stakeholders. These include our participation in the Global Health Innovative Technology Fund (GHIT), a Japanese public-private partnership established to address infectious diseases worldwide, as well as cooperation with programs spearheaded by Médecins Sans Frontières/Doctors Without Borders (MSF). We have also obtained support from the Bill & Melinda Gates Foundation for the development of new tuberculosis treatment methods, and we have formed alliances with various global companies with strengths in public health and operations in the areas where we do not have business operations (Mylan in India/South Africa and R-Pharm in Russia).

In March 2017, we launched a new delamanid clinical access program (DCAP) in cooperation with the South African government. The aim of the national program is to give patients with MDR-TB swift access to *DELTYBA* before regulatory approval. In other initiatives, Otsuka Pharmaceutical is working to establish sustainable drug delivery systems at affordable prices, so that patients around the world who need *DELTYBA* can be treated regardless of socioeconomic status or income level. As of June 2019, more than 80 countries are expanding use of *DELTYBA* based on this multifaceted approach.

Interview

An indispensable company in global health

At our R&D institutes, we conduct unique research that does not imitate other companies and pursue what only Otsuka can do. *DELTYBA* is the embodiment of such efforts. Tuberculosis is a serious global health problem, and our approach to the problem—the belief that somebody must keep confronting the disease—has remained unchanged even now after more than 40 years since Otsuka initiated its research. Based on our corporate philosophy “Otsuka-people creating new products for better health worldwide,” we will continue working with external stakeholders to benefit global health with a sense of speed and commitment. Through these activities, we will continue to address issues that have not been solved globally. In the process, we believe, we will fulfill our aim of becoming an indispensable contributor to people’s health worldwide.



Keiso Yamasaki
Otsuka Pharmaceutical
Co., Ltd.
Global Project Leader of
TB Project

Column

Next-generation tuberculosis drug candidate, OPC-167832

Otsuka Pharmaceutical is conducting research into tuberculosis drugs that will follow *DELTYBA*. The latest development is a compound called OPC-167832, which as of 2019 is undergoing initial trials in South Africa to confirm its safety and efficacy. OPC-167832 kills tuberculosis bacteria through a mechanism that inhibits the activity of enzymes that are essential for synthesizing mycobacterium tuberculosis cell walls. Because its mechanism of action differs completely from those of existing anti-tuberculosis drugs, including *DELTYBA*, it is expected to be effective as a treatment for various strains of TB. In developing the drug, we are also receiving support from the Bill & Melinda Gates Foundation, which has cited elimination of tuberculosis worldwide as one of its top priorities. We will continue engaging in TB R&D with the aim of establishing innovative treatment methods.

