Alexandre Yersin:

Medical Doctor and Scientist, Explorer, Veterinary Scientist and Agronomist

by

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Abstract

The second half of the 19th century and the beginning of the 20th century was characterized by a scientific boom in microbiology, immunology and vaccinology. Alexandre Yersin (1863-1943) grew up during that period, became physician and in 1886 the right hand of Emile Roux, the stronghold of Pasteur in his research. Together with Roux he identifies in 1889 the toxin as cause of diphtheria. But the horizon was too small in Paris and Yersin decided to move to South-East Asia in 1890. During that time Yersin took the opportunity to discover the mainland between the coast of Annam and Laos. In 1894 Yersin is commissioned by the Pasteur Institute and the French Government to go to Hong Kong to unravel the mystery of the bubonic plague epidemic. Yersin succeeds to identify the pathogen responsible for the plague which was named after him *Yersinia pestis*. In 1895 Yersin settles in Nha Trang where he establishes a lab and a farm in search for solutions to medical and more specifically veterinary diseases. Yersin became not only a "veterinarian" but also a "bioengineer" as he established an agricultural farm with plantations for rubber and quinine producing trees to help finance his research on veterinary diseases. After a live of dedication to science and commitment for the diseased and mostly poor people of Vietnam as well as their livestock, Yersin passes away in 1943 and is buried on his farm in Suoi Dau.

Keywords: Yersin, Pasteur, Vietnam, the plague, *Yersinia pestis*

Samenvatting

Op het einde van de 19de eeuw explodeert de wetenschappelijke kennis in microbiologie, immunologie en vaccinologie. In 1886 wordt Alexandre Yersin de rechterhand van Emile Roux, een rots in het onderzoek van Pasteur. Maar vlug blijkt de wetenschappelijke horizon voor Yersin te klein en besluit hij naar Indochina te varen om zich daar als scheepsdokter in te lijven op lokale lijnen. Als ontdekkingsreiziger doortrekt en beschrijft

hij het vaste land tussen de oostkust van Annam (Vietnam) en Laos. Maar in 1894 belast het Pasteur Instituut en de Franse regering hem met een wetenschappelijke missie naar Hong Kong om aldaar de oorzaak van de pestepidemie te achterhalen die er een ravage pleegt. Met succes identificeert hij er het oorzakelijke agens dat later *Yersinia pestis* naar hem wordt genoemd. Terug in Vietnam vestigt Yersin zich in Nha Trang, waar hij een labo opricht voor humane en vooral dierlijke ziekten, dat dan redelijk vlug opgenomen wordt in de rij van officiële buitenlandse Pasteur instituten. Yersin ontpopt zich daar niet enkel als wetenschappelijk dierenarts maar ook als landbouwexpert met een bomenplantage voor rubber en quinine ter financiering van zijn labo. Na een levenslange toewijding aan wetenschap en zorg voor zieken en armen in Vietnam en hun veestapel, sterft Yersin in 1943 in Nha Trang waar hij als Europeaan en Vietnamees begraven wordt.

Trefwoorden: Yersin, Pasteur, Vietnam, de pest, *Yersinia pestis*

Résumé

La seconde moitié du XIXe siècle et le début du XXe siècle ont donné lieu à une explosion scientifique en microbiologie, immunologie et vaccinologie. Alexandre Yersin (1863-1943) grandit durant cette période, devient médecin et en 1886 le bras droit d'Emile Roux, un pilier de Pasteur dans son labo. Avec Roux, il identifie en 1889 la toxine comme cause de la diphtérie. Mais l'horizon devint vite trop étroit à Paris et Yersin décide de partir en 1890 en Indochine. Pendant ce temps, Yersin en profite pour découvrir le continent entre la côte Est de l'Annam et le Laos. En 1894, Yersin est chargé par l'Institut Pasteur et le gouvernement Français de se rendre à Hong Kong pour percer le mystère de l'épidémie de la peste bubonique. Yersin réussit à identifier l'agent pathogène responsable de la peste qui portera son nom *Yersinia pestis*. En 1895, Yersin s'installe à Nha Trang où il construit un laboratoire et une ferme à la recherche de solutions aux maladies humaines mais surtout animales. Yersin est devenu non seulement un «vétérinaire» mais aussi un «bio-ingénieur» en établissant une ferme agricole avec des plantations d'arbres producteurs de caoutchouc et de quinine pour financer ses recherches sur les maladies vétérinaires. Après une vie de dévouement à la science et d'engagement pour les personnes malades et pour la plupart pauvres du Vietnam ainsi que pour leur bétail, Yersin décède en 1943 et est enterré dans sa ferme à Suoi Dau.

Mots clés: Yersin, Pasteur, Vietnam, la peste, *Yersinia pestis*

Preface

From 2004 to 2009, we had a VLIR-funded Belgian-Vietnamese project between the Catholic University of Leuven (KU Leuven), the Vrije Universiteit Brussel (VUB), the National Centre for Veterinary Diagnosis (NCVD) in Hanoi, the National Institute of Veterinary Research (NIVR) in Hanoi and the Central Vietnam Veterinary Institute (CVVI) in Nha Trang working on oedema disease in pigs. Oedema disease is a lethal disease caused by an exotoxine, produced by pathogenic intestinal strains of *Escherichia coli*, that is absorbed into the body, circulates through the blood system and provokes fluid extravasation throughout the body inducing general subcutaneous oedema as well as brain oedema with consequently neurological symptoms and eventually death. The project was successful in producing a protective vaccine against oedema disease by constructing a toxoid derived from the *E. coli* toxin by introducing two mutations (Oanh et al. 2012). As we were annually in Nha Trang for training and field work, we could not miss the fame of Alexandre Yersin and his adoration by the Vietnamese people. A visit to the Pasteur Institute and the museum got us more and more interested in that intriguing person. In 2003 on a mission to Nha Trang, we inquired with our fellow Vietnamese colleagues for a possible visit to the grave of Yersin but we were told that it is in a park, 10 km from the lab, closed to the public. However, in the afternoon they called upon us in the lab to drive to Suoi Dau. They had obtained the key to the gate, brought us bouquets of flowers to deposit onto the grave and incense sticks to lighten in front of the pagoda: what a thoughtful gesture of this wonderful people, elating their admiration for him! Yersin has two graves, one European, a tomb stone with name and a standing up-plate with picture and text, and a Vietnamese pagoda with his picture inside. We were so excited and so happy being able to pay that visit in honour of that great man. From then on my interest in that formidable man had been ignited. Many articles and books have been written on Yersin but the books of Mollaret and Brossollet (1985) and Perrot and Schwarz (2013) guided me in elucidating and describing the live of Yersin.

1. Introduction: political and geographical background

Alexandre Yersin (1863- 1943), born in Aubonne close to Morges (Canton Vaud, Switzerland), was a medical doctor who did his medical studies at different universities, first in Lausanne, Switzerland, then in Marburg, Germany and finally in 1885 in Paris, France. In 1886 he entered the lab of Louis Pasteur at the "École Normale Supérieure" close to the Panthéon, (the Pasteur Institute was only built later in 1888 on a different place close to Montparnasse) and worked there together with his senior Emile Roux, the closest collaborator of Pasteur, where they identified the pathological cause of diphtheria, the diphtheria toxin (Roux and Yersin 1888, 1889). In June 1888 he obtained his PhD on experimental tuberculosis in rabbits at the medical faculty of Paris. Two weeks after his

PhD defense, in the month of June, Roux send Yersin who mastered the German language (see medical studies in Marburg), to Berlin on a bacteriology course in the laboratory of the famous rival Robert Koch to improve the bacteriological knowledge in Pasteur's lab but even more so to get information how the course, practica and labs were organized in order to start themselves a bacteriology course the following year (Fantini 1994). Even plans on the infrastructure of Koch's laboratory have been recovered in the Pasteur Institute. The completely newly-built "Institut Pasteur" was officially inaugurated in November 1888 by President Sadi Carnot, and Roux and Yersin started the bacteriology course a few months later (figure 1). In 1889 Yersin obtained the French nationality. But feeling uneasy in lecturing, his adventurous soul got the overhand and in 1890 Yersin changes France for "Indochine" and enrolls as a medical doctor in the "Compagnie des Messageries Maritimes" on the passenger shipping line in Vietnam (part of Indochina, see later).

The young Yersin had grown up in a medical and political tumultuous period. The French-Prussian war from July 1870 to January 1871 had ended in the defeat of Napoleon III (treaty of Frankfurt, May 1871) and the coronation of the Prussian King Wilhelm I as Emperor of the United Germany in the Mirror Gallery of Versailles, all under the impulse and control of mastermind Otto Von Bismarck. Five million francs had to be paid as war damage to Germany. What a shame for France! Pasteur was so disgusted with the Germans that he returned his doctor honoris causa to the University of Bonn. The scientific relation between Pasteur and the German scientist Koch, who had served as army medical doctor in Orleans during the war, was thus on very bad terms and remained so for the rest of their lives.

France had been active overseas on conquering territories in the Far East. In 1862 Cochinchina became a French colony and twenty-five years later it obtained control over northern Vietnam by its victory over China in the Sino-French war (1884-85). French "Indochine", Indochina, was now composed of Cochinchina (south), Annam (middle) and Tonkin (north), making up together modern Vietnam, and the Kingdom of Cambodia (figure 2). Indochina became even larger after the Siamese-French war with the acquisition of Laos in 1893. This is thus the scientific and political background of France when Yersin arrived in 1890 in Indochina.

2. Yersin explores the inland (Hinterland) of Annam

Yersin started as a medical doctor on the shipping line Saigon-Manilla and one year later on the line between Saigon and Haiphong in present-day Vietnam. But he did not lose his scientific contacts with the Pasteur Institute and met already in 1892 the Pasteurian Albert Calmette in Saigon who as a medical doctor in the colonial forces was there on the request of Pasteur to create a lab for vaccine production against smallpox and rabies. Yersin had

never met Calmette before as he had already left the Pasteur Institute before Calmette enrolled in 1890 for the bacteriology course. From that moment on, they had a lifelong friendship. The research virus was still gnawing at Yersin and in 1892 he requests to travel to China where an outbreak of bubonic plague is going on in Long Tchéou (French consulate, now Longzhou) just at the border between Tonkin and China in order to identify the etiological cause of the bubonic plague that formed a threat to the French colony. But the Governor General of Indochina Jean-Marie de Lanessan refuses Yersin to leave the country. Yersin getting bored with his medical job on the shipping line, disembarks at the bay of Nha Trang which beauty attracted him on his passages with the shipping line, to explore the highlands of Indochina bordering Laos. At that time the highlands of Annam were still relatively unknown territory and Laos (east of Annam) will only be integrated into the colony the following year 1893. This initial attempt failed but a little later he could accomplish his first exploration from Nha Trang to Stung Treng along the Mekong into Cambodia (March 28, 1892 – June 9, 1892) (figure 3 and 4). He drew maps, met the local tribes and quite often took big risks. With all his acquired information, he was in fact of great service to the French forces. In December 1892, on advise of Calmette, he managed to enter the colonial army forces as medical doctor 2nd class (figure 5): later on in 1913 he will become Principal Doctor 1st class "colonel, five stipes" and will resign from the army in 1920. One year later in 1893, on request of the Governor General, he undertakes already his second exploration from Nha Trang to Saigon (February to October). That year his request to study the bubonic Plague in China was again refused by the same governor general. In 1894 he undertakes a third mission from Nha Trang to Da Nang. All these explorations have been carefully narrated by Yersin himself (Yersin 2016). Finally, on request of Pasteur he received the order from the French government to travel to the Chinese province Yunnan (figure 6) to identify the cause of the epidemics and to develop prophylactic measures. But thanks to the help of Calmette who was back in Paris, Yersin can convince the government to send him to Hong Kong instead, where the pest had already spread to and along the coast up to Xiamen (old name for Amoy, 500 km north of Hong Kong).

3. Yersin discovers the cause of the bubonic plague (black death)

The bubonic plague is one of the most devastating killer diseases in the history of humankind. The first pandemic (plague of Justinian) affected the Eastern Roman Empire (Byzantine Empire) and killed an estimated 25 million (6th century outbreak) to 50 million people (two centuries of recurrence). The second pandemic, the "Black Death" of the Middle Ages in Western Europe (1348-1352) originated in or near China and spread from Italy (sea ports for the Far East) throughout the other European countries: 25 million deaths (1/3 of the population). The next few centuries were marked by several localized or regional outbreaks. The Great Plague of Milan (1629-1631), the Great Plague of Sevilla

(1647), the Great Plague of London (1665–1666), the Great Plague of Vienna (1679), the Great Baltic plague (1708–1712), the Great Plague of Marseilles (1720), the Great Plague of 1738 (eastern Europe) and Caragea's Plague in Romania (1813–1814) were the major outbreaks of bubonic plague in Europe. The third pandemic started in the Yunnan province of South-West China spreading towards Guangdong province due to the migration of Chinese Muslims in Yunnan during the rebellion against the Manchu rulers of the Qing Dynasty (figure 6). From Hong Kong (1894) it spread to Bombay (1897), Suez, Madagascar, Alexandria, Japan, East Africa, Portugal, Brazil (1899), Manilla, Sidney, Glasgow, San Francisco (1900), Honolulu (1908), Java (1911), Ceylon (1914) and again Marseilles (1920) after its first epidemic two centuries before.

On June 15 1894, Yersin arrives in Hong Kong. Hong Kong had been established as a colony of the British Empire at the end of the first Opium War in 1841 (99-year lease). A few days earlier on June 12, a Japanese mission had already arrived in Hong Kong to help the British to unravel the cause of bubonic plague. Its famous leader, the 38 year-old Shibasaburo Kitasato, who had obtained his doctorate in Berlin under Koch a few years earlier (1885-91), was worldly known for his findings on tetanus and anti-tetanus serum (figure 7). He returned to Japan in 1892 where he started a private institute for bacteriology that was adopted by the state in 1899 as "Imperial Institute for Infectious Diseases" under his director- and professorship. He must probably have known Yersin who had followed the bacteriology course in Berlin when he was there in 1888. So we had two rivaling teams at the same moment in Hong Kong: the Pasteurian Yersin, 4 years back from Paris, and the Kochian Kitasato, 3 years back from Berlin. This whole mission has been beautifully narrated by Yersin himself in his Hong Kong diary (Yersin 1894). From the beginning onwards, the struggle was unfair. Kitasato, the world famous bacteriologist, was hosted with admiration, honours and all support by the Scottish doctor James Lowson in charge of the hospitals in Hong Kong. Arriving with all his equipment he was given immediately access to a lab in the Kennedy Hospital and all corpses of the plague were reserved for him. On his arrival three days later, Yersin was completely ignored by Lowson, he called him the Frenchman as he had never heard of Yersin, who was given only very poor lab accommodation in an open corridor (free passage) of the Kennedy Hospital and was unable (refused) to get corpses from the epidemic as they were all reserved for the Japanese: it started to resemble a Scottish-French struggle (Solomon 1997). On June 14th, thus one day before Yersin's arrival, Kitasato announced he had identified and isolated the cause of the plague from blood and got his results (or rather his admirer Lowson) known by telegram to *The Lancet* of June 23 (Editorial note 1894) and published two months later: a first note by Lowson with several pictures on August 11 (Lowson, 1894, figure 8) followed by a full publication by Kitasato himself on August 25 (Kitasato, 1894). Conversely, Yersin had 5 days of frustrating work on blood of diseased patients, the only samples Yersin could get hold on (although he suspected already that buboes were the target to examine but for

that you need corpses). However, with the help of his local guide and translator father Vigano, Yersin obtained finally some buboes of deceased people by bribing English sailors in charge of disposing the dead bodies. Immediately he was able to stain and isolate short rods, culture them, infect mice and guinea pigs, all dying the subsequent day with a typical bubo. Because his open passage corridor was not suited and not safe as a lab, Yersin built in two days with the help of father Vigano his own house with lab, a small mat-shed of straw and bamboo, next to the Alice memorial hospital, also a mat-shed but much bigger (figure 9). Within one week after his arrival Yersin had thus also isolated a culprit, sent bubo samples to Paris and reported them to the British authorities. After complaining to the British authorities, Yersin got now access to corpses and also detected the pathogen in dead rats and soil of infected quarters of the town. As the epidemic came to an end, Yersin decided to return to Saigon on August 3. His discovery letter was verbally reported on July 30 to the French Academy of Sciences by Emile Duclaux (director of the Pasteur Institute between 1895-1904) (Yersin 1894a) which was noticed by *The British Medical Journal* of August 18 (Editorial note, 1894a) and *The Lancet* of August 18 (Annotations 1894). In September, a full publication appeared in the *Annales de l'Institut Pasteur* (Yersin, 1894b, figure 10). But who was right? This question has been answered in the best way by the Japanese themselves. Already in 1895, Aoyama, the pathologist who assisted Kitasato in Hong Kong had doubts on the bacilli of the blood thinking they were systemic streptococci. In 1900 Tatsusaburo Yabe, head doctor of the Japanese navy, examined the cultures in the lab of Kitasato and confirmed that that they were a species of pneumococci: "The honor of the discovery of the pest bacillus comes to Yersin only and we regret sincerely that our distinguished microbiologist made an unbelievable mistake on the pest microbe". Finally Kitasato appeared confused as he gave later on contradicting statements on his own results. It seems that Kitasato announced himself at the Sixth Biennial Conference of the Far Eastern Association of Tropical Medicine at Tokyo in 1925 that "the discovery of the pest bacillus is due to the great Yersin and not to me" (Lagrange 1926). However, these quotes can be found neither in the conference proceedings, nor in the speech that Kitasato gave during that conference as the president of the Association. This question about who was right or wrong has been thoroughly examined (Howard-Jones 1975; Bibel and Chen 1976) and the published records show that Kitasato was mistaken about the identity of the plague pathogen but never admitted his error. How did it come that Yersin succeeded in identifying the correct pathogen where Kitasato failed? The difference may have laid in their methods: Yersin examined bubonic material that was full of pest bacteria while Kitasato used blood where these bacteria are almost absent. Secondly, Kitasato cultured at 37°C in his heated incubator while Yersin by lack of a heated incubator had to culture his samples at room temperature (30-32°C), a temperature that appears more appropriate to culture the pest bacteria.

4. Yersin fights the pest with antisera.

On his return to Saigon, Yersin is confronted with an epizootic of rinderpest in water buffalos. After a short mission for the Plague in Yunnan (the old request of the Governor General), Yersin can acquire a house on the peninsula between the bay of Nha Trang and the estuary of the Cai river, where he installs also a laboratory to examine the problem of rinderpest (figure 11). He manages quickly to reproduce the disease in buffalos but is again called away by the French Government to Madagascar for an inquiry on Blackwater Fever (malaria) and from there on to Paris (April 21 – August 4, 1895) where he succeeds with Calmette and Borrel in preparing a prophylactic anti-pest vaccine protecting rabbits and therapeutic equine antisera curing infected rabbits, guinea pigs and mice (Yersin, Calmette and Borrel 1895; Yersin 1897). Via Marseille, Aden, Colombo, Singapore, Saigon in 26 days, Yersin is back in Nha Trang on September 23 and is able to expand his lab infrastructure and stables for horses and buffalos with the help of the Governor General and the Ministry of Colonies (figure 11). The lab had to produce vaccines and equine antisera and requires consequently a farm with experimental and antisera-producing animals. But as stables close to the beach are not ideal (monsoons), the local Annamite authority allows him to move his horses, cows and buffalos to the citadel of Khane Hoa, eleven kilometers from Nha Trang, to where he commutes daily by bicycle (figure 12). In March 1896 the military veterinarian Eugène Pesas is recruited, indispensable for Yersin as veterinary tasks are increasing permanently. As bubonic pest re-emerges in Hong Kong, Canton and Amoy in the spring of 1896, Yersin leaves again for China but this time with his antisera. As this antiserum had never been tested on humans, Yersin was reluctant to use it because of ethical reasons. However, in Canton the catholic bishop Monseigneur Chausse pleads Yersin to treat Tisé, his young 18-year Chinese seminarian having fever and typical plague symptoms. Within less than 12 hours after treatment in the presence of the French consul of Canton, the patient recovers miraculously from illness. Like Pasteur before in Paris with his vaccine against rabies (1885), Yersin has now treated a patient with an antiserum of which the efficacy and safety had only been proven in animals. (Von Behring had treated a child with an anti-typhoid serum in 1891). In Amoy he was able to repeat successfully his treatment on 23 patients with only two deaths.

When in early spring 1887 the pest erupts in India, Yersin leaves for Bombay and Mandvi on the northwest coast of India. Here the Kochians and Pasteurians meet again, with that difference that Koch is now personally present. On request of the German government, Koch had left his mission on Rinderpest in the Cape Province of southern Africa to join the German mission on bubonic plague in India. On May 1, he joined for two months his associates Gaffky and Pfeiffer in Bombay who had started already their research (Lagrange 1938). Yersin was busy treating patients with his antisera prepared in Nha Trang but treatments had only mediocre results (50%) but improved later on using sera sent from

Paris. After 4 months, the Pasteurian Paul Louis Simon replaces Yersin and will soon discover that the rat flea is responsible for transmitting the plague by its bites between rats and humans. Yersin and Koch leave India around the same time: Koch goes to Dar es Salaam (Tanzania but at that time the German colony Tanganika) in July 1897 to examine malaria, nagana (cattle sleeping sickness), Texas fever (Babesia) and the pest that was now also present in East Africa, while Yersin returns in June 1897 to his lab in Nha Trang where he will continue his efforts against rinderpest but also other diseases. But one year later in 1898 he faces now in Nha Trang very close to the lab itself the pest, imported from China with pigs or escaped from his own lab (Lynteris 2019). After burning down houses and patient treatment with antisera, Nha Trang could be declared one year later free of the plague.

5. **Yersin establishes his lab and facilities for antisera and livestock diseases: The birth of the Pasteur Institute of Nha Trang**

Yersin had his house at the beach overseeing the estuary, the sea, the mountains and the village. After his first construction (1896) of a lab next to his house (figure 11) for production of horse antisera against the Plague, he built in 1899 a new and more elaborate lab a few hundred meters land inwards, the future Institut Pasteur of Nha Trang. The quadrangular compound had on one side the principal one-storey building (55 by 10 meters) with rooms for surgery, bleeding of animals, preparation of antisera and sterilizations on the ground floor, and three laboratories, the library and the office of Yersin on the first floor (figure 13). The other sides of the compound were composed of stables with boxes for 300 animals, horses or cattle, healthy, under or off experiment. Also three houses were constructed for his French or close collaborators. Yersin with his love for physics, mechanics, electricity and industrial revolutions, supervises all installations (see also chapter 7). He builds a wind mill for pumping water into a water tower that provides all his units of tap water, and electricity is produced by a generator which will serve a meal and bone crusher, hay chopper and also an ice machine, important for a lab in a tropical climate. The first mandate had been a lab to study the plague and production of antisera for treatment in future epidemics. But Yersin who was concerned about the wellbeing of the Vietnamese people put now his major attention on their livestock diseases who threatened continuously cattle and buffalos. Realizing that small laboratory animals did not suit for the study of livestock diseases, Yersin had to acquire a farm where he could station and breed his experimental large animals and procure them with the necessary feeds. In 1896 he obtained a concession of 500 hectares along the river Suoi Dau (figure 14) at a distance of 20 kilometers from his lab and moved there all his animals of Khane Hoa, his previous farm. The station of Suoi Dau served also as revalidation center for animals which had been bled on multiple occasions for antisera production and for a stock of experimental large animals. Slowly the Suoi Dau site was cleared from forest into 450

hectares of agricultural land with the rest reserved for grazing and stabling of his experimental livestock. For each animal disease the same path was followed, as he had learned in Paris and in Hong Kong: an in-field study of the disease outbreak, sampling, laboratory analysis in Nha Trang, isolation of the pathogen and production of antisera and possible vaccines. As mentioned before rinderpest got his major attention.

But again Yersin was halted in his work by a call in 1902 from his friend the new Governor General Paul Doumer (future president of France in 1931-32) to become director of the newly-established medical school in Hanoi, the first higher education facility in Vietnam. Yersin could not refuse. In 1902, 30 students out of 375 candidates were selected for the first year. Besides being director, Yersin was also responsible for teaching chemistry, physics and comparative anatomy. Eleven students passed and went to second year. But in 1903, Doumer is called back to Paris and replaced by the new Governor General Paul Beau who dislikes Yersin and places the school of medicine under the authority of the army. After consultation with Roux, Yersin accepts to quit the school to become director of the Pasteur Institutes in Nha Trang and Saigon. It will be only in 1919 that the school will deliver diplomas equivalent to Paris. From then on the university hospital is named "Hôpital Yersin" and is the only one of all the university French names that kept its name after the fall of Hanoi in 1947. When Yersin arrives back in Nha Trang he had passed the age of 40. During the following 30 years, he will concentrate on pathologies and production of antisera and vaccines for livestock diseases (table 1) (Yersin 1904). Research on rinderpest demonstrates the viral character of the pathogen and initiates the production of protective antisera. Production of a vaccine against anthrax starts in 1911. Bovine piroplasmosis, bovine and buffalo pasteurellosis (hemorrhagic septicemia), food and mouth disease were also under study. In 1932, a kennel for 75 dogs is constructed in order to produce a rabies vaccine with its production starting in 1934. One year later a pig stable is constructed for the production of antisera against classical swine fever. Also other diseases like chicken cholera, swine erysipelas, swine pasteurellosis, blackleg (*Clostridium chauvei*) and equine trypanosomosis (surra or dourine?) are tackled. In order to realize all this, Yersin is obliged to engage several veterinarians who are doing the research, experimental animal manipulations and the production of antisera and vaccines: Eugène Pesas (army, 1896-97†, died suddenly of malaria or of pest during manipulation in the lab, notice the pest outbreak around his lab in 1898), Albert Fraimbault (army, 1897-1902[?]), Charles Carré (army, 1897-1902[?]), Joseph Carougeau (army, 1899[?]-1902[?]), Jules Blin (army, 1901-02†), Henri Schein (1900-27†, rinderpest vaccine), Henri Jacotot (1922-47, figure 15) and René Vittoz (1929-45). All this research and work contributed enormously to the reduction of epizootic diseases and mortality of livestock in Indochina, e.g. while rinderpest killed 150,000 animals in 1900, only 5,000 died of rinderpest in 1940. Besides those veterinarians, help was also obtained for administration and other purposes: Anatole Gallois (administrator, ?-1917†) and his sons Robert and Augustin (-1948, Hevea), Joseph

Vassal (medical bacteriology/parasitology, 1904-09, surra), Georges Vernet (laboratory of chemistry and agronomy at Suoi Dau, 1902-18, Hevea) and Pernin (animal attendant at Suoi Dau, 1897-19). From the beginning, the Pasteur Institute of Nha Trang had been attached to the General Government of Indochina but came in 1904, when Yersin left the medical school of Hanoi, under the administrative and scientific direction of Emile Roux of the Pasteur institute of Paris. As mentioned before, the Pasteur Institutes of Nha Trang and Saigon (the latter founded by Calmette in 1890) were united under the name "Instituts Pasteur d'Indochine" with Yersin as director. He will fulfil that overall function up to 1918 when he hands it over to Noël Bernard. Yersin will remain director of the Nha Trang institute up to 1927 to hand it over to Henri Jacotot, his second in command since 1922. The honorary title of "Inspecteur Général des Instituts Pasteur d'Indochine", which includes the institutes of Saigon, Nha Trang, Hanoï (form 1926 onwards) and Da Lat (from 1936 onwards), is awarded to Yersin. He will continue to work at Nha Trang and exert his hobbies until his death in the night of March 1, 1943 during Japanese occupation but still French administration.

6. Yersin ensures the financial support of his lab as agronomist

Besides lodging his experimental animals in Suoi Dau, Yersin intended to make benefits of his agricultural enterprise to support his laboratory research and production of antisera and vaccines to protect the livestock of Vietnamese farmers. In 1896, Yersin starts to plant coffee trees, i.e. *liberia* and then *arabica*, but only *liberia* seems to resist the hot climate. In 1897 a successful plantation of 40 hectares was established for cocoa trees, indigenous to Central and South America. Then in 1898 kola trees for extraction of cocaine. Over the years, many other plants (muscat, pepper, vanilla, tobacco, rice, corn) were tested but abandoned or kept at small level because they generated little income or success. Small parcels of rice were kept to feed the horses instead of oats like in Europe. In 1923, 15 hectares received African oil palm trees which gave good revenues: after oil extraction from the palm nuts, the nut cakes were used as cattle feed. Two hectares of manioc were cultivated of which the roots made an excellent feed for cattle. Yersin tested also gutta-percha trees of which latex was harder than rubber latex and was highly valued. But this trial did not yield encouraging results. The most successful and economic agricultural production that Yersin undertook was the one of *Hevea braziliensis*, the rubber tree. The pneumatic discovery of Dunlop in 1888 interested the cycling and car-loving Yersin for its economical potentials. In 1898, Yersin orders 6,000 seeds for seeding 100 hectares. As mentioned before, Yersin had a like and feeling for technical innovations. The British were the first to introduce the rubber tree in Ceylon followed by the Dutch in Java. After visiting the Dutch research station "Buitenzorg" in Java, where different species of rubber trees were tested for Asian tropical conditions, Yersin decides to keep and expand even his *Hevea brasiliensis* plantations. With the help of Georges Vernet, an agronomist who will

be responsible for the chemistry lab in Suoi Dau and Nha Trang, Yersin starts his study on the acclimatization of hevea trees and the production of rubber. In 1905 he has his first collection of rubber, 1,316 kg for Michelin. In 1914 the total plantation of the Suoi Dau reaches 1,200 ha. Before the First World War he has 4,000 hevea trees on 307 hectares in Suoi Dau and from 1930 to 1940, he produces every year 100 tons of dry rubber, enough income to run the Pasteur Institute independently. As all this work was demanding a lot of labour, Yersin gave 80 hectares of arable land to his personnel where they could cultivate rice, the main food of the Annamite people.

Behind the plantation of Suoi Dau on an altitude of 1300-1400 meters in the Annamite mountains at a distance of 20 km, a second agricultural station in Hon-Ba was developed in 1914 for a plantation of cinchona trees for pure therapeutic reasons (figure 12). Malaria was one of the oldest endemics in South-East Asia where the tropical humid climate was home to the mosquito vector of the malaria pathogen *Plasmodium*. The supply of quinine, the therapeutic drug against malaria, produced from the barks of the cinchona tree, became restricted during and after the First World War and Yersin decided to solve that problem by starting his own local production. He constructs an uphill access road of 25 km to his new farm and builds there a chalet where he stays one to two weeks per month (figure 16) for studying the acclimatization and production yield of different species of cinchona. In 1917 he starts a small plantation with seeds of cinchona from Java that he had noticed and annotated on his visit to Buitenzorg in 1899. At that time, the Dutch owned 94% of the world production in Bandung on Java. Different species of *Cinchona*, i.e. *ledgeriana*, *succirubra*, a hybrid and *robusta*, were tested, grew successfully but perished after some years, due to the too thin humus layer covering the granite nature of the underground. Yersin did not give up, recruited a French chemist André Lambert for chemical analyses, researched the nutrient requirements (fertilizers and minerals) and acquired plots with better nutrient soil qualities (together with supplementation of fertilizers) around the area of Da Lat, namely in Dran (1923), Djiring (1926), Lang Bian (1927) and lastly also in Diom (1932), all mapped in figure 17. Between 1927 and 1935, Yersin and Lambert report their results in five “essais d’acclimatisation des arbres à quinquinas en Indochine” (Yersin and Lambert 1928, 1931). In 1931, Yersin can send 2.1 ton of bark from Dran and Djiring, to France which yield around 140 kg of quinine sulfate. In 1936, he was able to send 29,6 tons, good for around 2,000 kg of quinine sulfate and in 1938 41 tons giving around 3,200 kg quinine sulfate. Because of the healthy climate at the high altitude on the plateau of Lang Bian, Yersin opened there a health centre or sanatorium that will be at the origin of the town Da Lat. But Yersin was also interested in fruits and vegetables: trials started with success in 1918 in Hon Ba for cherries, peaches, pears, quinces, apples, prunes and figs but without success for apricots, chestnuts, almonds, redcurrants, raspberries and grapes. Vegetables such as cauliflower, peas, potatoes, green beans and lettuce were also successful (Yersin 1925). Also grasses such as

ray grass, timothy grass and foxtail and different leguminosae such as clovers for use in grazing lands met with success. Moreover, Yersin put also his attention successfully on a lot of ornamental flower plants. Da Lat will become the vegetable and flower garden of Saigon and a privileged relaxing and resting site for the French Saigon citizens and after independence also for the Vietnamese people. In 1897, the governor general Doumer had decided, in consultation with Yersin who had explored and cartographed the site already in 1893 during his excursions, to build there a meteorological station and in 1899 after ascending himself the plateau with Yersin, also to develop there a town, known later as Da Lat. In 1936 Yersin is invited in Da Lat and honoured by the Vietnamese to open a lyceum in his name and the establishment of a new Pasteur Institute as it appeared an ideal place for preparing antisera and vaccines.

7. Yersin, a real techie

As distances between his farms were quite big, Yersin, always interested in new technical revolutions, bought a Serpollet 5CV during one of his many visits to Paris. In July 1901, the car arrives and enables him to travel at 25 km/hour from Suoi Dau. In September 1901, he acquires another small car Clément and even a steam-powered canoe for excursions on the sea. In 1903 he buys a new Serpollet 6CV that he will drive in Hanoi during his stay there as director of the medical school. All these cars demand repair and services and Yersin employs an auto mechanic to help him in the technical aspects of the engines and also of his electro generator for his water pump in Suoi Dau. He even imports a caterpillar vehicle for Suoi Dau. In 1907 he buys a small Alcyon 11CV which is replaced by a Clément-Bayard 15CV in 1912. In 1925 he buys his last car, a Zèbre (105 km/hour) but sells it in 1930 after a near hit with a child and will never drive an automobile again. To enable easier communication between his dispersed farms, he installs in 1921 a wireless telegraphic communication in Nha Trang for contact with Hon Ba and Suoi Dau. Moreover, he acquires also a radio receptor enabling him to capture France. Also airplanes get his attention but this idea was quickly abandoned due to lack of airstrips which were too expensive to construct. Never mind, when air transport took off between France and Indochina, Yersin could satisfy his flying hunger by becoming a regular customer on air planes. He took the last Air France flight leaving Paris for Saigon on May 30 1940 before the Germans invaded France.

In 1882 on a passage to Paris, Yersin took lessons in astronomy and occultation and bought binoculars and sextants to help him in drawing maps during his explorations. When he starts his plantations, he wants to predict weather conditions and explores therefore higher atmospheres at 5,000m with steel-cabled kites. In 1908 he builds on top of his roof a dark sky observatory equipped with a Zeiss telescope. In 1910 he brings from Paris a prismatic astrolabe, later also a chronograph-recorder and starts recording star positions for geographic positioning (latitude) and precise local time determination. In 1929 he even

starts to measure the atmospheric electricity with an electrometer on different levels above the ground in the rainy and dry season, rainy days and summer storms. From 1930 to 36 he builds the climatic station at Da Lat. Finally during the last year of his life, he starts controlling the exactness of tides in the bay of Nha Trang by installing graded poles in the river estuary and in the sea, he can record from his veranda with his binoculars the water levels at regular times of the day and night.

8. Conclusion

Yersin was a wall-breaking scientist: besides the discovery of the diphtheria toxin, he identified the pathogen of the bubonic pest, and all this at the dawn of microbiology at the turn of the 19th century. Moreover, by his initiative and with the help of veterinary and medical scientists, he was able to fight human and livestock diseases through the sequential study of the pathology, the identification of the pathogen and the production of antisera and vaccines. One has to be a visionary and entrepreneur to get such an institution more or less self-reliant: by seeing an economic possibility in rubber and quinine, he researched with the help of agronomists on the acclimatization and selection of hevea and cinchona for rubber and quinine production, respectively. His previous explorations in the hinterland of Annam had enabled him to select the ideal places for his plantations and farms in order to fulfil his goals of helping and protecting the livestock of the poor Vietnamese people. What a wonderful life line for this man (figure 18). He always remained a modest person, never sought publicity, on the contrary, he was friend and caretaker of the locals having their simplicity in daily life. He preferred to intermingle with them: he was their doctor, advisor and problem solver, their consoler, pastor and mainstay, and was loved, honoured and even revered as one of them with the highest esteem. They named him “Ong Nam” as they knew he had the grade of colonel in the medical French colonial army; “Ong” meaning sir and “Nam” five in Annamite, referring to the five stripes of colonel on his uniform that he never wore (figure 19). Notwithstanding all their sufferings during the colonial period and wars of independence, Vietnam never removed Yersin’s name from streets, schools, lycea, research buildings and university faculties after independence. Yersin is practically the only figure of the colonial period who is still respected and revered in Vietnam. How wonderful it is to see that such a great scientist was such a modest and great philanthropist! We were really lucky but humbled that we could honour that man by flowering and incensing his grave and small pagoda (figure 20).

Acknowledgements.
We thank Michaël Davy of the Photothèque Institut Pasteur for helping us in obtaining permission to use the photos of the Institut Pasteur/Musée Pasteur, Institut Pasteur/Archives Alxandre Yersin and Institut Pasteur/Archives Instituts Pasteur d’Indochine.

We also wish to thank Zena Wakim from Editions Olizane to give us permission to use the picture of Yersin with elephant on the front cover of their book.

Table 1. Antisera and vaccine production against animal diseases at Pasteur Institute Nha Trang (from Mollaret & Brossellet, 1985; www.entreprises-coloniales.fr mise en ligne 3 mai 2015, dernière modification 5 septembre 2021)

	Disease	Year	Serum doses	Vaccine doses
Cattle and Buffalos	Rinderpest	1900	6500	
		1913	10,000	
		1923	114,435	
		1933	29,700	139,551 (vaccine Jacotot)
		1943	67,121	1,580,736
	Anthrax (Bacillus anthracis)	1904		39
		1923		4,200
		1933		3,755
		1942	475	
		1943	2,638	31,373
	Blackleg (Clostridium chauvoei)	1921		200
		1927	180	
		1931		13,280
		1940	850	
		1943		15,091
	Hemorrhagic septicemia (Pasteurella multocida)	1930	1,805	11,550
		1933	9,250	48,535
		1943	10,280	215,086
Swine	Classical swine fever	1935	400	442
		1943	6,490	19,009
	Swine pasteurellose (Pasteurella multocida)	1936	730	150
		1943	5,616	5,410
	Swine erysipelas (Erysipelothrix rhusiopathiae)	1940	200	
		1943	920	540
Dog	Dog rabies	1934		11,323
		1943		23,944
Chicken	Chicken cholera	1927	700	
		1933		1,912
		1943	2,725	62,506

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Figure 1

Teachers and students at the first “Cours de microbie technique” in 1889 at the Pasteur Institute. In the red circle from left to right: Charles Laveran (Nobel Prize 1907), Emile Roux, Élie Metchnikoff (Nobel Prize 1908) and Alexandre Yersin (©Institut Pasteur/Musée Pasteur)

Figure 2

Map of Indochina comprising Tonkin, Annam, Cochinchina, Laos and Cambodia.
https://commons.wikimedia.org/wiki/File:French_Indochina_subdivisions.svg

Figure 3.

Alexandre Yersin: photograph taken in March 1892 at Nha Trang before his first exploration (Coll. Henri Jacotot) (Perrot 2011)

Figure 4.

The three expeditions of Yersin between 1892-1894 (Lebreton-Mansuy 2009)

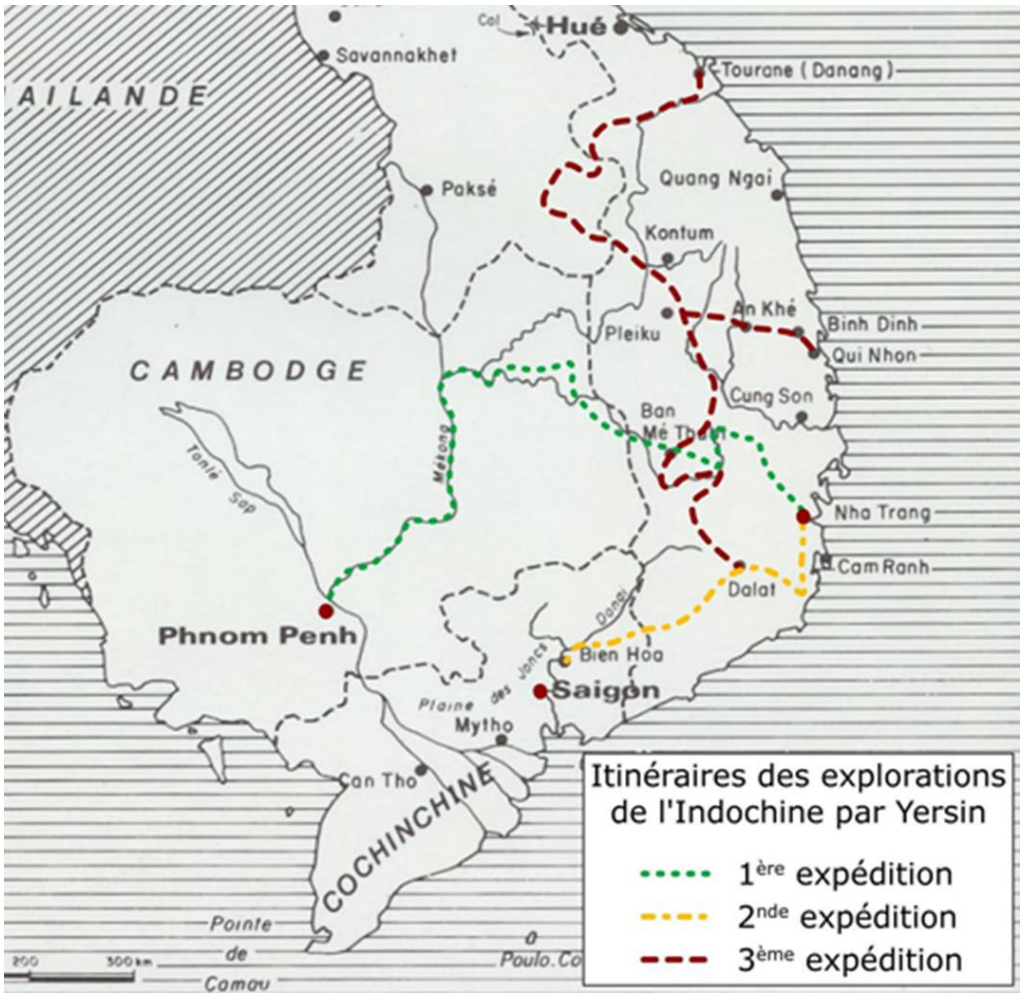


Figure 5.
Yersin as medical officer of the colonies in 1893 on exploration in Cambodia (© Album Yersin/Family Bastardot/DR) (Fleury 2016). Front cover of the book “Voyages chez les Moïs d’Indochine”, Editions Olizane, Geneve.

Figure 6.

Spread of the Plague from Yunnan to Guangdong province in China

Figure 7.

The great scientist Shibasaburo Kitasato (1853-1931) 1889 (https://nl.ziyadmedical.com/6072548-indomitable-shibasaburo-the-discovery-of-antibodies-infectious-diseases). On the right side a Kipp's apparatus for hydrogen production to fill flasks for culture of anaerobic bacteria, the tetanus and diphtheria bacilli. From 1885-91 he worked in the laboratory of Koch, in 1889 was the first person to grow the tetanus bacillus in pure culture, and in 1890 cooperated with Emil von Behring in developing the serum therapy for tetanus using his pure culture. Together with Emil von Behring, he was nominated in 1901 for the first Nobel Prize for Physiology or Medicine for their therapeutic treatment of patients with antisera, but strangely only Von Behring was awarded.

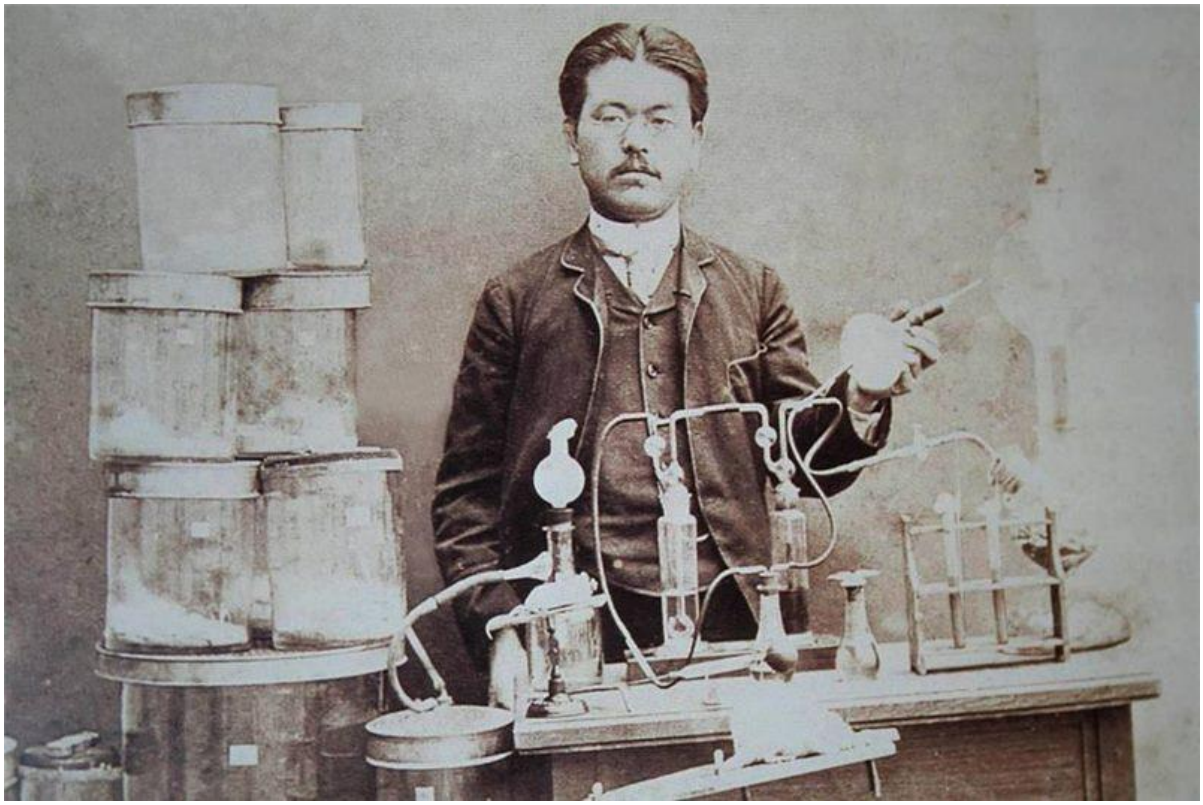


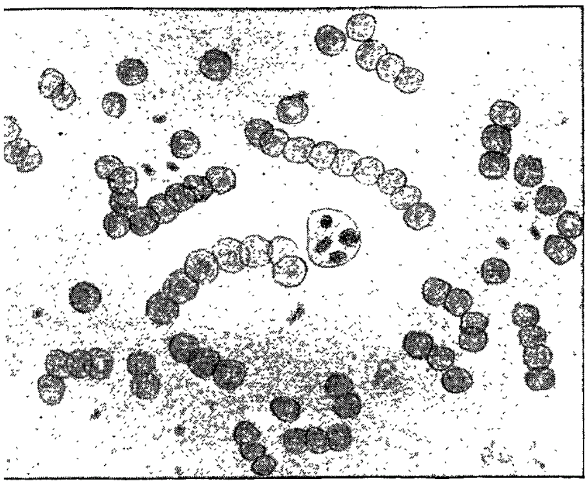
Figure 8.

Beginning of the publication of Lowson – Kitasato on the identification of the Plague bacillus in The Lancet 1894 August 11.

THE PLAGUE AT HONG-KONG.

WE have received the following notes from Dr. J. A. Lowson of Hong-Kong, who has forwarded a number of preparations of the plague bacillus, some of them prepared for him by Professor Kitasato, others prepared by himself, of which we give several representations. The organism—which is a bacterium resembling the bacilli found in the hæmorrhagic septicæmias, except that the ends are somewhat more rounded—when stained lightly appears almost like an encapsuled diplococcus, but when more deeply stained it has the appearance of an ovoid bacillus, with a somewhat lighter centre, especially when not accurately focussed. When, however, it is focussed more accurately it is still possible to make out the diplococcus form. It is quite possible that the capsule has been produced artificially,

FIG. 1.

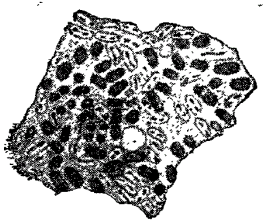


Ob. 1/12 homog. + oc. 8 compens.; length of tube 140 mm. Bacilli and blood from case of plague. Illustration of preparation made by Professor Kitasato and forwarded by Dr. Lowson.

Ob. 1/12 homog. + oc. 8 compens.; length of tube 180 mm. Bacilli in blood of mouse. Illustration of preparation made by Professor Kitasato and forwarded by Dr. Lowson.

of the appearance of the micro-organisms when cultivate outside the body; but he says: "I have recently been s

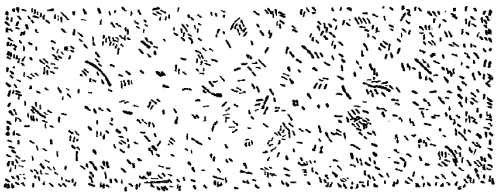
FIG. 3.



Ob. 1/12 homog. + oc. 8 compens.; length of tube 180 mm. Illustration of preparation of splenic pulp in case of plague made by Dr. Lowson.

engaged in looking after the sick, organising hospital work inspecting insanitary houses, and looking after the disposa

FIG. 4.



Ob. 1/12 homog. + oc. 8 compens.; length of tube 140 mm. Illustration of plague bacillus prepared by Professor Kitasato and sent by Dr. Lowson

of the dead that I have been unable to find time to do mor than send you these few notes and specimens, which, how ever, I thought might be of interest to some of you readers."

Figure 9.

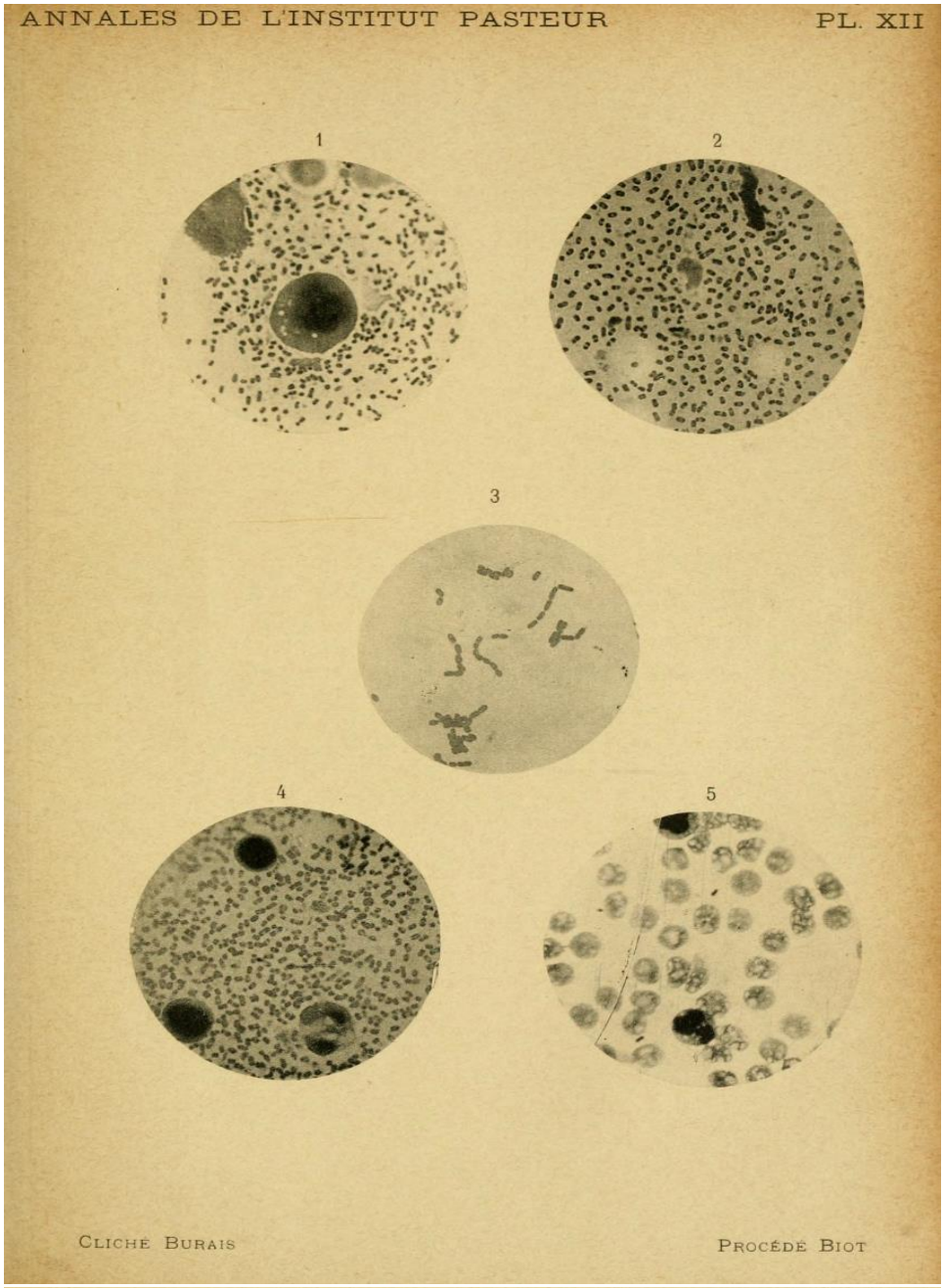
Hong-Kong – Doctor Yersin at the entrance of his mat-shed (handwritten diary of Yersin 1894, Institut Pasteur) (©Institut Pasteur/Archives Alexandre Yersin)

Hong Kong – Big mat-shed as one of the three hospitals for plague patients. On the left one can see a part of my house (from handwritten diary of Yersin 1894, Institut Pasteur) (©Institut Pasteur/Archives Alexandre Yersin)

Hong Kong – Grande paillotte formant un des trois hôpitaux pour les pestiférés.
A gauche, on aperçoit une partie de ma maison

Figure 10.

Plate 12 of publication of Yersin on the identification of the pest bacillus in Annales de l'Institut Pasteur 1894 September



EXPLICATION DES PHOTOGRAPHIES. PL. XII.

PHOT. 1. — Pulpe du bubon d'un Chinois atteint de peste.
PHOT. 2. — Pulpe de ganglion d'un rat mort spontanément de la peste.
PHOT. 3. — Culture jeune du cocco-bacille de la peste dans le bouillon.
PHOT. 4. — Pulpe de ganglion d'une souris inoculée avec une culture.
PHOT. 5. — Sang recueilli chez un homme mourant de peste foudroyante, 1/4 d'heure avant la mort.
Il n'y a que deux bacilles dans le champ.

Figure 11.

Upper picture ©Institut Pasteur/Musée Pasteur: Yersin's house in 1898 on the peninsula with laboratories on the right and the water tower on the left within the compound of his Pasteur Institute. View of the corner of the compound from the estuary of the Cai river towards the bay of Nha Trang in northeast direction.

Middle picture: The peninsula in a hand-drawn map of Yersin (©Institut Pasteur/Archives Instituts Pasteur d'Indochine). To the left the fisherman's village "Village de la Pointe" (at the end of the peninsula), in the middle the "Institut Pasteur" with stable for carriage horses (a), house of veterinarians (V), factory and warehouse (b), stable for horses under experiment (c), water tower (blue), Yersin's house (Y) and laboratories (d) with monkey compartment and mongoose housing. Arrow: viewing direction of Yersin's house in previous picture.

Lower picture (©Institut Pasteur/Musée Pasteur): complete view with house, labs, water tower and the river estuarium of Nha Trang

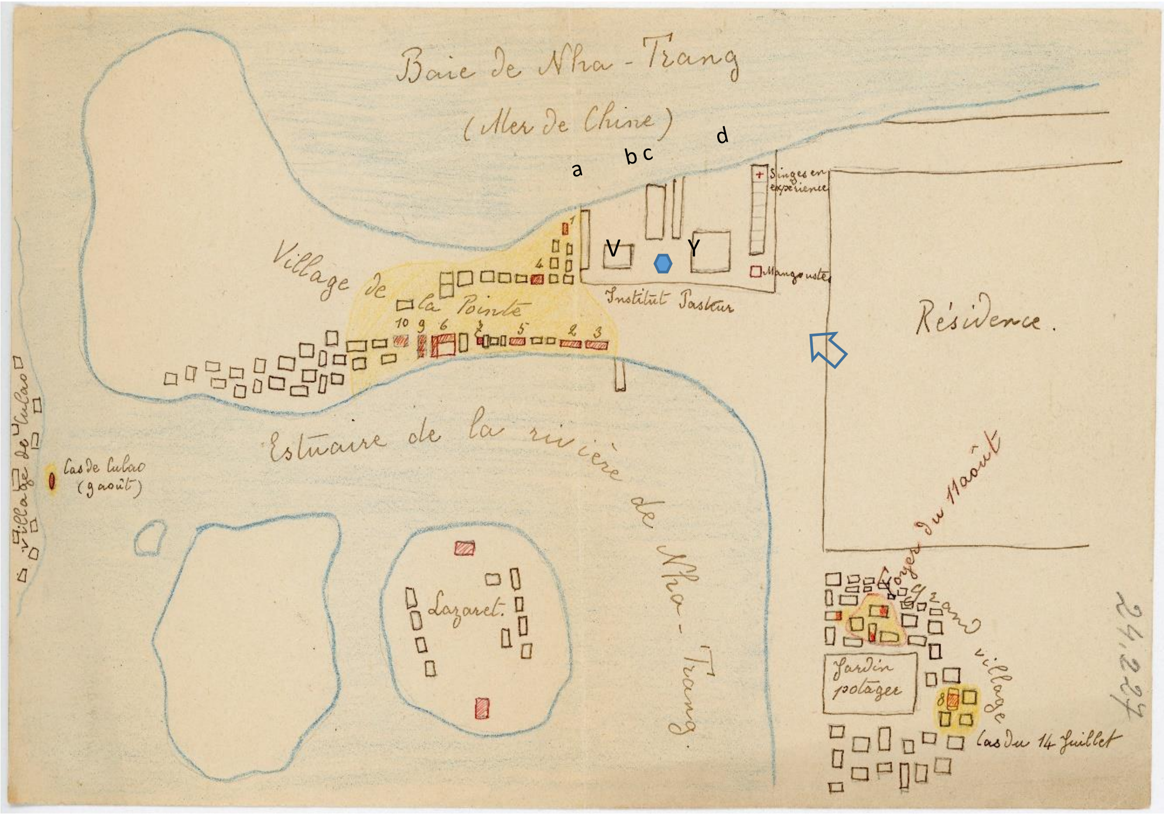

Baie de Nha-Trang
(Mer de Chine)
a
b c
d
Singes en expérience
V
Y
Mangoustes
Village de la Pointe
Institut Pasteur
Résidence.
Estuaire de la rivière de Nha-Trang
Village de Culao
Cas de Culao (9 août)
Lazaret.
Foyer du 11 août
Grand village
Jardin potager
Cas du 14 Juillet
24,227

Figure 12.

Locations of Pasteur Institute and its farms, Khane Hoa, Suoi Dau and Hon Ba.

Figure 13. L'Institut Pasteur of Nha Trang build by Yersin between 1900-1904 a six hundred meters south of his house along the beach. Photo 1920-1929. (https://www.flickr.com/photos/13476480@N07/50523254303/in/photostream/).

Figure 14.

House of Yersin in Suoi Dau ©Institut Pasteur

Figure 15.

Alexandre Yersin with Henri Jacotot (Perrot 2011) (Coll. Henri Jacotot)

Figure 16.

Vintage watercolor of the settlement at Hon Ba (Aquarelle, coll. Famille Ducrest) (Perrot 2011). Yersin's house is in the middle, the others houses are of staff and laboratories.

Figure 17.

Cinchona plantation farms of Yersin: Hon Ba, Lang Bian, Dran, Diom and Djiring

Figure 18.

Life line of Alexandre Yersin

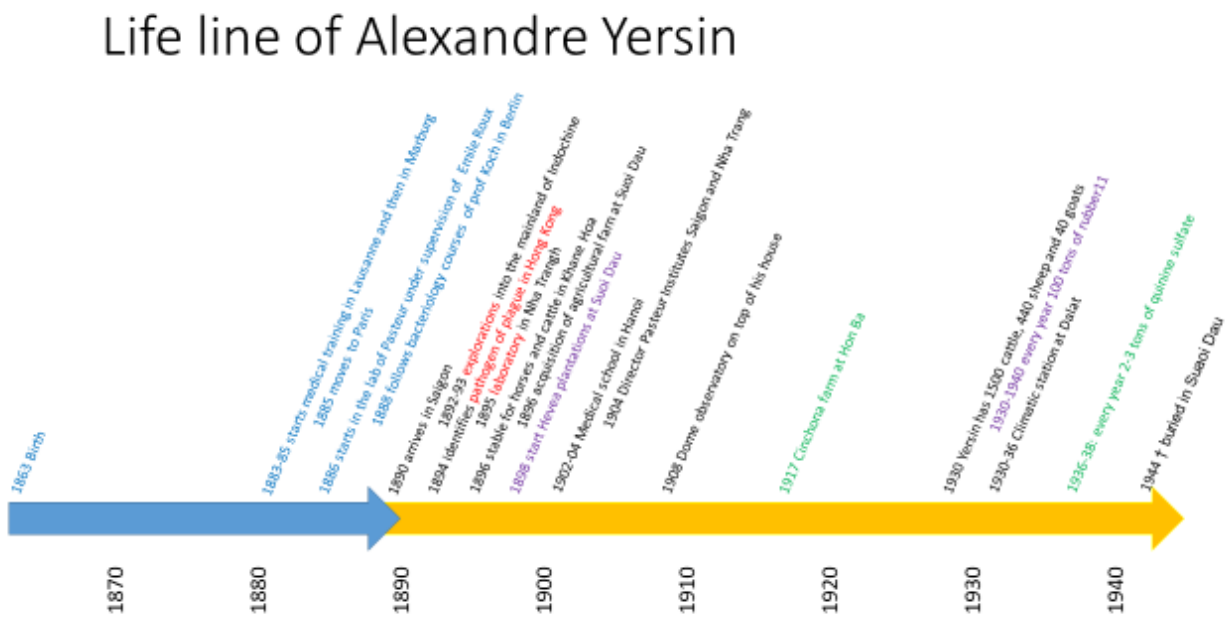


Figure 19.

Docteur Alexandre Yersin 1933 (©Institut Pasteur/Musée Pasteur) or Ong Nam (Monsieur 5, five stripes)

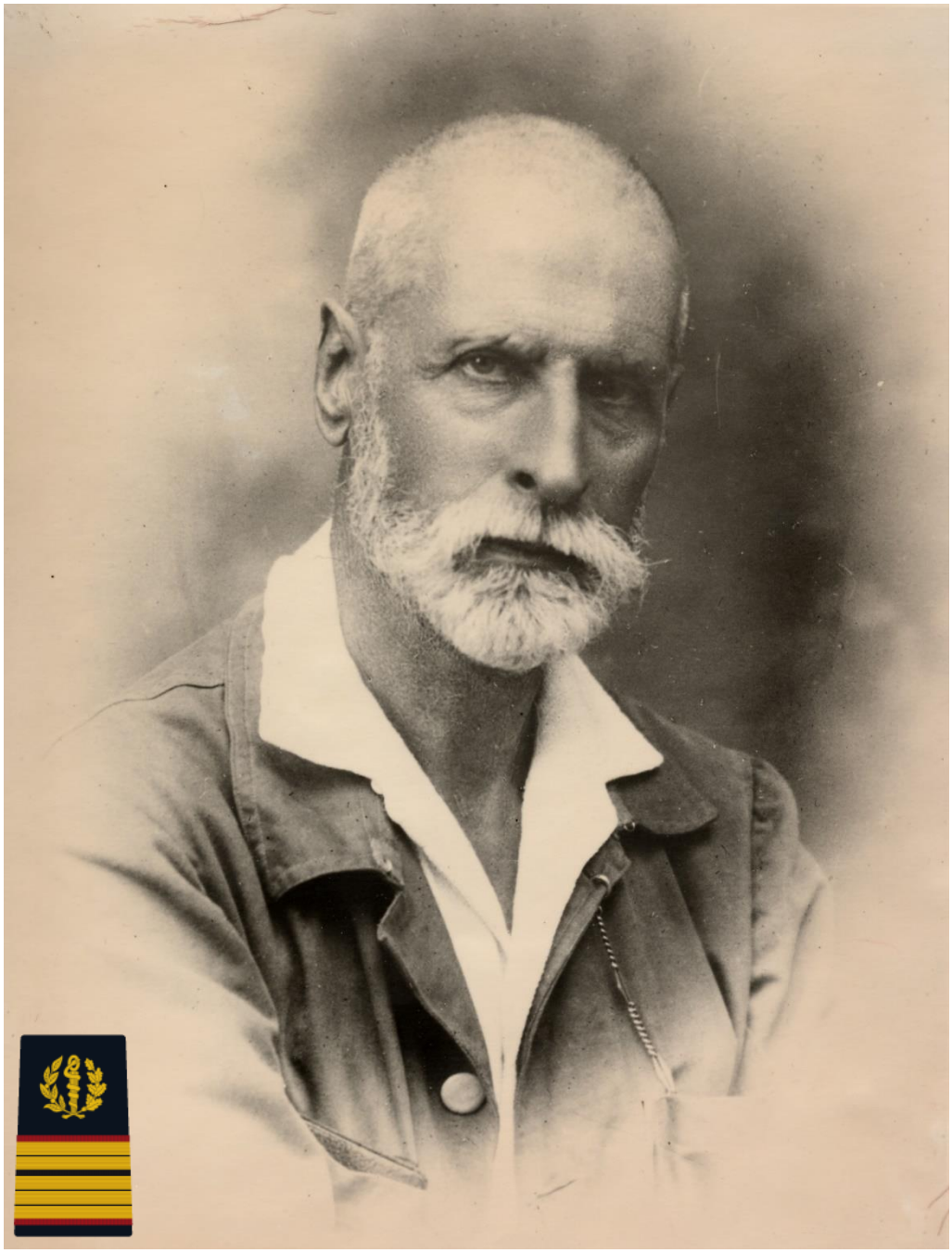


Figure 20.

Honouring Yersin with our Vietnamese partners and friends at his burial site in Suoi Dau (2009). Tombstone and pagoda