ELSEVIER

Technology in Society 27 (2005) 39–53

Technology In Society

www.elsevier.com/locate/techsoc

Vaccine innovations in an age of uncertainty: BCG in France

Tzung-wen Chen[a,b,*]

[a]*Centre de Sociologie des Organisations (CSO), CNRS and Institut d'Etudes Politiques de Paris, France*
[b]*Graduate Institute of Technology and Innovation Management (TIM), National Chengchi University, Taipei, Taiwan*

Abstract

The Bacille Calmette–Guérin vaccine (BCG) remains one of the most widely used vaccines against infectious disease since it first appeared in the early 1900s. The development of BCG and its adoption into the vaccination schedule was, however, controversial. This paper reviews the history of BCG innovations, including its development in France, its worldwide diffusion, and its connection with public health policy. The research finds that, while knowledge-centered scientific activities played an important role in vaccine innovations, decision making vis-a-vis public acceptance of the vaccine relies more on the characteristics of the vaccine and is shaped by collective actions taken by diverse social actors. This article provides a community-based framework to explain the collective actions that overcame the uncertainty caused by limitations in technology and knowledge.

Keywords: Vaccine innovation; BCG; Institut Pasteur; Community of innovation

1. Introduction

With the urgent demand for new weapons against emerging infectious diseases, vaccine innovations have attracted the attention of public health experts and social scientists. Perhaps the most critical issue is how to finance research and development of new vaccines under the so-called 'market failure' effect, given that vaccines are generally considered a public good [1,2]. Indeed, vaccine innovations have been crucial in

* Address: Centre de Sociologie des Organisations (CSO), CNRS and Institut d'Etudes Politiques de Paris, France. Tel.: +33 14 661 1439.
E-mail address: twchen@free.fr.

0160-791X/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.techsoc.2004.10.004

the prevention of epidemics since the first vaccine against smallpox was developed in the late eighteenth century. Economic considerations are not, however, the only dimension in vaccine innovation. It is a complicated social process, as exemplified by the dramatic history of the discovery and application of polio vaccines [3].

Among the vaccines developed in the early age of vaccinology, the anti-tuberculosis vaccine known as the Bacille Calmette–Guérin vaccine (BCG), is considered a successful case because it is one of the most widely used vaccines and still in use all over the world. However, in contrast to smallpox, which has been eliminated worldwide with a vaccine, tuberculosis still exists and seems to have increased in severity in recent years [4]. The BCG vaccination is thus one of the most controversial, as efficacy is always a reason of argument [5–7]. The evolution of BCG is, therefore, a heuristic model of vaccine innovations in which the interactions between the scientific and social sectors have played a critical role.

Instead of a necessity, the BCG innovation is more likely the fruit of collective actions contributed by the vaccine discoverers, the scientists, and society. Therefore, the present research reveals details of these actions, which are widely supposed to be heuristic, in order to reevaluate the facts behind the vaccine innovation. To illustrate the complicated interactions between the scientific knowledge and the social and political contexts, this research will focus on the case in France, where BCG was discovered.

2. Research background

2.1. Safety and cost issues

Unlike other medications, where the end users are often in poor health, vaccines are generally adopted by public agencies to inoculate a mass of healthy people to prevent an epidemic. This causes a fundamental difference between general pharmaceutical innovation and vaccine innovation. In other words, when a vaccine is given to a healthy public, the safety requirements and relatively high costs associated with attaining those requirements are major issues in vaccine innovation [8].

It has been estimated that an average of 15 years is needed to move from the development of a new drug in the laboratory to completion of the three trial phases [9]. While new technology in the post-genomic era might shorten the time required for laboratory work, innovation of a new vaccine may involve up to five phases, including two post-licensing phases for safety reviews [10]. These disadvantageous factors, combined with the inequality of living standards between industrialized and less-developed countries, are obstacles to vaccine innovations, and they should be removed by intervention from the public sector in order to increase the incentive for innovation [2].

These facts represent the status quo of vaccine innovation without historical and social considerations. The structure of the current pharmaceutical industry, which is dominated by a few ‘big pharmas’ was formed gradually over decades, in coincidence with the progressive pace of the biotechnology and new biological revolutions, so the pattern of vaccine research and production can be expected to change as well [11]. Concerns about cost and safety have evolved over a century of vaccine development that was strongly influenced by related scientific knowledge and social institutions.

2.2. Knowledge insufficiency

The role of a vaccine in society can also be controversial because, due to limitations in scientific and technological knowledge, a vaccine cannot promise 100 percent efficacy [12]. Even today, acquiring the knowledge required to develop a new vaccine is still a major challenge to scientists—the AIDS vaccine a typical example [13]. Without complete scientific understanding, vaccinology is partly empirical and partly rational [14].

When it comes to applying vaccines to the public, empirical considerations have been much stronger, especially in the infancy of immunology before and between the two World Wars. The vaccine against smallpox is a good example. Although it was discovered in 1798 by Edward Jenner of England, and began in 1808 to be freely distributed by a newly established public institute, vaccination was not compulsory for newborns until 1853, a delay of more than a half century [15].

A mass vaccination is generally regarded as the ultimate achievement of a vaccine innovation. But with insufficient immunological knowledge, mass vaccination can only be accomplished through social consensus or other special situations, such as war. The 'evidence-based' approach, in which many trials and a series of statistical works are carried out to prove the vaccine's safety and efficacy, is considered the best way to persuade the public to accept the vaccine [10]. The five-phase trial process to bring a new vaccine to the market is based on this rationale.

The evidence-based approach includes several sectors that contribute to the good practice and safety of a vaccine [10]. These sectors include the laboratory, the manufacturing sector, clinical researchers, the regulatory sector, clinics, the public health sector, post-licensing surveillance, and statistics.

2.3. Collective-action framework

Given the characteristics of a vaccine in society, a multi-actor perspective is required for the sociological analysis of vaccination [16]. The present research proposes a collective-action framework that examines the dynamics of vaccine innovation. In a multi-actor perspective, the actors involved in vaccine-related activities include vaccine researchers, medical professionals, vaccine users, and policy makers.

Louis Pasteur used his first human vaccine to cure a child infected with rabies [17] despite incorrect and partial explanations of the principles of immunity. This historical fact illustrates the possibility of a successful vaccine application without accurate scientific knowledge. Because knowledge about immunity may still be ambiguous and/or inaccessible when a vaccine is widely applied, in this research we include in the definition of vaccine innovation the social application of the vaccine. Thus certain stages in vaccine innovation can be separated from the specific knowledge of immunity because, in the end, the object of vaccine innovation is to make the vaccine accepted by the public in order to prevent diseases, and universal vaccination is the ultimate goal. Therefore, in addition to the actors involved in the multi-actor perspective, more social actors should be considered in the process of vaccine innovation. Accordingly, in the collective-action framework, the first task is to identify the various actors involved in the innovation of a vaccine.

As a result of collective actions, the vaccination decision-making process, including individual choice and vaccination policy, is thought to be a contingent process in which the power structure among the actors is a determining factor [18]. Moreover, insufficient knowledge of the vaccine can be the source of bounded rationality in vaccination decision-making. The collective-action framework, therefore, emphasizes the role of power when analyzing collective actions.

3. Methodology

This research uses the historical case study method, in which historical archives, technological and scientific papers, and other related publications are collected and analyzed to reconstruct the story of BCG innovation.

In the following case study, the BCG innovation is described in five phases. The first phase includes the early days of investigation into an anti-tuberculosis vaccine and the development of the initial BCG vaccine, all of which occurred prior to the 1920s. The second phase is the clinical trials of BCG in the 1920s. The third phase is the distribution of BCG since the mid-1920s. The fourth phase, overlapping the third phase, is the BCG promotion and immunization policy 5–10 years before and after the Second World War. The final phase is today's situation.

4. BCG vaccine innovations

4.1. Early developments

The French tradition of vaccine research began with the germ theory proposed by Louis Pasteur (1822–1895). One of his major contributions to human immunology was establishing the principles for making a live attenuated vaccine using the first anti-rabies vaccine in the early 1880s [17,19]. After that discovery, the Institut Pasteur of Paris was established in 1887 to produce and distribute enough rabies vaccine to meet demand [20], and branches were established to manufacture the vaccine locally.

A major branch was established in Lille where Louis Pasteur was the director of the Faculté de Sciences in the mid-1850s. At the request of regional representatives, Pasteur, in his last days, assigned Albert Calmette to create the Institut Pasteur on his behalf in Lille in 1895. Already a member of the Institut Pasteur in Paris, Calmette was a trained physician and microbiologist who had spent several years in Asia and elsewhere working on medical missions before taking charge of the new institute. The Institut Pasteur in Lille was initially established to produce rabies vaccine to meet local demand. Later, in 1897, Camille Guérin joined Calmette. He was a doctor of veterinary medicine whose father had died of tuberculosis in 1882.

Lille is an industrial city in the north of France. Historical research shows that the severity of tuberculosis had a significant correlation with industrialization before preventive methods were discovered [21]. In addition, the labor force in Lille was strongly affected by this infectious disease at a relatively higher rate than other agricultural

regions at that time. Each year, about 300 people among the 100,000 residents died of the disease, not counting those who contracted chronic tuberculosis [22].

Attracted by Pasteur's reputation and the Institut he established, a regional conference on tuberculosis, led by Calmette and his colleagues, was held in 1900. The participants included senior officers of the Lille city and department governments, members of anti-tuberculosis associations, deans and professors of medical schools, and industrial representatives. The conference reached the conclusion that a new tool for preventing tuberculosis should be developed through the collective efforts of the participants. Therefore, with the city of Lille providing a research site, the regional government providing financial support, and the industrial sector providing the subjects for trials, the development of a new anti-tuberculosis vaccine was launched [23].

As tuberculosis was one the most severe infectious diseases, several research groups in other parts of the world were also trying, at about the same time, to prevent an epidemic [24]. German scientist Robert Koch, who first identified the tubercle bacillus as the cause of human tuberculosis in 1882, was also a pioneer in vaccine development. While several new methods for controlling tuberculosis were being tested [25], the Calmette group in Lille chose the live-attenuated approach established by Louis Pasteur to develop the vaccine.

A breakthrough in their research came in 1906 when they discovered that the *Mycobacterium bovin*, cultured artificially in beef bile, was characterized by rapid reproduction and variation [23]. Therefore, they began to culture a strain of *M. bovin* originating from a cow with tuberculous mastitis in a medium that contained glycerol, potato slices, and beef bile. The organism was painstakingly subcultured every 3 weeks, with each cycle called a 'passage.' The virulence of the cultured bacillus was gradually attenuated through passage after passage. By the mid-1910s, some animal trials of the bacillus were successful, as the virulence seemed to have been completely attenuated.

The research on the anti-tuberculosis vaccine was interrupted during World War I, which lasted from 1915 to 1918, but cultivation of the bacillus continued. After the war, Calmette moved to Paris to become vice director of Institut Pasteur of Paris, serving beside then—director Dr Emile Roux. The vaccine research was restarted in Paris soon, thereafter, in 1919. At that time, most of the work consisted of animal trials of the vaccine, which was considered harmless to living bodies after 13 years of attenuation. With these initial successes, the new vaccine was named Bacille Calmette–Guérin, after the two major developers.

4.2. Clinical trials

The first human trial of the BCG vaccine was carried out by Dr Weill-Hallé at the Hôpital de la Charité of Paris in 1921. As many newborn infants in this hospital came from families affected by tuberculosis, they were in danger of contracting the disease. The first baby fed BCG was an orphan whose mother had recently succumbed to tuberculosis, and the grandmother, also a tuberculosis patient, was supposed to raise the baby.

The first human trial and the successive 589 trials on newborns in the hospital, conducted under Dr Weill-Hallé in the following several years, resulted in a relatively low

mortality rate for the infants, with only about two percent of deaths caused by tuberculosis [26]. This success was seen as strong evidence for the efficacy of BCG. Therefore, beginning in 1924, Calmette and his colleagues provided free BCG strains to physicians in France and abroad for their local clinical trials of the vaccine [27].

Even though safety issues regarding BCG were continually raised by pediatricians and physicians during the late 1920s, Calmette and his colleagues at the Institut Pasteur, as well as other BCG supporters, struggled to provide satisfactory explanations that gained the trust of the public. A series of statistical works during that period, using data collected from all over France and the colonies, as well as work done by foreign experts in their own countries, were viewed as important proofs of the safety of BCG [28].

From October 15 to19, 1928, an international conference on BCG was held in the Institut Pasteur by the Comité d'Hygiène de la Société des Nations. The conference, bringing together French and foreign experts, especially those from Italy, Spain, Germany, Austria, Russia, and the Nordic countries, was for the purpose of promoting applications of the BCG vaccine [29].

In the history of BCG, the most serious event was undoubtedly the Lübeck accident. In July 1929, a BCG strain sample was sent from Institut Pasteur to the hospital in Lübeck in northern Germany for local culture and further distribution for use on newborns. The sample was, however, accidentally contaminated with the virulent Kiel strain, which had been introduced in the hospital in September for the purpose of making antibodies. The contaminated BCG was later applied to 252 babies, of whom 73 died soon after inoculation and 136 developed chronic tuberculosis [26]. With the help of scientific analysis by German scientists Bruno Lange and Ludwig Lange, the German court ruled in 1932 that the BCG strain was innocent.

While the Lübeck accident was seen as a political issue arising out of tense French–German relations at the time [30], the accident gave Calmette and his supporters opportunity to stabilize the position of BCG in the scientific community. The first opportunity was the Seventh Conference of the International Union against tuberculosis held in Oslo in August 1930 even while the inquiry into the Lübeck accident was still in progress. Calmette's work was hailed at the conference and received support from all participants, including those from Germany [29]. The second opportunity was a favorable vote on BCG taken by the Académie de Médecine, which represented the public opinion of the French medical community. The vote was held on July 7, 1931, just 6 months before the final judgment was rendered on the Lübeck accident.

With this kind of support, Calmette continued to proclaim the inoffensive nature of the BCG, and he finally won government support. As stated in a letter from the Ministry of Public Health to each Departmental Government in April 1932:

> [BCG] is absolutely inoffensive, and the final judgment of the recent Lübeck process gave the medicine and the public a full assurance of this harmless nature that has elsewhere been confirmed by a special commission of the Académie de Médecine in July 1931. (…*est parfaitement inoffensive et le jugement rendu à la suite du process recent de Lübeck est de nature à rassurer pleinement les médecins et le public sur*

cette innocuité qu'une Commission spéciale de l'Académie de Médecine avait d'ailleurs affirmée en Juillet 1931).

Since improper environmental control was the major cause of the Lübeck accident, Calmette further emphasized the importance of safety controls in the culture of BCG [31]. This concern about safety and the increasing demand for BCG forced the Institut Pasteur, in 1932, to construct a new site specifically for the production of BCG. According to an internal document, the amount of BCG doses produced per year given by the Institut Pasteur rose from 850 in 1924 to 124,737 in 1932.

4.3. Diffusion of the BCG vaccine

The Lübeck accident also spotlighted another problem with BCG. Because there was little preservative technology at that time, the strain had to be distributed in its unstable state. This made the BCG strain an 'open source' that was diffused freely and could be modified by experts all over the world after the late 1920s. The distribution of various BCG strains in the world is listed in Table 1.

The initial Pasteur strain was the one developed by Calmette in 1921, following 231 passages after first being isolated in Lille 13 years before. Table 1 shows that the Pasteur strain was sent to Russia in 1924 for the first time. While distribution of the strains to foreign countries continued, the original Pasteur strain continued to undergo culturing at the Institut Pasteur. This process ended in 1961 when a new method for preserving the strain, called lyophilization, was developed. The final strain was cultured for a total of 1173 passages and was thus called the Pasteur-1173 strain.

The wide spread of the BCG strains and their independent cultures at different sites during the first 40 years of distribution are seen as the major cause of the diversified performances of the BCG vaccinations [32]. The differences in the characteristics of the strains are a selection criterion for vaccine manufacturers [33]. For example,

Table 1
Distribution of major BCG strains

Sub-strain	Mother strain	Year obtained
Russia	Pasteur	1924
Moreau	Pasteur	1925
Japan	Pasteur	1925
Sweden	Pasteur	1926
Phipps	Pasteur	1926
Denmark	Pasteur	1931
Tice	Pasteur	1934
Frappier	Pasteur	1937
Birkhaug	Pasteur	1946
Prague	Denmark	1947
Connaught	Frappier	1948
Glaxo	Denmark	1954
Pasteur	Pasteur	1961

Source: Behr and Small, 1999 [50].

the Glaxo-1077 strain is the most popular strain because of its high reproduction rate per unit dose.

4.4. Vaccination strategy and immunization policy

Calmette, who respected individual freedoms and personal rights, was himself against compulsory vaccination with BCG. He wrote:

> I think that, except for the vaccination against smallpox that has been carried out for more than a 100 years, no other vaccination should be compulsory because we cannot spoil the personal freedom and it is better to persuade people that their interest is to protect themselves from the infectious diseases when we provide them freely the tools, which is what we do with BCG. (*…j'estime que, sauf la vaccination anti-variolique, mise en pratique depuis plus de cent ans, aucune vaccination ne doit être rendu obligatoire, parce qu'il ne faut porter aucune atteinte à la liberté des individus et qu'il vaut mieux les convaincre que leur intérêt est de se préserver des maladies infectieuses quand on leur en fournit gratuitement les moyens, ce qui est le cas pour le BCG.*) [34, pp. 8,9].

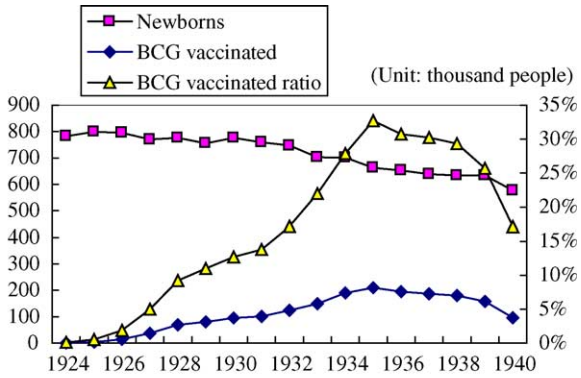
These words reveal his strategy for promoting BCG. The vaccine would be provided freely to physicians and midwives, and parents would be persuaded to allow their newborn babies to be inoculated. Since the vaccine was supplied freely, for the sake of public health, Calmette also communicated with the Minister of Public Health to subsidize the production of vaccine at the Institut Pasteur. One result was that in 1931, the annual budget of the Institut Pasteur was 10.8 million francs, of which 4 million francs were specifically earmarked from the government for BCG production.

Moreover, since the Minister of Public Health supported BCG, Calmette asked the local government to promote vaccination through the governmental administrative system. He first asked the Minister to send favorable messages to local governments, and then, in the name of Institut Pasteur, he communicated directly with the governments, explaining the innocuousness of BCG and the right way to use it.

Because of his long involvement in the anti-tuberculosis movement, Calmette (and by implication, BCG) was strongly supported by the Comité National de Défense contre la Tuberculose (CNDT), a national anti-tuberculosis association. The support of CNDT was important not only because of the association's high-profile position against tuberculosis but also because of subsidies for BCG development that could be obtained from the Rockefeller Foundation through the CNDT [35,36].

The model for BCG production and distribution, established by Calmette, continued after his death in 1933. Since BCG had already become an important vaccine by the mid-1930s, its production was the only activity at the Institut Pasteur to receive subsidies from the government [37]. Unfortunately, further development of the BCG vaccination program was interrupted when World War II broke out.

Fig. 1 shows the increasing number of newborns and those vaccinated with the BCG in France from 1924 to the beginning of the Second World War. The number of vaccinations reached a peak of 32.7 percent in 1935, and stabilized at above 30 percent until the war.



Sources: Number of newborns: INSEE; numbers of vaccinated: Institut Pasteur

Fig. 1. Evolution of BCG vaccination in France before World War II.

This means that prior to the war, approximately one-third of newborns received the BCG vaccine each year.

Following World War II, BCG's status as the primary vaccine against tuberculosis was firmly established. The vaccine won a historic victory in 1948 at the First International BCG Congress held in Paris. Dr Guérin, co-developer of BCG, was chairman of the Congress, and he subsequently became president of the Académie de Médecine in 1951. The Congress, convened in memory of Calmette, gathered more than 200 experts from 33 countries [38]. Most of the participants reaffirmed the efficacy and safety of BCG and concluded that BCG vaccination should be popularized. The most concrete result of the Congress was the decision by the World Health Organization and the United Nations Children's Fund to promote vaccination using BCG in several countries beginning in 1948 [25].

Contrary to Calmette's views, the French government passed a law in 1950, which defined certain high-risk groups that were required to receive mandatory vaccinations with BCG. This was only the fourth mandatory vaccine in history, following vaccines against smallpox, diphtheria (1938), and tetanus (1940) [39]. Those who were considered at high risk included children living collectively, those having contact with tuberculosis patients, people serving in the medical, social and public services, and workers in industry [40]. Although criticized by certain experts [5], the law was implemented in 1954. Since then, the BCG vaccination has become institutionalized and acquired a legislated status in society. For the following 30 years after its first authorized inoculation in 1924, BCG continued to be prepared at the Institut Pasteur of Paris and distributed all over France.

4.5. Current issues

A vaccine is called efficacious because it stimulates the immune system to induce an adaptive immune response against a particular pathogen. However, a number of details

regarding the mechanisms of that response are still unclear. This is particularly true for BCG. Even though BCG is the most widely used vaccine, the BCG vaccination strategy and immunization policy are frequently reviewed and criticized. For example, since there is a lack of evidence to support the efficacy of BCG inoculation for adults, a revaccination policy using BCG was abolished in several countries and will be amended in France [7,41,42].

Another problem with BCG is that the strains are considered resistant to all major chemotherapeutic drugs [43]. As there is now believed to be some relationship between tuberculosis and AIDS, issues have been raised about the resistant effects of BCG to AIDS therapeutic approaches [44].

By virtue of the success in deciphering the genome sequence of the *Mycobacterium tuberculosis* [45], new directions for developing better anti-tuberculosis vaccines have been proposed, including modification of the present BCG vaccine, isolation of new strains, protein or DNA recombinant vaccines, and global approaches [46]. However, the BCG is still today the only vaccine against tuberculosis because of the special characteristics of the tubercle bacillus and our limited knowledge of tuberculosis, BCG, and their relations in the human body [47].

5. Discussion

5.1. Application-oriented vs. quasi-contract research

Even though the development of BCG evolved out of Louis Pasteur's rabies vaccine, when the characteristics of BCG and the rabies vaccine are compared, there are several fundamental differences. First, Pasteur's rabies vaccine was a live-attenuated virus, whereas the BCG is live-attenuated bacteria. Second, the rabies vaccine was developed for therapeutic use, as only patients infected with rabies were inoculated. In contrast, the BCG is for use in healthy people to prevent tuberculosis.

These differences imply that rabies is transmitted in very limited ways and that patients are relatively rare, as compared with the highly contagious tuberculosis which threatens people living collectively. Accordingly, Pasteur's motivation for developing the rabies vaccine was more likely based on personal interest, whereas the work of Calmette and Guérin occurred under high social expectancy and was driven by strong social demand.

Moreover, unlike Pasteur, who was a pioneer, Calmette and Guérin were in a competitive environment in which several methods to combat tuberculosis were under development at the same time around the world.

Therefore, the birth of BCG could be considered an innovation driven by demand. With its pragmatic base, Calmette's work was application-oriented rather than purely scientific. Moreover, since the early development of BCG was supported by regional entities in Lille, the work was more like today's contract research. In other words, the innovations of BCG were characterized by informal agreements between the researchers and society, which can be called 'quasi-contract research'. This kind of research held strong promise for the researchers, who could devote themselves for several years to developing a vaccine. Cultivation of the initial BCG strain required thirteen years.

Before that, several years had been spent looking for the right bacillus strain and developing the best way to culture it. The cost for this long-term research was therefore absorbed by its special social settings.

5.2. Community of practice and community of innovation

As most researchers know, obtaining a patent is vital to the scientific progress of vaccine innovations. However, during the early stages of BCG innovation, little in the way of a patent system existed. Two factors prevented BCG researchers from seeking protection of their intellectual property rights. One is the so-called 'Pasteur tradition': instead of being protected by patent, vaccine production should be carried out in the laboratory under strict controls, thus preventing competition in the market [48]. The other factor is technological limits on preserving BCG before 1961. The effect of the latter on knowledge diffusion is similar to the open source model. However, innovations of BCG took place in a few research centers because safety requirements built a wall that contained the knowledge therein.

Partly by nature and partly by strategy, free and wide distribution of the BCG strains to research centers around the world and open access to the culture knowledge in the Institut Pasteur in Paris established a professional community in which the BCG-related knowledge could be exchanged frequently. That community further enforced the dominant position of the BCG vaccine in the medical society. Various conferences and congresses on tuberculosis and BCG were occasions to cohere their consensus as well as identity. Accordingly, BCG was primarily promoted by a 'community of practice' [49] comprised of international experts in related fields.

On the other hand, even though the Pasteur tradition was based on public interest, strong commitment to the application of the BCG vaccine, as in the case of Dr Calmette, represented typical entrepreneurship. Calmette's personality played an important role in vaccine innovations. His participation in the anti-tuberculosis movement, talent for communication with physicians and politicians, and insistence on research results established a strong social base for the further development of BCG. Owing to his strategies for promoting BCG, Calmette's role changed from 'vaccine discoverer' to 'medical expert with human sympathy.' His position at the Institut Pasteur also gave him added credibility. Moreover, the Lübeck accident seemed to him a turning point in vaccine safety, moving away from naïve scientific arguments to a politically correct approach. Such factors gave him the power to facilitate social communication and to promote BCG and vaccination.

With the development of BCG, we can identify two strongly interrelated dimensions. The first one is the professional dimension, in which BCG gained knowledge support from the community of practice. The second one is the social and political dimension, in which actors from various sectors competed to obtain social resources for their own interests, which were not necessarily economically oriented. Calmette and his camp successfully leveraged the social dimension in favor of BCG partly because of their efforts in the scientific dimension. The field for social resource competition can be defined as a 'community of innovation' if the resources are for the purpose of innovation. As related to

Table 2
Communities in BCG innovation

	Community of practice	Community of innovation
Members	Vaccine researchers and scientists Medical professionals Public health researchers Microbiologists, etc.	Institut Pasteur Medical and related professional associations Anti-TB associations Ministries and regional governments Third-party foundations International organizations etc.
Activities	Knowledge exchange through training programs Research collaborations Conferences and other scientific activities	Financial, legislative, policy and other complementary support for BCG development, production and distribution Public communication
Objects	Improvement of BCG efficacy and safety Scientific support for BCG	Social applications of BCG Promotion of BCG vaccination, policy-making, production and distribution etc.
Opponents	Rival theory and evidences against BCG	Competitive tools and methods against TB Anti-vaccination groups
Resources	Resource required for knowledge development	Social and political resources
Collective value	Paradigm building and maintenance	Public safety with highest efficiency and lowest cost
Result	BCG as a dominant and standard approach to prevent tuberculosis	Institutionalization of BCG vaccination (compulsory vaccination)

BCG innovation, the characteristics of the community of practice and community of innovation are summarized in Table 2.

5.3. Evolution of the community of innovation and institutionalization of vaccination

The inoffensive characteristics of BCG were the primary issue raised by Calmette and his campaigners who promoted the vaccine. The effects of the Lübeck accident and the response of the medical authorities reinforced this characteristic. From the letter issued by the Minister of Public Health in the early 1930s, it is apparent that this idea had been fully accepted by policymakers.

Owing to the war, no further action was taken by the public sector until the late 1940s. However, recognition of BCG as a safe tool against tuberculosis was, to the politicians and public health promoters, the best approach to fighting the disease, even though its efficacy might have been questioned. We learn that public policymakers and the vaccine developers place different values upon the vaccine. At this point, the development of the BCG vaccination program was dominated by the public sector rather than by the community of practice, which kept studying the statistical results of BCG efficacy. BCG vaccination therefore became institutionalized, as compulsory vaccination was required

by immunization policy. From the evolution of the community of innovation, we observe how power among the various actors influenced the results of innovation.

The institutionalization of vaccination is, however, a paradox for further innovation of the vaccine. On one hand, as social resources for preventing tuberculosis gathered around the BCG approach, other methods had fewer possibilities for development. On the other hand, the BCG approach was unsatisfactory in many aspects, and further development seemed difficult. Moreover, institutionalizing the vaccine into compulsory vaccination shrinks the group of vaccine innovators by excluding the end users. That is, the individuals, since then, have had no right to vote for the vaccine. These facts reveal the rigid character of the community of innovation after institutionalization.

6. Conclusion

This research reviewed the history of BCG innovation from its early days in Lille to the formulation of an immunization policy. From the collective-action perspective, the research illustrates that vaccine innovation is a dynamic social process that occurs not only because of the uncertainty caused by limitations in technology and knowledge about BCG vaccinology, but also because of power shifts among different groups of social actors. Therefore, decisions about public acceptance of the vaccine rely more on the characteristics of the vaccine, and can be shaped by collective actions contributed by a range of diverse social actors.

We propose a community approach that includes these actors whose collective actions reach a consensus that overcomes the uncertainty of knowledge as well as diversified opinions about the vaccine. Moreover, the power shift from the community of practice to dominance by the community of innovation is observed as a critical point in BCG innovation.

References

[1] Pauly MV, Cleff BE. The economics of vaccine policy. In: Pauly M, Sepe SJ, Sing M, Willian MK, editors. Supplying vaccines: an economic analysis of critical issues. Amsterdam: IOS Press; 1996.
[2] Kremer M. Innovation policy and the economy. In: Jaffe AB, Lerner J, Stern S, editors. Creating markets for new vaccines. Cambridge, MA: MIT Press; 2001.
[3] Blume S, Geesink I. A brief history of polio vaccines. Science 2000;288:1593–4.
[4] Butler D. New fronts in an old war. Nature 2000;406:670–2.
[5] Ferru M. la faillite du BCG. Paris: PUF; 1977.
[6] Roche PW, Triccas JA, Winter N. BCG vaccination against tuberculosis: past disappointment and future hopes. Trends Microbiol 1995;3:397–401.
[7] Lévy-Bruhl D, Barrault Y, Decludt D, Schwoebel V. Faut-il arrêter le BCG? (should bcg vaccination be discontinued in France?) Médecine et Maladies Infectieuses 2003;33:188s–192.
[8] Rappuoli R, Miller HI, Falkow S. The intangible value of vaccination. Science 2002;297:937–9.
[9] Robbins-Roth C. From Alchemy to IPO: the business of biotechnology. Cambridge, MA: Perseus; 2000.
[10] Nalin DR. Evidence based vaccinology. Vaccine 2002;20:1624–30.
[11] Galambos L, Sewell JE. Networks of innovation: vaccine development at Merck. Sharp and Mulford 1995; 1895:1995.

[12] Wilson CB, Marcuse EK. Vaccine safety—vaccine benefits: science and the public's perception. Nat Rev Immunol 2001;1:160–5.
[13] McMichael A, Hanke T. HIV vaccines 1983–2003. Nat Med 2003;9:874–80.
[14] Hilleman MR. Vaccines in historical evolution and perspective: a narrative of vaccine discoveries. Vaccine 2000;18:1436–47.
[15] Lambert RJ. A Victorian national health service: state vaccination 1855–71. The Historical Journal 1962; 5:1–18.
[16] INSERM. Vaccinations: actualités et perspectives. Paris: Les Editions INSERM; 1999.
[17] Hannoun C. La vaccination. Paris: Presses Universitaires de France; 1999.
[18] Friedberg E. Local order: dynamics of organized action. Greenwich CT: JAI Press; 1997.
[19] Plotkin SL, Plotkin SA. A short history of vaccination. In: Plotkin SA, Orenstein WA, editors. Vaccines. 3rd ed.. Philadelphia: W.B. Saunders; 1999.
[20] Delaunay A. L'Institut Pasteur: des origines à aujourd'hui. Paris: Editions France-Empire; 1962.
[21] Dubos R, Dubos J. The white plague: tuberculosis, man, and society, 3rd ed. New Brunswick, NJ: Rutgers University Press; 1996 [paperback].
[22] Kervran R. Albert Calmette et le BCG. Paris: Hachette; 1962.
[23] Guérin C. Albert Calmette à Lille: 1895–1919 souvenirs. Paris: Masson et Cie; 1948.
[24] Calmette A, Guérin C, Boquet A, Nègre L. La vaccination préventive contre la tuberculose par le BCG. Paris: Masson et Cie; 1927.
[25] Smith KC, Starke JR. Bacille Calmette–Guérin vaccine. In: Plotkin SA, Orenstein WA, editors. Vaccines. 3rd ed.. Philadelphia, PA: W.B. Saunders; 1999. Chapter 8.
[26] Gheorghiu M. Le BCG vaccin contre la tuberculose: leçons du passé pour aujourd'hui. In: Moulin AM, editor. L'Aventure de la vaccination. Paris: Fayard; 1996. Chapter 15.
[27] Turpin R. Souvenirs des premières applications humaines de la vaccination par le BCG. Le Semaine des Hôpitaux. Annales de Pédiatrie 1967;6/2:345–8.
[28] Calmette A, Guérin C, Negre L, Boquet A. Prémunition des nouveau-nés contre la tuberculose par le vaccin BCG (1921 á 1926). Paris: Marcel Giard; 1926.
[29] Bernard N, Nègre L. Albert Calmette: sa vie, son oeuvre scientifique. Paris: Masson et Cie Eds; 1939.
[30] Bernard L. Le Drame de Lübeck et le BCG. Paris: Masson et Cie; 1931.
[31] Calmette A. Epilogue de la Catastophe de Lübeck. Masson et Cie: Paris; 1931.
[32] Behr MA. BCG—different strains, different vaccines? Lancet Infect Dis 2002;2:86–92.
[33] Fine PEM, Carneiro IAM, Milstien JB, Clements CJ. Issues relating to the use of BCG in immunization programmes: a discussion document. Geneva: Department of Vaccines and Biologicals, World Health Organization; 1999.
[34] Calmette A. A propos du BCG. La Protection des Animaux (juillet) 1932;8–9.
[35] Murard L, Zylberman P. La mission Rockefeller et le CNDT. Revue d'Histoire Moderne et Contemporaine 1987;34:257–81.
[36] Liebenau J, Robson M. L'Institut Pasteur et l'Industrie pharmaceutique. In: Morange M, editor. L'Institut Pasteur: Contributions à son histoire. Paris: La Devouverte; 1991. Chapter 3.
[37] Nègre L. L'Institut Pasteur et son oeuvre scientifique. Paris: La cause; 1935.
[38] Institut Pasteur. Le Premier Congrès International du BCG. Paris: Institut Pasteur; 1948.
[39] Bégué P. Vaccination en France: rationnel et evolution du calendrier vaccinal. Annales de l'Institut Pasteur: la vaccinologie 2002;21–36.
[40] Bouvrain-Dartevelle AS. Essai sur l'évolution de la vaccination par le BCG. Ph.D. dissertation, Faculté de Médecine, Université de Paris; 1956.
[41] Barrault YB, Lévy-Bruhl D, Schwoebel V. Impact épidémiologique d'une modification de la politique de vaccination par le BCG en France. Paris: Institut de Veille Sanitaire; 2001.
[42] Bader JM. La France se prépare à abandonner le BCG. Le Figaro 2003;20.
[43] Agger EM, Andersen P. A novel TB vaccine: towards a strategy based on our understanding of BCG failure. Vaccine 2002;21:7–14.
[44] Kaufmann SHE. Is the development of a new tuberculosis vaccine possible? Nat Med 2000;6(9):955–60.
[45] Cole ST, et al. Deciphering the biology of *Mycobacterium tuberculosis* from the complete genome sequence. Nature 1998;393:537–44.

[46] Gicquel B. Vers de nouveaux vaccines antituberculeux. Annales de l'Institut Pasteur: la vaccinologie 2002;67–78.
[47] McMurray DN. Recent progress in the development and testing of vaccines against human tuberculosis. Int J Parasitol 2003;33:547–54.
[48] Cassier M. L'engagement des chercheurs vis-à-vis de l'industrie et du marché: normes et pratiques de recherche dans les biotechnologies. In: Alter N, editor. Les logiques de l'innovation. Paris: La Découverte; 2002. Chapter 6.
[49] Brown JS, Duguid P. Organizational learning and communities-of-practice: toward a unified view of working, learning, and innovation. Organization Science 1991;2(1):40–57.
[50] Behr MA, Small PM. A historical and molecular phylogeny of BCG strains. Vaccine 1999;17:915–22.

Tzung-wen Chen received his Ph.D in Technology and Innovation Management from the National Chengchi University, Taipei. Currently, he is pursuing another doctoral program in Sociology in France. His research interests focus on the historical, social, and political aspects of industrial innovation in the electronics and biotechnological sectors.