The Scourge of TUBERCULOSIS (TB) in 1950's ENGLAND

PREAMBLE:

My Paternal GRANDFATHER, WILLIAM GEORGE HAYWARD WARD was born in Portsmouth, Hampshire, England in 1875 and he died in 1954 in the INFECTIOUS DISEASES WARD of the St. Mary's Hospital in Portsmouth, after a lifespan of 79-years during which, like many other Englishmen of that time, he had lived and worked in the industrial City of Portsmouth, laying railway track for the newly formed Southern Railway and breathing the polluted air of a City burning coal to heat tens of thousands of homes and exhaust fumes from thousands of vehicles. In World War 1 he joined the British Army in France and endured years of trench warfare in France, with rain, mud and poisonous gas such as Chlorine, Phosgene and Mustard Gas.

No wonder he died eventually of the dreaded killer, "TB"…

In the early 1900s, if somebody had Tuberculosis, they would've found themselves as a resident of a Sanatorium such as WAVERLY HILLS outside of Louisville, Kentucky. The advent of VACCINES caused closures of such institutions all around the United States.

HISTORY OF TUBERCULOSIS (TB):

The history of TUBERCULOSIS (TB) encompasses the origins of the disease, "TB" through to the vaccines and treatment methods developed to contain and mitigate its impact.

Throughout history, the disease "TB" has been variously known as CONSUMPTION, PHTHISIS, and the WHITE PLAGUE. It is generally accepted that the causative agent, *Mycobacterium tuberculosis* originated from other, more primitive organisms of the same genus *Mycobacterium*.

In 2014, results of a new DNA study of a tuberculosis genome reconstructed from remains in southern Peru suggest that human tuberculosis is less than 6,000 years old. Even if researchers theorize that humans first acquired it in Africa about 5,000 years ago, there is evidence that the first tuberculosis infection happened about 9,000 years ago.

TUBERCULOSIS (TB) spread to other HUMANS along trade routes. It also spread to DOMESTICATED ANIMALS in Africa, such as goats and cows. Seals and sea lions that bred on African beaches are believed to have acquired the disease and carried it across the Atlantic to South America. HUNTERS would have been the first HUMANS to contract the disease there.

Although relatively little is known about its frequency before the 19th Century, its incidence is thought to have peaked between the end of the 18th Century and the end of the 19th Century. Over time, the various cultures of the world gave the illness different names: *phthisis* (Greek), *consumptio* (Latin), *yaksma* (India), and *chaky oncay* (Incan), each of which make reference to the "drying" or "consuming" effect of the illness, *cachexia*.

In the 19th Century, TB's high mortality rate among young and middle-aged adults and the surge of *Romanticism*, which stressed feeling over reason, caused many to refer to the disease as the "romantic disease".

A ROMANTIC DISEASE

> **"Chopin coughs with infinite grace."**
>
> **—George Sand in her letter to Madame d'Agoult**

The Russian writer ANTON CHEKHOV, who died of TUBERCULOSIS in 1904.

TUBERCULOSIS IN EARLY CIVILIZATION

In 2008, evidence for tuberculosis infection was discovered in human remains from the Neolithic era dating from 9,000 years ago, in *Atlit Yam*, a settlement in the Eastern Mediterranean. This finding was confirmed by morphological and molecular methods; to date it is the oldest evidence of tuberculosis infection in humans.

Evidence of the infection in humans was also found in a Cemetery near Heidelberg, in the Neolithic bone remains that show evidence of the type of angulation often seen with spinal tuberculosis. Some authors call TUBERCULOSIS the first disease known to mankind.

Signs of the disease have also been found in Egyptian mummies dated between 3,000 and 2,400 BC. The most convincing case was found in the mummy of PRIEST NESPEREHEN, discovered by Grebart in 1881, which featured evidence of SPINAL TUBERCULOSIS with the characteristic *psoas abscesses*. Similar features were discovered on other mummies like that of the PRIEST PHILOC and throughout the Cemeteries of Thebes. It appears likely that AKHENATEN and his wife NEFERTITI both died from TUBERCULOSIS, and evidence indicates that hospitals for tuberculosis existed in Egypt as early as 1,500 BC.

The Ebers papyrus, an important Egyptian medical treatise from around 1550 BC, describes a pulmonary consumption associated with the cervical lymph nodes. It recommended that it be treated with the surgical lancing of the cyst and the application of a ground mixture of acacia seyal, peas, fruits, animal blood, insect blood, honey and salt.

The OLD TESTAMENT mentions a consumptive illness that would affect the Jewish people if they stray from God. It is listed in the section of Curses given before they enter the land of Canaan.

Typical OPEN AIR TB RECOVERY Hospital Ward (Circa 1950)

EPIDEMIC TUBERCULOSIS

In the 18th and 19th century, tuberculosis (TB) had become epidemic in Europe, showing a seasonal pattern. In the 18th Century, TB had a mortality rate as high as 900 deaths (800–1000) per 100,000 population per year in Western Europe, including in places like London, Stockholm and Hamburg. Similar death rate occurred in North America. In the United Kingdom, epidemic TB may have peaked around the year 1750, as suggested by mortality data.

In the 19th Century, TB killed about 25% of the adult population of Europe. In Western Continental Europe, epidemic TB may have peaked in the first half of the 19th century. In addition, between 1851 and 1910, around 4,000,000 died from TB in ENGLAND and WALES – more than 35% of those aged 15 to 34 and 50% of those aged 20 to 24 died from TB. By the late 19th Century, 70%–90% of the urban populations of EUROPE and NORTH AMERICA were infected with the *Mycobacterium tuberculosis*, and about 80% of those individuals who developed active TB died of it. However, mortality rates began declining in the late 19th Century throughout Europe and the United States.

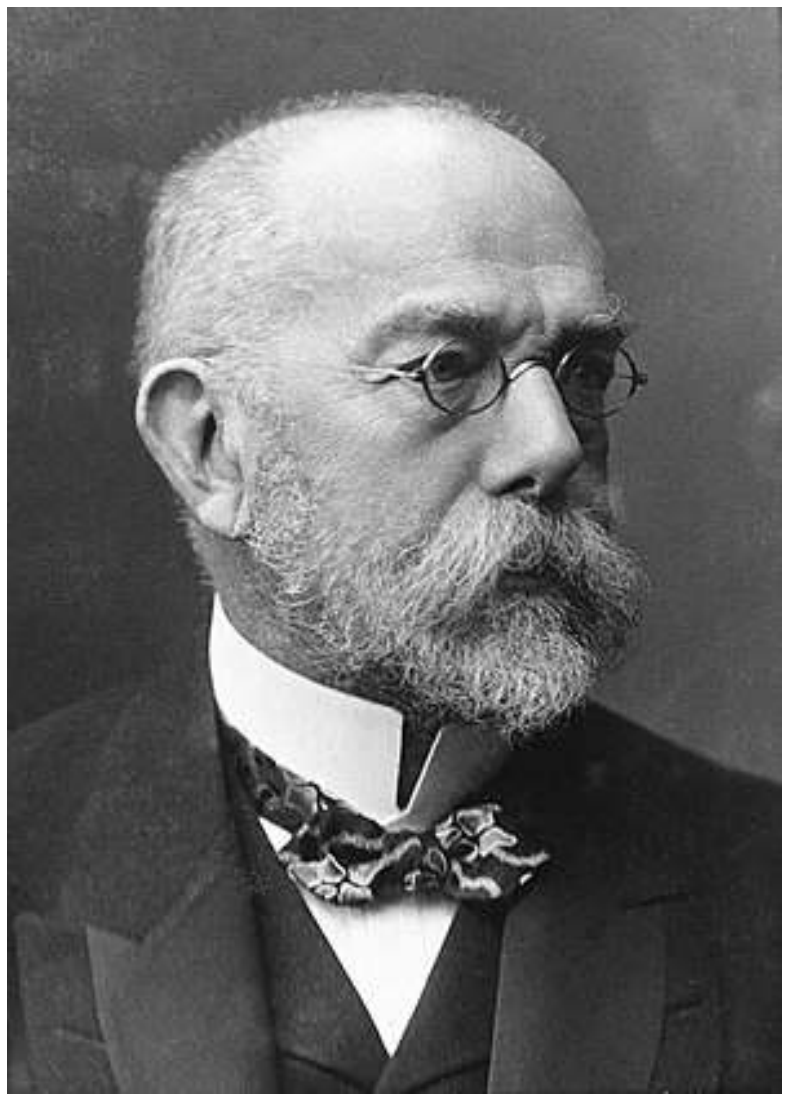
At the time, Tuberculosis was called *the robber of youth,* because the disease had higher death rate among young people. Other names included *the Great White Plague* and *the White Death,* where the "white" was due to the extreme anaemic pallor of those infected. In addition, TB has been called by many as the "Captain of All These Men of Death".

It was during this Century that tuberculosis was dubbed *the White Plague*, *mal de vivre*, and *mal du siècle*. It was seen as a "romantic disease". Individuals with tuberculosis were thought to have heightened sensitivity. The slow progress of the disease allowed for a "good death" as those affected could arrange their affairs. The disease began to represent *spiritual purity* and *temporal wealth,* leading many young, upper-class women to purposefully pale their skin to achieve the "consumptive appearance". British poet Lord Byron wrote, *"I should like to die from consumption"*, helping to popularize the disease as the disease of artists. George Sand doted on her phthisic lover, Frédéric Chopin, calling her a "poor melancholy angel".

In France, at least five novels were published expressing the ideals of tuberculosis: Dumas's *La Dame aux camélias*, Murger's *Scènes de la vie de Bohème*, Hugo's *Les Misérables*, the Goncourt brothers' *Madame Gervaisais* and *Germinie Lacerteux*, and Rostand's *L'Aiglon*. The portrayals by Dumas and Murger in turn inspired operatic depictions of consumption in Verdi's *La traviata* and Puccini's *La bohème*. Even after medical knowledge of the disease had accumulated, the redemptive-spiritual perspective of the disease has remained popular[74] (as seen in the 2001 film *Moulin Rouge* based in part on *La traviata*; the 2013 film *The Wind Rises*, based in part on a 1937 novel about tuberculosis; and the musical adaptations of *Les Misérables*).

In large Cities, the Poor had high rates of tuberculosis. Public-health physicians and politicians typically blamed both the poor themselves and their ramshackle tenement houses (conventillos) for the spread of the dreaded disease.

People ignored public-health campaigns to limit the spread of contagious diseases, such as the prohibition of spitting on the streets, the strict guidelines to care for infants and young children, and quarantines that separated families from ill loved ones.



ROBERT KOCH

SCIENTIFIC ADVANCES

Though removed from the cultural movement, the scientific understanding advanced considerably. By the end of the 19th Century, several major breakthroughs gave hope that a cause and cure might be found.

One of the most important physicians dedicated to the study of phthisiology was René Laennec, who died from the disease at the age of 45, after contracting tuberculosis while studying contagious patients and infected bodies. Laennec invented the stethoscope, which he used to corroborate his auscultatory findings and prove the correspondence between the pulmonary lesions found on the lungs of autopsied tuberculosis patients and the respiratory symptoms seen in living patients. His most important work was *Traité de l'Auscultation Médiate* which detailed his discoveries on the utility of pulmonary auscultation in diagnosing tuberculosis. This book was promptly translated into English by JOHN FORBES in 1821; it represents the beginning of the modern scientific understanding of tuberculosis. Laennec was named professional chair of Hôpital Necker in September 1816 and today he is considered the greatest French clinician.

LAENNEC'S work put him in contact with the vanguard of the French Medical Establishment, including PIERRE CHARLES ALEXANDRE LOUIS. Louis would go on to use statistical methods to evaluate the different aspects of the disease's progression, the efficacy of various therapies and individuals' susceptibility, publishing an article in the *Annales d'hygiène publique* entitled "Note on the Relative Frequency of Phthisis in the Two Sexes". Another good friend and co-worker of Laennec, GASPARD LAURENT BAYLE, published an article in 1810 entitled *Recherches sur la Pthisie Pulmonaire,* in which he divided pthisis into six types: tubercular phthisis, glandular phthisis, ulcerous phthisis, phthisis with melanosis, calculous phthisis, and cancerous phthisis. He based his findings on more than 900 autopsies.

In 1869, JEAN ANTOINE VILLEMIN demonstrated that the disease was indeed contagious, conducting an experiment in which tuberculous matter from human cadavers was injected into laboratory rabbits, which then became infected.

On 24 March 1882, ROBERT KOCH revealed the disease was caused by an infectious agent. In 1895, WILHELM RÖNTGEN discovered the X-ray, which allowed physicians to diagnose and track the progression of the disease, and although an effective medical treatment would not come for another fifty years, the incidence and mortality of tuberculosis began to decline.

19th-century tuberculosis mortality rate for New York and New Orleans			
		Deaths/Year/1000 people	
Year	Population	White people	Black people
1821	New York City	5.3	9.6
1830	New York City	4.4	12.0
1844	New York City	3.6	8.2
1849	New Orleans	4.9	5.2
1855	New York City	3.1	12.0
1860	New York City	2.4	6.7
1865	New York City	2.8	6.7
1880	New Orleans	3.3	6.0
1890	New Orleans	2.5	5.9

ROBERT KOCH, a Prussian physician, discovered the CAUSE OF TUBERCULOSIS.

VILLEMIN'S experiments had confirmed the contagious nature of the disease and had forced the medical community to accept that tuberculosis was indeed an infectious disease, transmitted by some etiological agent of unknown origin. In 1882, Prussian Physician ROBERT KOCH utilized a new staining method and applied it to the sputum of tuberculosis patients, revealing for the first time the causal agent of the disease: *Mycobacterium tuberculosis*, or Koch's bacillus.

When he began his investigation, Koch knew of the work of Villemin and others who had continued his experiments like Julius Conheim and Carl Salmosen. He also had access to the "pthisis ward" at the Berlin Charité Hospital.[86] Before he confronted the problem of tuberculosis, he worked with the disease caused by anthrax and had discovered the causal agent to be *Bacillus anthracis*. During this investigation he became friends with Ferdinand Cohn, the Director of the Institute of Vegetable Physiology. Together they worked to develop methods of culturing tissue samples. 18 August 1881, while staining tuberculous material with *methylene blue*, he noticed oblong structures, though he was not able to ascertain whether it was just a result of the colouring. To improve the contrast, he decided to add *Bismarck Brown*, after which the oblong structures were rendered bright and transparent. He improved the technique by varying the concentration of alkali in the staining solution until the ideal viewing conditions for the bacilli was achieved.

After numerous attempts he was able to incubate the bacteria in coagulated blood serum at 37 degrees Celsius. He then inoculated laboratory rabbits with the bacteria and observed that they died while exhibiting symptoms of tuberculosis, proving that the bacillus, which he named *tuberculosis bacillus*, was in fact the cause of tuberculosis.

He made his result public at the Physiological Society of Berlin on 24 March 1882, in a famous lecture entitled *Über Tuberculose*, which was published three weeks later. Since 1882, 24 March has been known as World Tuberculosis Day.

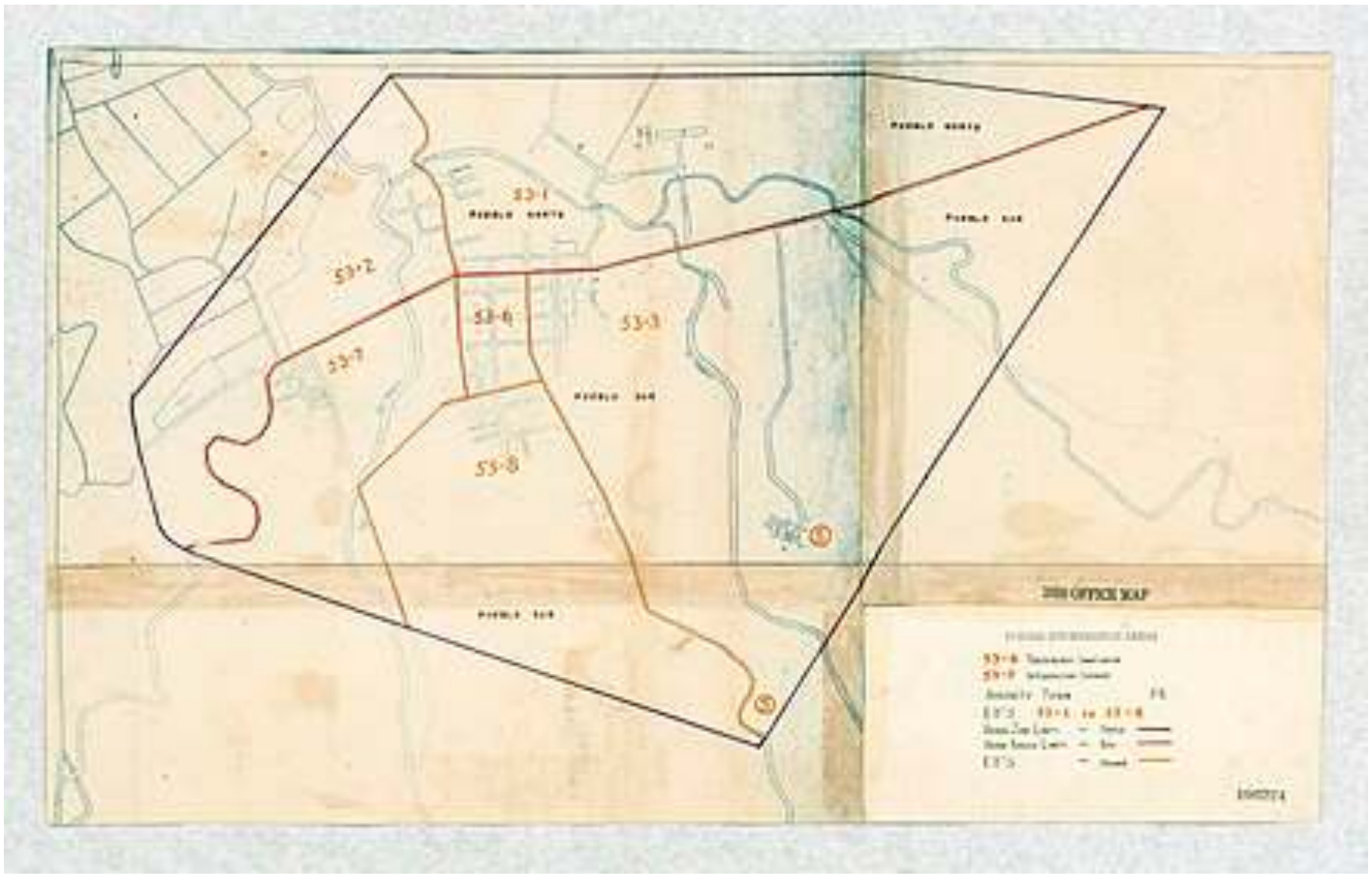
On 20 April 1882, Koch presented an article entitled *Die Ätiologie der Tuberculose* in which he demonstrated that *Mycobacterium* was the single cause of tuberculosis in all of its forms.

In 1890 Koch developed tuberculin, a purified protein derivative of the bacteria. Data on experimental inquiry published in Deutsche Landwirthschafts - Zeitung provided immediate practical industry benefits in the form of the Tuberculin test as an aide to diagnosis in both sick and healthy cattle. Tuberculin proved to be an ineffective means of immunization but in 1908, Charles Mantoux found it was an effective intradermic test for diagnosing tuberculosis.[91][92]

If the importance of a disease for mankind is measured from the number of fatalities which are due to it, then tuberculosis must be considered much more important than those most feared infectious diseases, plague, cholera, and the like. Statistics have shown that 1/7 of all humans die of tuberculosis.

—Die Ätiologie der Tuberculose, Robert Koch (1882)

SANATORIUM MOVEMENT



1950 Census Enumeration District Map of Aibonito, Puerto Rico, United States, indicating a "Tuberculosis Sanatorium" to be a special (Census) enumeration area.

The advancement of scientific understanding of tuberculosis, and its contagious nature created the need for institutions to house affected individuals.

The first proposal for a tuberculosis facility was made in paper by George Bodington entitled *An essay on the treatment and cure of pulmonary consumption, on principles natural, rational and successful* in 1840. In this paper, he proposed a dietary, rest, and medical care program for a hospital he planned to found in Maney. Attacks from numerous medical experts, especially articles in *The Lancet*, disheartened Bodington and he turned to plans for housing the insane.

Around the same time in the United States, in late October and early November 1842, Dr. John Croghan, the owner of Mammoth Cave, brought 15 Tuberculosis Patients into the cave in the hope of curing the disease with the constant temperature and purity of the cave air. Patients were lodged in stone huts, and each was supplied with a slave to bring meals. One patient, A.H.P. Anderson, wrote glowing reviews of the cave experience:

Some of the invalids eat at their pavilion's while others in better health attend regularly the table d'hote which is very good indeed, having a considerable variety and being almost daily (I've noted but 2–3 omissions) graced with a saddle of venison or other game.—A. H. P. Anderson

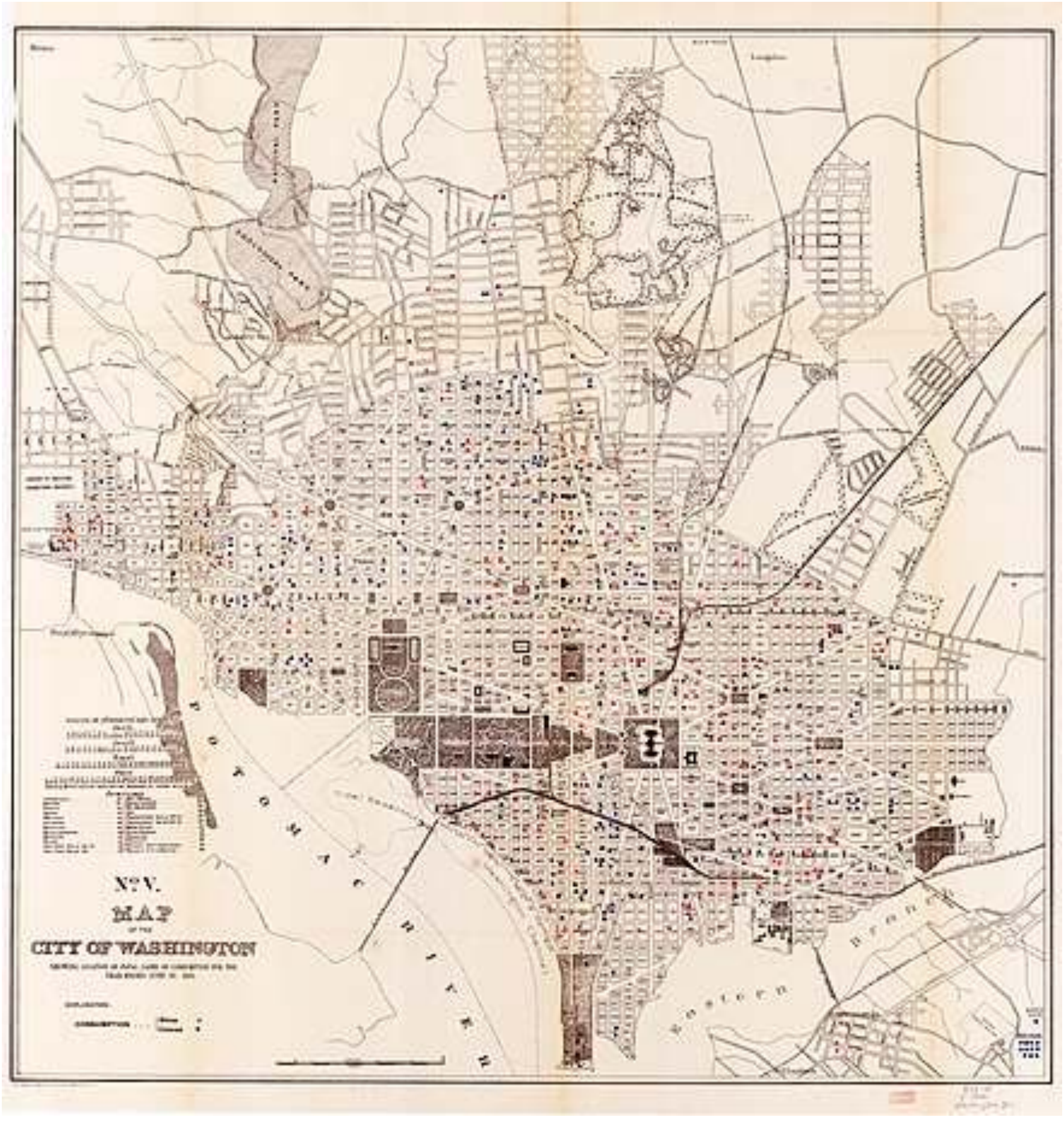
By late January, early February 1843, two patients were dead and the rest had left. Departing patients died anywhere from 3-days to 3-weeks after resurfacing; JOHN CROGHAN died of tuberculosis at his LOUISVILLE residence in 1849.

HERMANN BREHMER, a German physician, was convinced that tuberculosis arose from the difficulty of the heart to correctly irrigate the lungs. He therefore proposed that regions well above sea level, where the atmospheric pressure was less, would help the heart function more effectively. With the encouragement of explorer ALEXANDER VON HUMBOLDT and his teacher J. L. SCHÖNLEIN, the first ANTI-TUBERCULOSIS SANATORIUM was established in 1854, 650 metres above sea level, at GÖRBERSDORF. Three years later he published his findings in a paper *Die Chronic Lungenschwindsucht und Tuberkulose der Lunge: Ihre Ursache und ihre Heilung*.

BREHMER and one of his patients, PETER DETTWEILER, became proponents for the SANATORIUM MOVEMENT, and by 1877, Sanatoriums began to spread beyond Germany and throughout Europe. Dr. EDWARD LIVINGSTON TRUDEAU subsequently founded the ADIRONDACK COTTAGE SANATORIUM in Saranac Lake, New York in 1884. One of Trudeau's early patients was author ROBERT LOUIS STEVENSON; his fame helped establish Saranac Lake as a Center for the Treatment of Tuberculosis. In 1894, after a fire destroyed Trudeau's small home laboratory, he organized the SARANAC LABORATORY FOR THE STUDY OF TUBERCULOSIS; renamed the Trudeau Institute, the Laboratory continues to study Infectious Diseases.

PETER DETTWEILER went on to found his own Sanatorium at Falkenstein in 1877 and in 1886 published findings claiming that 132 of his 1022 patients had been completely cured after staying at his institution. Eventually, Sanatoriums began to appear near large Cities and at low altitudes, like the SHARON SANATORIUM in 1890 near Boston.

Sanatoriums were not the only treatment facilities. Specialized Tuberculosis Clinics began to develop in major metropolitan areas. Sir ROBERT PHILIP established the ROYAL VICTORIA DISPENSARY FOR CONSUMPTION in Edinburgh in 1887. Dispensaries acted as special Sanatoriums for early Tuberculosis cases and were opened to lower income individuals. The use of dispensaries to treat middle and lower-class individuals in major Metropolitan areas and the coordination between various levels of Health Services Programs like Hospitals, Sanatoriums, and Tuberculosis Colonies became known as the "EDINBURGH ANTI-TUBERCULOSIS SCHEME".



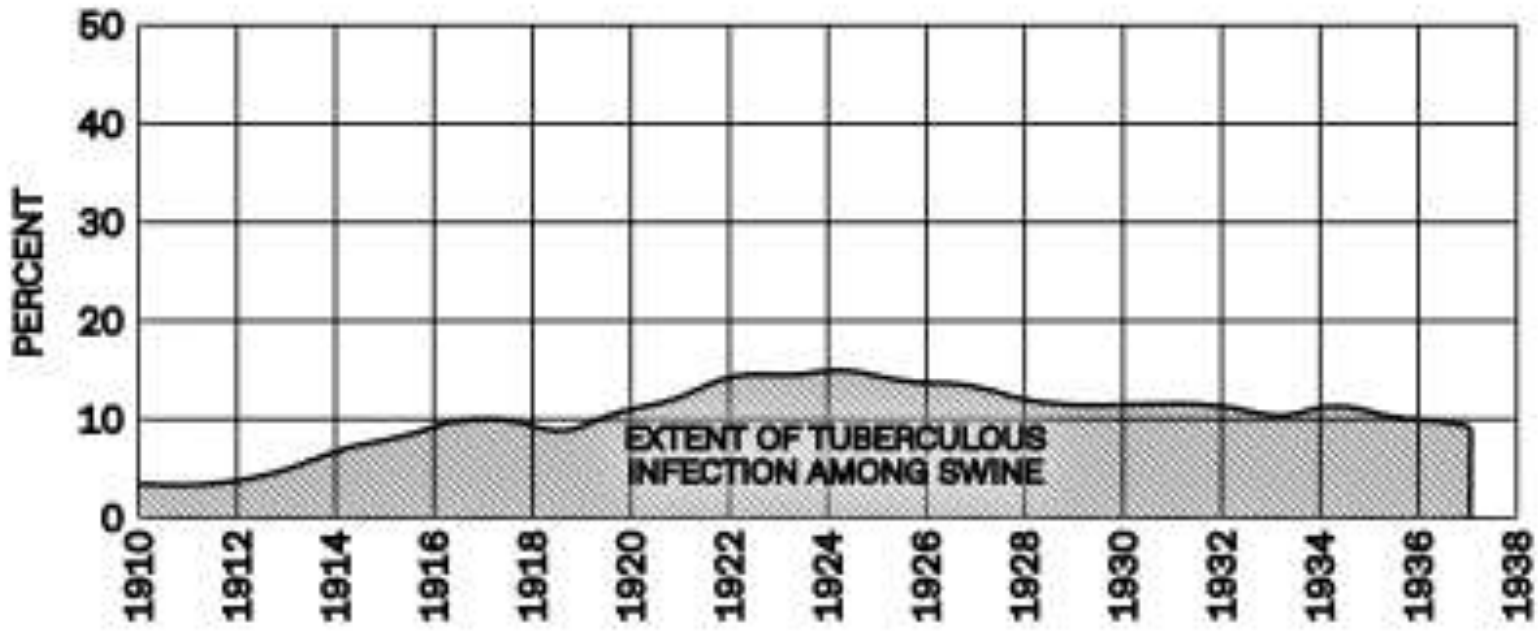
A map of deaths from tuberculosis in Washington, D.C. in 1900–1901.

At the beginning of the 20th Century, TUBERCULOSIS was one of the UK's most urgent health problems. A Royal Commission was set up in 1901, The Royal Commission Appointed to Inquire into the Relations of Human and Animal Tuberculosis. Its remit was to find out whether tuberculosis in animals and humans was the same disease, and whether animals and humans could infect each other. By 1919, the Commission had evolved into the UK's Medical Research Council.

In 1902, the INTERNATIONAL CONFERENCE ON TUBERCULOSIS convened in Berlin. Among various other acts, the conference proposed the Cross of Lorraine be the international symbol of the fight against tuberculosis. National campaigns spread across Europe and the United States to tamp down on the continued prevalence of tuberculosis.

After the establishment in the 1880s that the disease was contagious, TB was made a notifiable disease in Britain; there were campaigns to stop spitting in public places, and the infected poor were pressured to enter sanatoria that resembled prisons; the sanatoria for the middle and upper classes offered excellent care and constant medical attention. Whatever the purported benefits of the fresh air and labor in the sanatoria, even under the best conditions, 50% of those who entered were dead within five years (1916).

The promotion of Christmas Seals began in Denmark during 1904 as a way to raise money for tuberculosis programs. It expanded to the United States and Canada in 1907–1908 to help the National Tuberculosis Association (later called the American Lung Association).



A chart showing the rate of tuberculosis in inspected livestock in a 1938 publication of the United States Department of Agriculture.

In the United States, concern about the spread of tuberculosis played a role in the movement to prohibit public spitting except into spittoons. Public health measures were inaugurated to track and control the prevalence of tuberculosis in livestock that could be transmitted to humans.

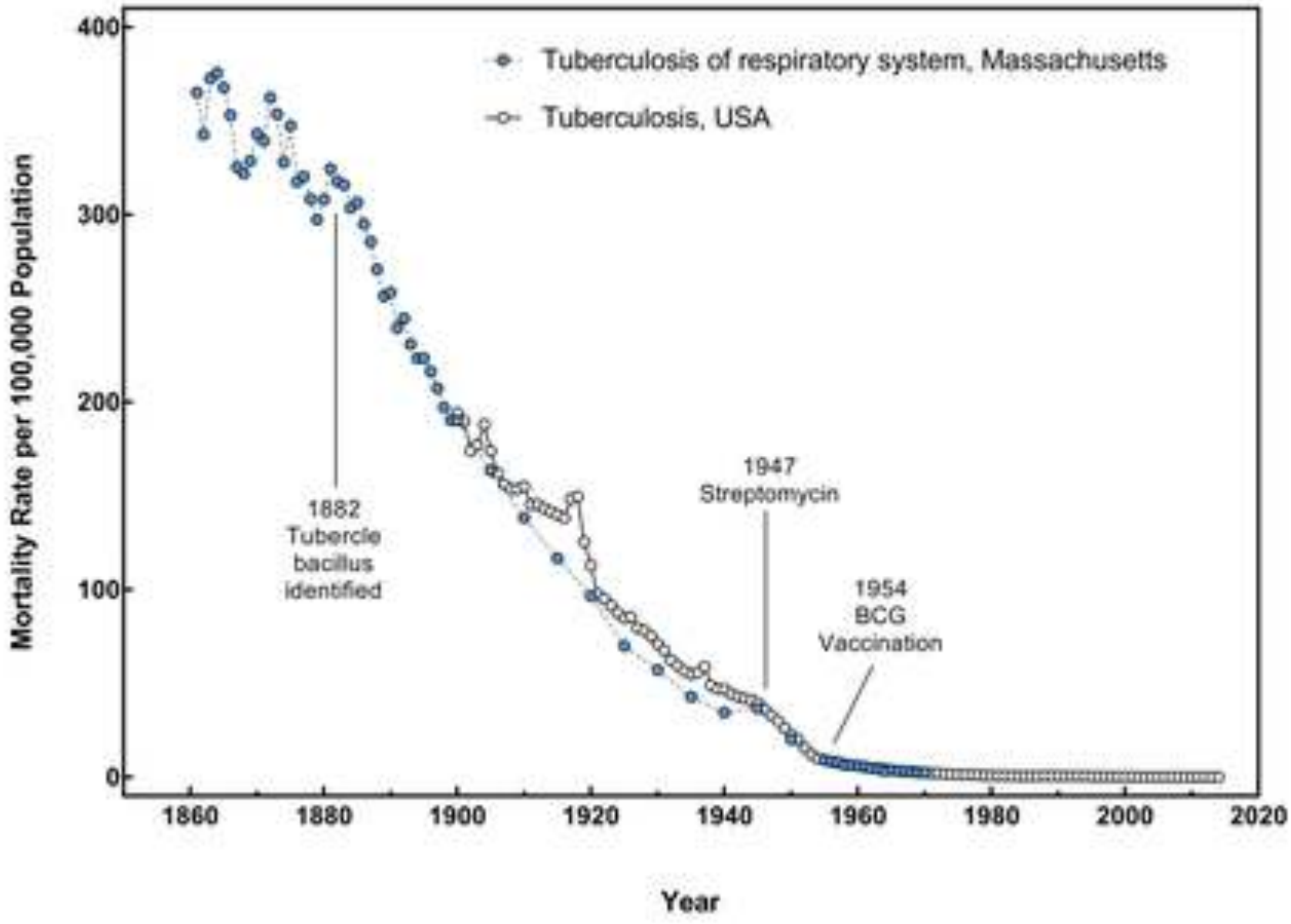
VACCINES

The first genuine success in IMMUNIZING against TUBERCULOSIS was developed from attenuated bovine-strain tuberculosis by ALBERT CALMETTE and CAMILLE GUÉRIN in 1906. It was called "BCG" (*Bacille Calmette-Guérin*). The BCG Vaccine was first used on humans in 1921 in France, but it was not until after World War II that BCG received widespread acceptance in Great Britain and Germany. In the early days of the British National Health Service X-ray examination for TB increased dramatically but rates of vaccination were initially very low. In 1953 it was agreed that secondary school pupils should be vaccinated, but by the end of 1954 only 250,000 people had been vaccinated.

By 1956 this had risen to 600,000, about half being school children.

In Italy, Salvioli's diffusing vaccine (*Vaccino Diffondente Salvioli*; VDS) was used from 1948 until 1976. It was developed by Professor Gaetano Salvioli (1894–1982) of the University of Bologna.

TREATMENTS



Tuberculosis mortality in the USA from 1861 to 2014.

Specialist Nurse at 18-bed 'FRESH AIR SCHOOL' for children with TB. Royal Victoria Hospital, Montreal. 1939.

As the Century progressed, some surgical interventions, including the **pneumothorax** or **plombage** technique—collapsing an infected lung to "rest" it and allow the lesions to heal—were used to treat Tuberculosis. Pneumothorax was not a new technique by any means. In 1696, **Giorgio Baglivi** reported a general improvement in tuberculosis patients after they received sword wounds to the chest. **F.H. Ramadge** induced the first successful therapeutic pneumothorax in 1834, and reported subsequently the patient was cured. It was in the 20th Century, however, that Scientists sought to rigorously investigate the effectiveness of such procedures. **CARLO FORLANINI** experimented with his **artificial pneumothorax technique** from 1882 to 1888 and this started to be followed only years later. In 1939, the ***British Journal of Tuberculosis*** published a study by **Oli Hjaltested** and **Kjeld Törning** on 191 patients undergoing the procedure between 1925 and 1931; in 1951, Roger Mitchell published several articles on the therapeutic outcomes of 557 patients treated between 1930 and 1939 at **Trudeau Sanatorium** in **Saranac Lake**. The search for a medicinal cure, however, continued in earnest.

During the Nazi occupation of Poland, SS-Obergruppenführer WILHELM KOPPE organized the execution of more than 30,000 Polish patients with tuberculosis – little knowing or caring that a cure was nearly at hand. In Canada, Doctors continued to surgically remove TB in the indigenous patients during the 1950s and 60s, even though the procedure was no longer performed on non-Indigenous patients.

In 1944 **Albert Schatz**, **Elizabeth Bugie**, and **Selman Waksman** isolated **STREPTOMYCIN** produced by a bacterial strain ***Streptomyces griseus.*** **Streptomycin was the first effective antibiotic against *M. tuberculosis*.** This discovery is generally considered the beginning of the Modern Era of Tuberculosis. **PARA-AMINOSALICYLIC ACID**, discovered in 1946, was used in combination with Streptomycin to reduce the emergence of drug resistant variants, which greatly improved patient outcomes. The true revolution began some years later, in 1952, with the development of **ISONIAZID,** the first **ORAL MYCOBACTERICIDAL DRUG.** The advent of **RIFAMPIN** in the 1970s hastened recovery times, and significantly reduced the number of Tuberculosis Cases until the 1980s.

The British epidemiologist **THOMAS MCKEOWN** had shown that "treatment by STREPTOMYCIN reduced the number of deaths since it was introduced (1948–71) by 51 per cent…". However, he also showed that the mortality from TB in England and Wales had already declined by 90 to 95% before Streptomycin and BCG-vaccination were widely available, and that the contribution of antibiotics to the decline of mortality from TB was actually very small: *'...for the total period since cause of death was first recorded (1848–71) the reduction was 3.2 per cent'*. These figures have since been confirmed for all Western Countries (see for example the decline in TB mortality in the USA) and for all then known infectious diseases. **MCKEOWN explained the decline in mortality from infectious diseases by an improved standard of living, particularly by better nutrition, and by better hygiene, and less by medical intervention.** McKeown, who is considered as the Father of Social Medicine, has advocated for many years, that with drugs and vaccines we may win the battle but will lose the war against Diseases of Poverty. **Thereto, efforts and resources should be primarily directed toward improving the standard of living of people in low resource countries, and toward improving their environment by providing clean water, sanitation, better housing, education, safety and justice, and access to medical care.**

Particularly the work of Nobel laureates **ROBERT W. FOGEL** (1993) and **ANGUS DEATON** (2015) have greatly contributed to the recent re-appreciation of the McKeown thesis. A negative confirmation of the McKeown thesis was that increased pressure on wages by IMF loans to post-communist Eastern Europe were strongly associated with a rise in TB incidence, prevalence and mortality.

In the UNITED STATES there was dramatic reduction in Tuberculosis cases by the 1970s. As early as the 1900s, public health campaigns were launched to educate people about the contagion. In later decades, posters, pamphlets and newspapers continued to inform people about the risk of contagion and methods to avoid it, including increasing public awareness about the importance of GOOD HYGIENE. Though improved awareness of GOOD HYGIENE PRACTICES reduced the number of cases, the situation was worse in the POOR NEIGHBOURHOODS. Public clinics were set up to improve awareness and provide screenings. In Scotland, Dr. Nora Wattie led the Public Health innovations both at local and national level. This resulted in sharp declines through the 1920s and 1930s.

TUBERCULOSIS RESURGENCE

Hopes that the disease could be completely eliminated were dashed in the 1980s with the rise of drug-resistant strains. Tuberculosis cases in Britain, numbering around 117,000 in 1913, had fallen to around 5,000 in 1987, but cases rose again, reaching 6,300 in 2000 and 7,600 cases in 2005. Due to the elimination of public health facilities in New York and the emergence of HIV, there was a resurgence of TB in the late 1980s. The number of patients failing to complete their course of drugs was high. New York had to cope with more than 20,000 TB patients with multi-drug-resistant strains (resistant to, at least, both RIFAMPIN and ISONIAZID).

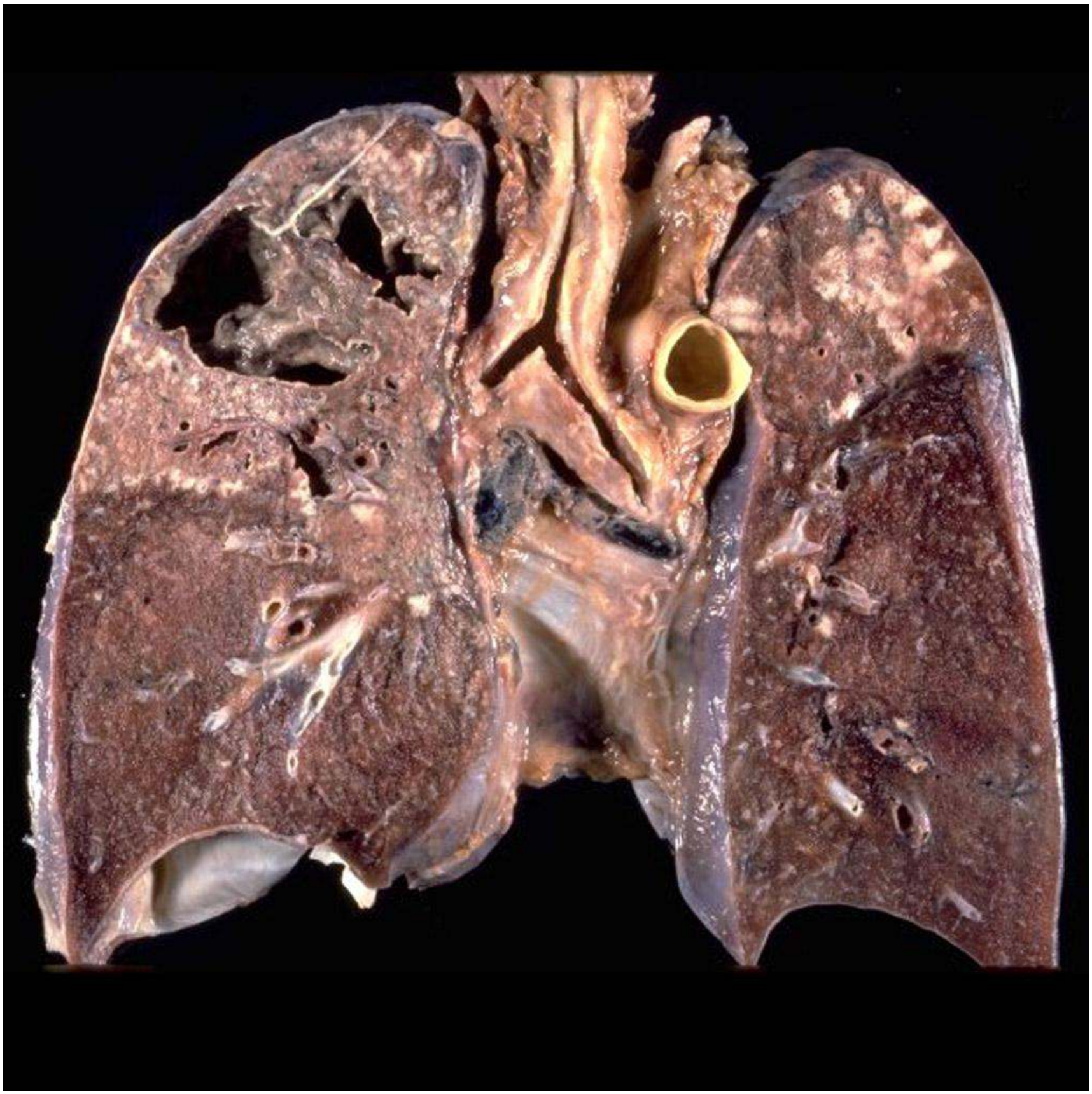
In response to the resurgence of tuberculosis, the World Health Organization issued a declaration of a GLOBAL HEALTH EMERGENCY in 1993. Every year, nearly half a million new cases of multi-drug-resistant tuberculosis (MDR-TB) are estimated to occur worldwide.

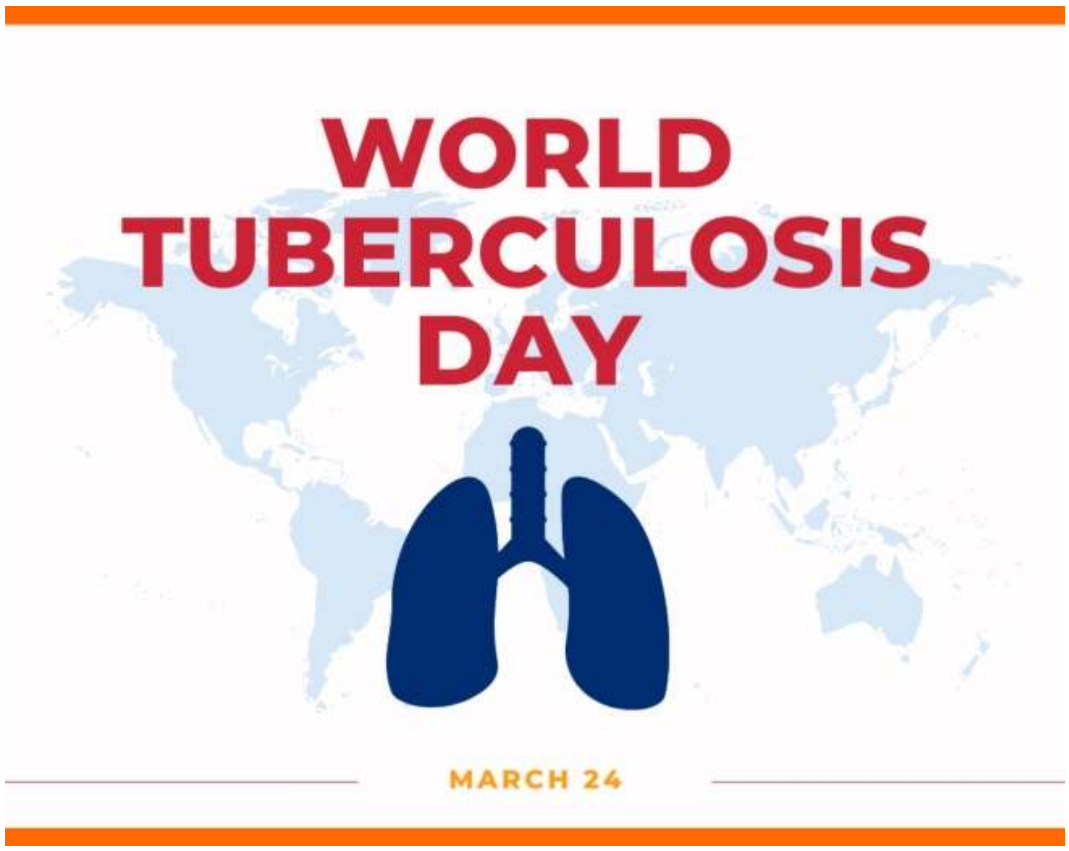
A CASE STUDY: Cavitating Pulmonary Tuberculosis (gross pathology)

Author: Yale Rosen, M.D. Patient Data: 40-year old Female; Died in hospital of unrelated cause;

CAVITATING PULMONARY TB: Extensive necrosis with cavitation, usually occurring in the upper lung or apex, is a characteristic feature of "secondary" or "adult type" tuberculosis. This is probably related to persistence of *M tuberculosis* from a prior primary infection. Cavities form when necrosis involves the wall of an airway and the semi-liquid necrotic material is discharged into the bronchial tree from where it is usually coughed up and may infect others. This infected material may seed other parts of the lung via the airways to produce a tuberculous bronchopneumonia. If swallowed, infection of the G.I. tract may result. Communication of the centres of the tuberculous lesions with the airway exposes the bacteria to a high concentration of oxygen and promotes their proliferation.

The risk of the spread of infection to non-infected persons from individuals with cavitary tuberculosis is very high.



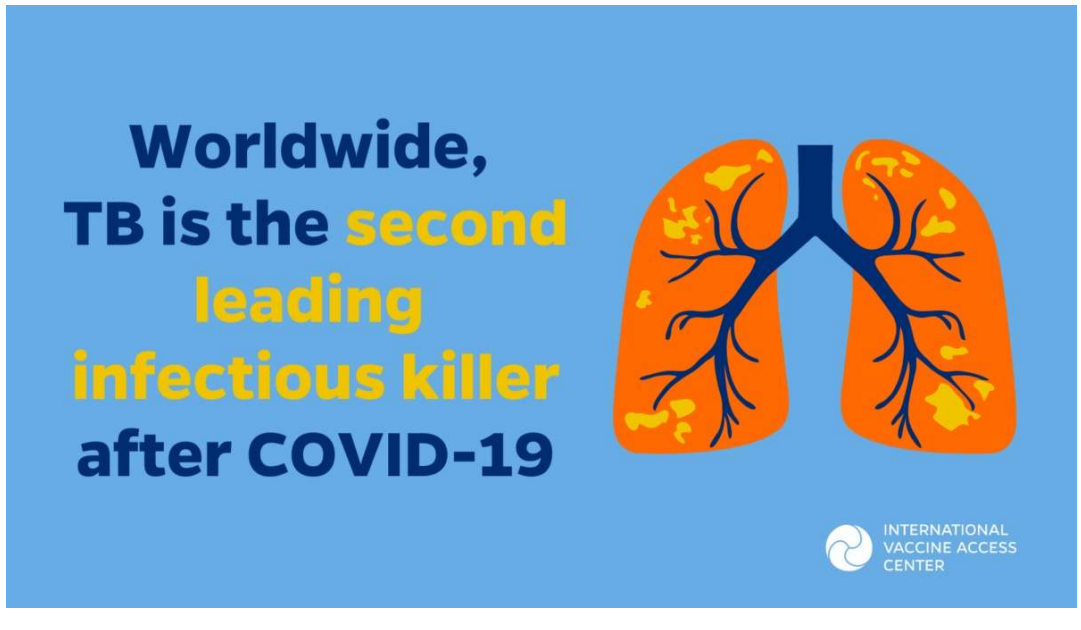


What disease has infected millions of people, killing an estimated 1.5 million people a year, without drawing a fraction of the attention of the COVID-19 pandemic?

The answer is TUBERCULOSIS (TB). New, more effective vaccines are needed to reduce the morbidity and mortality of TB, fight the rising threat of AMR, and address inequities in disease burden and economic impact.

What disease has infected millions of people, killing an estimated 1.5 million people a year, without drawing a fraction of the attention of the COVID-19 pandemic? The answer is tuberculosis.

Tuberculosis (TB) is a leading cause of infectious disease deaths worldwide—a person dies from TB every 20 seconds. According to the World Health Organization (WHO), TB is currently "the second leading infectious killer after COVID-19.". TB has the heaviest impact on the world's most poor and vulnerable populations, worsening existing inequalities: More than 95% of tuberculosis cases occur in low- and middle-income countries (LMICs), with an estimated two-thirds of total cases occurring in just eight high-burden countries[3]. In 2021, there were an estimated 10.6 million active TB cases, including 1.2 million cases of TB among children. Those who survive the disease often experience economic hardship and long-term health impacts.



The Bacille Calmette-Guérin (BCG) vaccine is the only vaccine currently available to protect against TB. BCG has been in use for a century and provides critical protection to 100 million newborns globally each year. While the BCG vaccine provides good protection for young children, the vaccine's efficacy wanes throughout the lifespan, providing negligible protection to those over 5 years old. TB mainly affects adults, leaving millions vulnerable to the devastating effects of this vaccine-preventable disease. To end the TB epidemic, it is critical to develop vaccines that are effective against TB in all age groups.

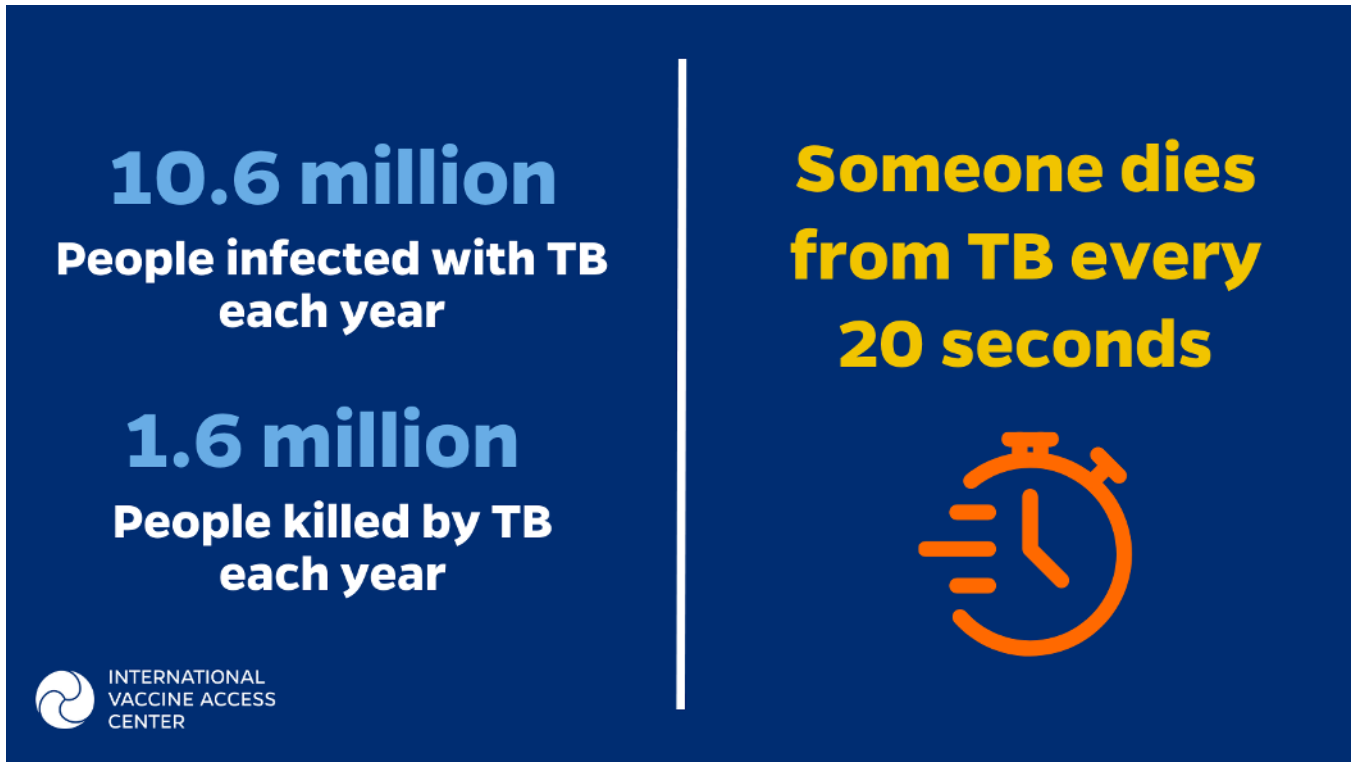
The Non-Specific Benefits of the BCG Vaccine: Protection Beyond TB

Despite its inability to protect adults from TB, BCG is a life-saving vaccine for infants and children under five. Beyond protecting against TB in early childhood, evidence suggests the BCG vaccine may also protect infants against other infections, ultimately reducing all-cause mortality in some contexts. Studies have found that BCG is one of the few vaccines providing additional immunity beyond the target pathogen, called non-specific specific effects or heterologous effects.

- **In a series of studies of low birthweight newborns in Guinea-Bissau, administering the BCG vaccine at birth was associated with a 38% reduction in all-cause mortality within the four weeks after birth.**

- **A 2023 meta-analysis examined 16 studies conducted among children and adults in both low- and high-income settings. BCG vaccination was associated with a 44% lower risk of non-TB respiratory infections, a 33% reduction in infection-related mortality, and a 38% reduction in sepsis-related mortality.**

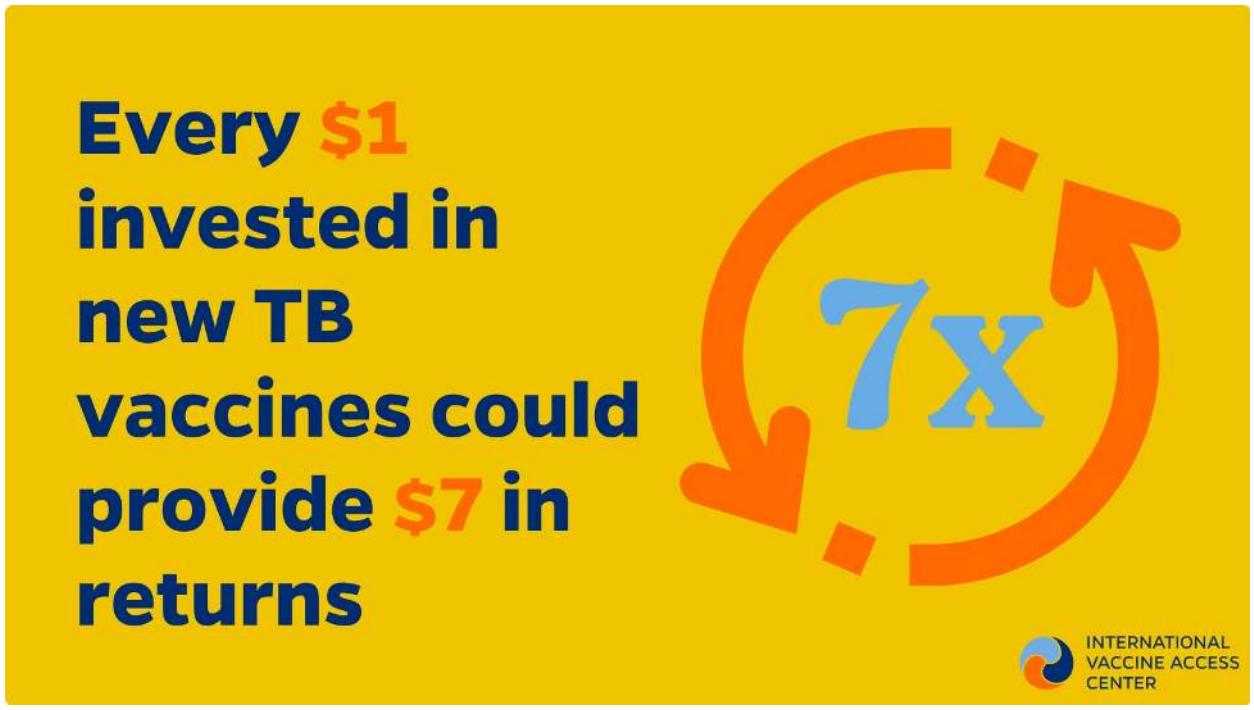
Researchers don't fully understand how BCG offers this broad protection, but one possible explanation is trained immunity — when immunization against one infectious agent can influence a person's immune response to subsequent infection(s) by an unrelated infectious agent. Another theory is that BCG immunization can influence an infant's body response to subsequent routine immunizations. It's also possible that these benefits are affected by the timing of vaccination, as research suggests that the BCG vaccine should be given within the first month of life. More research is needed to fully understand the mechanisms behind these non-specific effects and to determine the optimal timing and dosing for maximum health benefits.



TB and ANTIMICROBIAL RESISTANCE: A GROWING HEALTH SECURITY CRISIS

TB is a major contributor to the global burden of antimicrobial resistance (AMR), or the ability of disease-causing microorganisms (such as bacteria and viruses) to become resistant to drugs and treatment. Killing 700,000 people each year, AMR is considered a major global public health threat and by 2050 is projected to cause more deaths than cancer. The rise of multi drug-resistant TB (MDR-TB) is an emerging threat to global health security, with the majority of cases going undetected.

- **Drug-resistant TB accounts for approximately 1 in 3 deaths attributable to AMR.**
- **In 2021, there were an estimated 450,000 cases of MDR-TB globally, an increase of approximately 3% since 2020[3]. These accounted for 3.6% of new cases of TB and nearly 1 in 5 of those previously treated.**
- **Drug-resistant TB accounts for approximately 1 in 3 deaths attributable to AMR.**
- **MDR-TB can require up to two years of treatment, including eight months of daily injections, and an estimated 14,000 pills over the course of the treatment.**
- **The length and complexity of treating MDR-TB substantially increases health care costs. For example, it costs nearly 25-times more to treat MDR-TB than drug-susceptible TB in South Africa, contributing to a disproportionate portion of the Country's TB budget.**



The fight against AMR and MDR-TB will require a multi-pronged approach, and it will not be easy. TB vaccines can help by reducing the incidence and transmission of TB, which would in turn reduce the need for antimicrobial treatment and help to slow the emergence of AMR. Because vaccines prevent infections in the first place, they play an indispensable role in combatting the global crisis of drug resistance.

AN ECONOMIC CASE FOR TB VACCINES

Research indicates that like other immunizations, BCG vaccination is generally cost-effective, particularly in high-incidence settings. However, these cost savings are not passed downstream to the families affected by TB; treatment for the disease can take months and can lead to catastrophic health costs for families. This is one reason why preventing TB is an important consideration for equity: TB is most likely to impact those who will have the greatest challenges covering the costs of treatment, transportation to a health center, and lost wages. Low-income populations are generally at a higher risk of developing TB, possibly because they have higher exposures to risk factors such as living and working in crowded and poorly ventilated spaces and less access to health care. As a result, they are more likely to be saddled with the catastrophic treatment costs of TB.

- **According to a review of national patient cost surveys from 23 countries, the percentage of households affected by TB experiencing catastrophic costs ranged from 13–92%, with a pooled average of 47%[23]. This means that globally, nearly one in two families affected by TB will spend more than 20% of their household income on treatment, a catastrophic expense for many families.**

- **Research in Ghana demonstrates that TB costs can push households below the poverty line, particularly for those already living in the middle or lower half of the income distribution[24].**

- **The financial impact of TB continues after treatment. Among families participating in a study in South Africa, 35% of previously employed mothers stopped working to care for children who had permanent disabilities from surviving tuberculosis meningitis [25]. Nineteen percent of families reported financial loss as a result of caring for children who were disabled by the disease.**

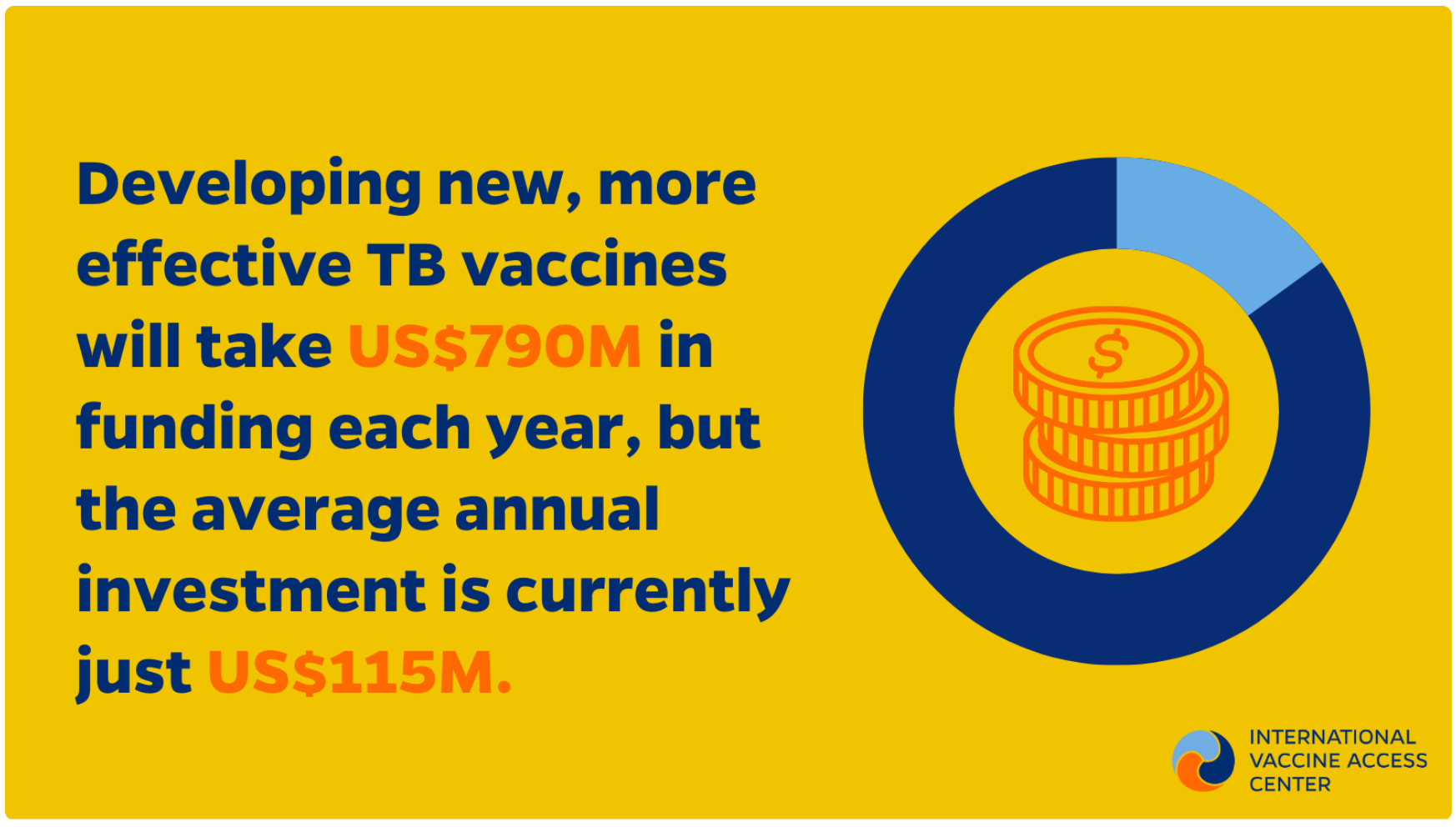
The *WHO End TB Strategy* outlines eliminating the number of TB-affected families facing catastrophic costs as one of its goals, and there is clearly work to be done to meet this ambitious goal.

"The development and roll-out of new TB vaccines could yield health and economic benefits on a similar scale to some of the most influential health interventions in poorer countries in recent years."

Developing new TB vaccines that protect adolescents and adults will require a significant investment, but Health Economists project that these vaccines will save money in the long run, thanks to averted treatment costs and the boost to the economy associated with a healthy workforce. These vaccines are also expected to advance health equity, as the benefits of new TB vaccines are expected to provide the greatest benefits for those who currently bear the highest disease burden.

- **A 2023 modelling study estimates that a TB vaccine for adolescents and adults would be cost-effective in 70% of settings and could save up to US$474 billion by 2050[28]. In this scenario, every US$1 invested in TB vaccines would provide US$7 in returns.**

- **A second modelling study[29] shows that more than half of TB cases averted by a new vaccine would be among the two poorest income quartiles. These two income quartiles would also account for 46% of averted treatment costs, as well as 66% of cases of catastrophic costs.**



Looking Ahead: The Future of TB Vaccines

New, more effective vaccines are needed to reduce the morbidity and mortality of TB, fight the rising threat of AMR, and address inequities in disease burden and economic impact. The BCG vaccine does not adequately protect older children, adolescents, and adults against TB, and continuing to neglect these populations will only exacerbate this growing crisis.

There are at least 16 new TB vaccines currently in development, but significant funding is needed to push these new vaccines through the research pipeline. It is estimated that it will take US$790 million per year to advance TB vaccines, though the average annual investment for the past several years has been just US$115 million. These vaccines must be prioritized to reduce the burden of this devastating disease and end the TB pandemic.