

## French Scientists Albert Calmette and Camille Guerin, Co-inventors of the Bacillus Calmette-Guerin (BCG) Vaccine to Protect Against Tuberculosis at the Pasteur Institute of Lille: A Short Historical Overview

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### ABSTRACT

This paper presents historical facts, pivotal figures, and significant locations that led to the development of the Bacillus Calmette-Guerin (BCG) vaccine at the turn of the 20<sup>th</sup> century to combat tuberculosis. We reviewed historical publications and gathered original data about the co-inventors, Albert Calmette and Camille Guerin, and the birthplace of their discovery, the Pasteur Institute of Lille, France. This historical overview highlights the co-inventors' distinct personalities and the local political drive to unify scientific efforts to rid the northern region of France of contagious diseases. Owing to their relentless dedication, the vaccine is aptly named after its creators. It is a fitting tribute, as Calmette and Guerin combined their expertise, courage, and determination to develop this exceptional preventive medicine. This review underscores their contributions to the creation of the BCG vaccine and their lasting impact.

**Keywords:** Bacillus Calmette-Guerin (BCG), France, history, Lille, Pasteur Institute, tuberculosis.

### INTRODUCTION

#### The Place Where It All Began: The Pasteur Institute of Lille

At the end of the 19<sup>th</sup> century, diphtheria was prevalent in Lille, the northern capital of French Flanders. Concurrently, in September 1894, Emile Roux, a close associate of Louis Pasteur, delivered a notable scientific lecture in Budapest on serotherapy, an effective treatment method for this ailment. Roux detailed how an anti-diphtheria serum had been developed at the Pasteur Institute in Paris, which had been established in 1888. Motivated by hope, a delegation from Lille promptly traveled to meet Louis Pasteur in Paris. Mr Gavelle, the First Deputy Mayor of Lille in charge of hygiene, together with Professors F. Combemale and Th. Barrois from the Faculty of Medicine, sought to highlight the urgency of addressing the diphtheria epidemic in Lille.<sup>1</sup> Despite Louis Pasteur's frail condition—he would pass away in September 1895—Emile Roux met with them. The delegation expressed their desire to control the diphtheria epidemic and their aspiration to manufacture the serums locally. They were firmly committed to establishing a facility in their own town, modeled after the Pasteur Institute. Despite his failing health, Louis Pasteur personally endorsed this initiative. He signed the foundational document of the Pasteur Institute of Lille, writing the following to Lille Mayor Gery Legrand:

*"Paris, November 18, 1894, Mister Mayor, let me introduce Dr. Calmette, whose collaboration was infinitely precious to both Dr. Roux and me. We think Dr. Calmette is the best experimenter to establish the service you and your team generously wish to create for the preparation of antidiphtheria serums, and he is surely the best manager for a hygiene laboratory. Please accept, Mister Mayor, the assurances of my highest consideration, along with the particular memory I have of your welcome last May."*

Thus, Louis Pasteur personally penned the founding document of the Pasteur Institute of Lille shortly before his death, appointing Albert Calmette as his trusted representative. At the time, Calmette, a bright 31-year-old colonial medical officer, sought to advance his career in bacteriology, but neither the Health Ministry nor the Pasteur Institute of Paris could offer him a suitable position. Despite his youth, Calmette was well-prepared for the role, having already established the Saigon Bacteriological Institute. On November 23, 1894, the treaty that definitively linked Albert Calmette to Lille was approved by the city council. From that moment on, Albert Calmette's life and the destiny of the Pasteur Institute of Lille were intimately connected—discussing one invariably means discussing the other. We will explore this connection in the following sections.

## HISTORICAL OVERVIEW

### Albert Calmette (1863–1933)

Albert Calmette was born in Nice in 1863 and grew up in Auvergne and French Brittany.<sup>2</sup> Initially aspiring to be a sailor, he pursued his studies at the Navy Medical School in Brest, where he excelled and ultimately became a physician in the Colonial Medical Corps. In this capacity, he embarked on numerous missions to China, Gabon, Saint-Pierre-et-Miquelon, and Hong Kong. In 1888, Calmette married Emilie de la Salle and they had three children. Initially self-taught in microbiology and exotic pathologies, he diligently attended Emile Roux's microbiology courses at the Pasteur Institute in Paris starting in 1890, abandoning naval medicine to dedicate himself to exploring Louis Pasteur's significant discoveries.

In 1891, at Dr. Roux's suggestion, Louis Pasteur sent Calmette to the then-French colony of Indochina, now Vietnam. Once there, Calmette introduced a vaccination campaign against smallpox, which had been responsible for 90% of infant deaths in the region. Under Calmette's leadership, 500,000 vaccinations were administered within a year, significantly reducing the incidence of smallpox. Additionally, Calmette initiated a rabies vaccination campaign, proven effective throughout the provinces of Southeast Asia. He also conducted research into the venom of the Asian cobra to develop treatments for local envenomations.



**Figure 1.** Interior of the Museum at the Pasteur Institute in Lille, showcasing furniture that once belonged to the Calmette family or to Louis Pasteur during his time in Lille (1854–1857). Photo credit: Line Bourel.

In 1891, at the age of 28, Albert Calmette established the Pasteur Institute of Saigon, now relocated to Ho Chi Minh City, marking the first Pasteur Institute outside France. Albert Calmette's early tenure was marked by both medical and managerial achievements, embodying "philanthropy and its benefits" during that era.<sup>3</sup> His time in Saigon concluded in 1893. However, as previously mentioned, upon his return to France, Calmette waited nearly another year before receiving an assignment that matched his considerable talents and experience.

Thus, in November 1894, at the age of 31, Albert Calmette was dispatched to Lille to establish a laboratory for hygiene and, more importantly, the production of vaccines and serums. This appointment, made on Louis Pasteur's recommendation and strongly supported by Lille's elected officials and medical community, quickly led to Calmette beginning work on the new institute. Like Louis Pasteur in Paris, Calmette lived on site, as close as possible to the laboratories (Fig. 1). He quickly

established a temporary laboratory at the historical site of the Faculty of Sciences, recruited the necessary staff, and arranged temporary accommodation for his family starting January 1, 1895. Calmette was known for his extraordinary work ethic and exceptional organizational skills. From February 15, 1895, he began preparing diphtheria serums and producing vaccines urgently needed by doctors and hospitals throughout the northern region. He also conducted research into antivenom serotherapy. He was greatly appreciative of the warm welcome he received and remembered it fondly 35 years later.

The municipality allocated a one-hectare plot of land, valued at 400,000 then-French francs (FF), situated next to a busy traffic axis and rail facilities on the “Boulevard Louis XIV.” In 1894, a fundraising campaign was launched to finance the construction of the future Pasteur Institute of Lille. Initially, 250,000 then-FF were raised. Subsequently, the general councils, the city of Lille, and surrounding cities provided annual subsidies, benefiting from the vaccines and serums. The foundation stone was laid on November 20, 1895. To balance the budget, Calmette personally invested in the institute, contributing 300,000 then-FF. Later, in 1904–1905, substantial donations from Danel and Ledieu-Dupaix facilitated the creation of new laboratories and a 40-horse stable for serum production. Clearly, the Pasteur Institute of Lille (IPL) was established due to strong local political support and is seen as a project advancing hygiene and public health for the city and its region. Under Calmette’s leadership, a formal agreement was signed with the Lille town council. Indeed, the IPL holds a unique status and importantly, it operates independently of the Institute Pasteur de Paris (IPP).

The first installations at the IPL quarters were completed by mid-February 1898, and under Director Calmette’s leadership, operations continued uninterrupted. The laboratory was transferred very efficiently in record time. Although the IPL was founded on November 18, 1894, the inauguration of the new institute on Boulevard Louis XIV took place on April 9, 1899. Since Louis Pasteur had passed away in September 1888, his widow, several descendants, and his son-in-law traveled to Lille for the event. Albert Calmette welcomed his guests with great honor, and a well-known photograph captures him offering his arm to Mrs. Pasteur while placing his hand on the shoulder of a young descendant of the esteemed scientist.

Final acceptance of the building work occurred on June 14, 1899. Initially, the IPL focused on developing anti-rabies and smallpox vaccinations starting in 1902, and anti-typhoid vaccination beginning in 1915. Its mission also included the preparation and distribution of therapeutic serums, such as anti-diphtheria, and anti-venom serums, a pursuit that Calmette began in Saigon and which necessitated greenhouses for breeding snakes.

Turning our attention to Albert Calmette’s personality, he was an excellent writer and even better speaker. He was highly effective and successfully disseminated his scientific work widely. Appointed Professor of Hygiene and Bacteriology at the IPL in 1898, he taught both theoretical and practical classes, effectively educating the public, bacteriologists, and brewers. Calmette also recognized the importance of political engagement and was actively involved in the city’s life, maintaining excellent relationships with leaders across various sectors—academia, politics, industry, and more. A modern Pasteurian, Calmette linked his institute with regional industries, thus benefiting distilleries, breweries, malting plants, starch factories, sugar industries, and others with his expertise. While based in Lille, Calmette helped establish several other Pasteur Institutes and participated in numerous international congresses and missions.

During the First World War, Calmette voluntarily returned to military service. He was appointed deputy director of the health service for the 1<sup>st</sup> military region in Lille, organizing auxiliary military hospitals to care for wounded soldiers and civilians.<sup>4</sup> After the armistice, Calmette learned of his appointment as deputy director of the IPP following Metchnikoff’s death and he left Lille in July 1919. By that time, the IPL had acquired an international reputation. He was elected to the French Academy of Medicine in 1919 and to the French Academy of Sciences in 1927, underscoring his solid scientific reputation.

Among Calmette’s first collaborators were his first two preparators: Rolants, a chemist, Delearde, a physician, and three laboratory technicians, one of whom was responsible for looking after the horses. The team later expanded to include Sanguineti, a scientist; Boullanger, an agricultural engineer; Marmier, a physician with qualifications in physics; Woehrel, a secretary with literary value who organized many congresses and missions; and, most notably, Guerin, a veterinary surgeon.

### **Camille Guerin (1872–1961)**

Camille Guerin was born in Poitiers in 1872, and was just 10 when his father died of tuberculosis in 1882. Between 1892 and 1896, Camille Guerin studied at Alfort, becoming a skilled veterinary surgeon and biologist.

Recruited by the Pasteur Institute in Lille in 1897, Guerin became one of Albert Calmette’s closest collaborators, being nine years his junior. At the IPL, he performed many meticulous tasks essential to the production of vaccines, particularly the smallpox vaccine, and animal serums. After the First World War, in 1919, he became head of the department and conducted further research on vaccines and venoms. Guerin remained in Lille until 1928, when Calmette invited him to join the Pasteur Institute in Paris to contribute to the national and then

international development of BCG. On March 6, 1958, Camille Guerin wrote this moving message to the director of the IPL: *“Will you tell your colleagues that I left half my heart in Lille, and that the other half is not yet healed from this abandonment.”*

Between 1928 and 1942, Guerin conducted his research at the Pasteur Institute in Paris. In 1928, he became head of the tuberculosis department, working alongside Calmette until the latter’s death in 1933. In 1939, Guerin was appointed vice-president of the National Committee of Defense Against Tuberculosis. He ardently advocated for the global expansion of BCG vaccination under World Health Organization (WHO) supervision. He also served as a scientific expert to the League of Nations in Geneva, recognized internationally for his work on smallpox. In 1942, he officially retired but continued to lead an ‘active retirement’ at the IPP.

His career culminated in numerous honors. In 1948, he was appointed chairman of the first international BCG congress. In 1951, he was elected President of the French Academy of Medicine, and in 1955, he received the *Grand Prix* for Scientific Research from the French Academy of Sciences. He passed away in 1961 at the age of 88 at the Pasteur Hospital in Paris. Throughout his life, Camille Guerin remained committed to Calmette and his primary research focus: combating tuberculosis. The development of BCG vaccine is largely attributed to his perseverance and meticulous application.

### The Discovery and Development of BCG (1904–1928)

In 1900, one in seven people died of tuberculosis. Today, the situation remains dire, as tuberculosis still claims a life every 15 seconds worldwide.<sup>5</sup> Starting in 1901, the ‘Emile Roux Tuberculosis Dispensary,’ adjacent to the IPL’s main building, began welcoming patients. Here, individuals were not only received but also advised, supported, and treated, while social and medical assistants received training.

To outline the chronology of discovery, in 1905, Guerin found that the bovine tuberculosis bacillus (*Mycobacterium bovis*) could immunize animals without inducing the disease. By 1908, Calmette and Guerin had developed methods to attenuate the virulence of *Mycobacterium bovis*. This process involved successive transplantations of a virulent strain onto a special medium composed of potatoes soaked in 5% glycerol-treated beef bile. A non-virulent but still immunologically active preparation was obtained. In 1908, the earliest publication on the BCG of Calmette et Guerin Vaccine (BCG) appeared. In 1912, the first immunization of cattle was carried out. Between 1915 and 1918, Lille was occupied by the Germans, and scientific research had to be interrupted. In 1921, after 230 passages of BCG culture, Calmette and Guerin obtained a vaccine suitable for human use. The first BCG injection took place on

July 18, 1921. By 1928, BCG vaccination was widely available worldwide. The discovery was largely due to the tenacity of Camille Guerin, who for 13 years, 230 times in succession, kept *Mycobacterium bacillus* emulsified with beef bile.

At that time, BCG was a decisive weapon against tuberculosis, which was responsible for a quarter of all infant deaths in Europe. This vaccine was distributed worldwide in the late 1920s, and each country subsequently maintained its own stockpile. In these other laboratories, BCG was maintained under the same conditions as at the Pasteur Institutes, with the same purpose. The aim was to prevent the BCG from reverting to a virulent form, while preserving its efficacy and therefore its effectiveness. Over the following decades, each of these laboratories developed its own “daughter strains” of the BCG, named after the laboratory, country, or person with whom they were associated.

Tragically, on April 26, 1930, 72 children in Lübeck, Germany, died after being vaccinated with BCG. It was a disaster. A vehement campaign to discredit BCG and Calmette ensued. An investigation revealed that the unfortunate sequence of events was due to human error in handling: a virulent strain of tuberculosis bacillus had contaminated the BCG. This incident delayed the introduction of vaccination in Germany. Although exonerated, Calmette was deeply affected by the slander and the damage it had caused. He died in 1933 at the age of 73, just a few days before Dr. Roux, who had chosen him as a successor at the head of the Pasteur Institute in Paris.

There have been numerous controversies concerning the prevention of tuberculosis, one of which involves the efficacy of the BCG vaccine. In various clinical trials, estimates of efficacy have ranged from 80% protection to no benefit, with the reasons for these discrepancies still not clearly understood. For example, compulsory BCG vaccination, implemented in France in 1950, was discontinued in 2007 in favor of targeted vaccination for at-risk children.<sup>6</sup> Today’s detractors of vaccination, who often speak louder and more broadly than scientists, overlook the significant role it has played—and continues to play—in combating infectious diseases. This is particularly distressing when it occurs in the homeland of Pasteur, Calmette, and Guerin.

### Remembering Calmette and Guerin at Lille’s Pasteur Institute

At the Pasteur Institute of Lille, the historic construction is known as the “Albert Calmette Building.” In the courtyard, a newer structure, which accommodates part of the biological analysis department, is named the “Camille Guerin Building.” While the historic building boasts an elegant façade on the *Boulevard Louis XIV*, its postal address is *1 Rue du Professeur*



**Figure 2.** Laboratory items previously owned by Calmette and Guerin. Photo credit: Line Bourel.

*Calmette.* The street perpendicular to *Rue du Professeur Calmette* and parallel to *Boulevard Louis XIV* is named *Rue Camille Guerin*.

In 1979, a museum was established at the very location where BCG was discovered, where Camille Guerin had his office for 31 years. Before the Institute of Biology of Lille (IBL) was constructed in the IPL courtyard in the mid-1990s, Camille Guerin's old animal house, with his name still on the doorbell, could still be seen. The creation of the IBL led to the demolition of this historic structure. The museum was temporarily relocated to the Emile Roux Dispensary, which dates from the same era. Since 2017, the museum has been reinstated and is now situated on the first floor of the "Albert Calmette Building".<sup>7</sup> It typically displays six sealed tubes containing the original strain and items from Calmette and Guerin's laboratory (Fig. 2).<sup>8</sup> A plaque on the wall reads: "*In this laboratory, Albert Calmette and Camille Guerin, united as much by scientific spirit as by heart, pursued the research that led to the prevention of tuberculosis by BCG.*"

It should be noted that the "Albert Calmette Building" has been primarily dedicated to science and was completely remodeled in the 1980s under the direction of Jean Samaille (1974–1994), with each level being split in two. Anecdotally, the author of this article worked as a student in a laboratory set up in part of the apartments once occupied by the Calmette family. A bust of Albert Calmette faces the courtyard entrance to the building. Beneath this courtyard, where children Georges and Andre Calmette used to play in the 1900s, a nuclear magnetic resonance laboratory was installed ten meters underground in the 1990s. This scientific area is known as the Calmette Campus.



**Figure 3.** Original strains of *Bacillus Calmette and Guerin*. This photograph was taken on Friday, March 23, 2018. Absent from the rack are the three tubes that were opened the previous day, Thursday, March 22, 2018 by Dr. Philippe Supply. Photo credit: Line Bourel.

Albert Calmette wrote in his memoirs:

*"My only merit is to have avoided spreading myself too thinly over too many subjects and to have studied with perseverance those that attracted me. I devoted myself almost entirely to the study of venoms and tuberculosis. The latter has absorbed me without interruption since 1900. I think it is thanks to this continuity of thought and effort that I have been able to make myself useful. I hope that my children and grandchildren will be inspired by the same rule of conduct. I hope it will be given to me to work until my eyes close and I fall asleep, my soul at peace, with the conscience of having done what I could."*

## CONCLUSION

The Bacillus Calmette and Guerin (BCG) vaccine was developed at the turn of the 20<sup>th</sup> century to combat tuberculosis. This work highlights the importance of the co-inventors' respective personalities and the local political will to unite scientific efforts to alleviate the northern region of France from contagious diseases. The BCG vaccine is aptly named after its co-inventors. This is fitting as Calmette and Guerin combined their expertise, courage, and determination to develop this outstanding preventive medicine.

Even today, researchers at the Pasteur Institute in Lille continue to combat tuberculosis, following in the footsteps of Calmette and Guerin. The story of the BCG vaccine is not yet complete. For instance, on Thursday, March 22, 2018, Philip Supply, research director at the CNRS, reopened three of the six tubes containing the original strains (Fig. 3). His team endeavored to replicate and study with 21<sup>st</sup>-century scientific tools what Soline Roy described in her article "an imperfect vaccine but never equalled, a GMO (Genetically Modified Organism) before its time."

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