A distinctive nation: vaccine policy and production in Japan

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Introduction

Public health authorities in every nation have devised distinctive policies to deal with the prevention and spread of infectious diseases, what Jeffrey Baker has referred to as a national 'style' of vaccination.¹ While Japan's climate and geography as an island nation in the Far East have had a direct impact on the prevalence of certain infectious diseases, preventive vaccination policies, which were influenced by numerous factors ranging from changing societal expectations and pressure from parent, patient and physician groups to new scientific discoveries, may have had an even greater impact on the formation of Japan's distinctive approach to immunisation and production.²

One reason for Japan's distinctive vaccination policies is the long history of outside influences on its institutional framework. German, and more recently, American contacts have had a profound effect on Japan's most fundamental regulatory institutions as well as other features such as regulators' preference for full self-sufficiency in vaccines and domestically developed strains. Another area where Japan remains distinctive is regulators' approach to risk. This can be illustrated by two policy choices: approval of fewer vaccines than in other developed nations and extreme caution vis-à-vis the introduction of combination vaccines. In 1983, the US routine vaccine schedule was identical in number (eight vaccines) to that of Japan; however, in the mid-1980s the situation began to diverge considerably. By 2011, the number listed in the former had doubled while Japan's list remained virtually unmodified (Table 8.1).

Table 8.1 Vaccine schedules in Japan and the United States, 2011

Japan	United States
Diphtheria	Diphtheria
Pertussis	Pertussis
Tetanus	Tetanus
Polio (OPV)	Polio (IPV)
Measles	Measles
Rubella (offered only to adolescent girls before 1994)	Mumps
Japanese encephalitis	Rubella
BCG	Hepatitis B
*Influenza (individuals over 65)	Rotavirus
	Pneumococcal
	Varicella
	Hepatitis A (children; recommended for high risk groups)
	Hib
	Meningococcal (for high risk groups)
	Influenza (children/yearly)
	HPV

*Type II vaccination.

Source: Infectious Disease Surveillance Center (Japan)

<http://idsc.nih.go.jp/vaccine/dschedule/lmm11EN.pdf#search=%27Japanese+vaccine+schedule+2011%27>.

Centers for Disease Control and Prevention (USA)

www.cdc.gov/Mmwr/preview/mmwrhtml/mm6005a6.htm.

Although the number of routine vaccines has proliferated in western nations, particularly since the 1980s, in Japan, a country whose population is one of the world's healthiest and the leader in life expectancy, the number has actually decreased since the end of the Second World War.³ Given the assumption that disease prevention through vaccination is basic to maintaining good health, this paradox merits closer investigation. Japan's divergence from widely accepted international norms of vaccination, particularly the rejection of the commercially successful combination vaccines, provides another paradox, given the country's otherwise full integration into the system of global capitalism and active participation in all the major institutions of world health.

Through examples of Japanese vaccination policy choices primarily from the early post-war period to the 2000s, this chapter illustrates the ways that Japanese policy makers took a different policy approach from other nations and explores the reasons why.

As analysed throughout this volume, the collective consciousness of citizens, which was formed by the history of vaccine-induced adverse events, differs in every nation. In Japan, apart from some widely publicised cases of adverse vaccine-induced reactions, the topic of vaccination generated relatively little public interest. However, the H1N1 epidemic in 2009 marked a true turning point. This outbreak received extensive media coverage and heightened general awareness of the dangers of infectious diseases.

A measles epidemic in 2007 resulting in nationwide school and university closures, an alarming rise of rubella cases in recent years and reports of adverse reactions to the HPV (human papillomavirus) vaccine also piqued citizens' interest in public health issues, while also sensitising them to the importance of making informed vaccination choices.⁴ This chapter traces the formation of the collective consciousness in Japan by examining some of the most distinctive features in Japan's vaccination history and the ways in which health authorities have dealt with outbreaks and prevention.

The historical legacy

From an early date, the state played the key role in the formation of Japan's distinct approach to dealing with the spread of infectious disease. In the 1630s, the Tokugawa government (1603–1868) officially closed the country to contact with the outside world for some 250 years. This was not simply a momentous political decision. By limiting foreign exchanges, administrators had also unwittingly enacted the first nationwide public health policy. The fact that Japan remained a 'closed nation', or *sakoku* in Japanese, for so many years also had a limiting effect on the incursion of infectious diseases from abroad. After the start of the Meiji period (1868–1912) one of the first large-scale public health threats was cholera, which began to spread nationwide after the imposition of the so-called 'unequal treaties' forcing the 'opening of the nation', or *kaikoku*, and Japan's official entry into the global economy. As shown in this chapter, Japanese policy makers have

followed a similar pattern of artificially ‘opening’ and ‘closing’ the nation, not to foreigners, but to new vaccines as well as new forms of vaccine delivery, namely combination vaccines. The metaphors of the country’s ‘closing’ and ‘opening’ are used again in this chapter in the more modern context of Japan’s vaccination policy.

Transfers of knowledge and institutions were also of vital importance to Japan’s history of vaccination. Japan continued to open its doors throughout the Meiji period by dispatching scientists to foreign universities, particularly in Germany, which created enduring professor-student relationships. By the late Meiji period, the number of dispatches gradually diminished due to the need for their assistance at home at newly opened universities and research institutions. During the Taishō period (1912–26), connections with Germany became strained due to Japan’s position in the First World War. Despite this, scientific activities continued as bacteriologists turned their attention to the causes of diseases endemic to Japan. One of the first important findings was that of Inada Ryōkichi and Idō Yutaka, whose research was first published in Japan in 1915. They identified the causative agent of Weil’s disease, the vaccine for which would be listed on Japan’s first vaccination schedule.⁵ Noguchi Hideyo’s work on infectious diseases is also widely recognised, particularly in Japan where his image began to appear on the 1000-yen note in 2004.⁶

While Kitasato Shibasaburō is perhaps Japan’s most prominent bacteriologist, there were many others, including his student Shiga Kiyoshi, who returned to Japan in 1924 with a BCG strain from the Pasteur Institute. Like Kitasato, Shiga left Japan to do research in Germany where he worked with Paul Ehrlich as did Hata Sahachirō, another researcher at Kitasato’s institute and developer of arsphenamine 606, the first medicine in the world for the treatment of syphilis and first synthetic chemical. In 1897, Shiga discovered the bacillus causing dysentery, *Shigella dysenteriae*, while working at Kitasato’s newly opened Institute for the Study of Infectious Diseases. Kitasato, a scientist who truly embodied a European approach through his involvement not only in research on infectious diseases but also in the commercial production and sale of sera, was rare among Japan’s early scientists. Kitasato can be credited for bringing to Japan an institute-based model of sera and vaccine research combined with commercial production. Even today, institutes are the principal

suppliers of vaccines in Japan, as opposed to most other countries, where virtually all of the vaccine-producing institutes and laboratories have closed and been replaced by large, multinational pharmaceutical companies.

Organisational foundations

The institutionalisation of Japan's model for vaccine production got underway in 1893 with the establishment of the Institute of Infectious Diseases (IID), what the historian of Japanese science and technology James Bartholomew has referred to as 'the most important research facility built [in Japan] before World War I'.⁷ The IID played a major role not only in scientific research on sera and vaccines but also in contributions to the formation of science and technology in Japan. Kitasato, who oversaw its activities until it was placed under the Ministry of Education, made a vital contribution to the institutionalisation of a research-based Japanese vaccine production model as a private sector activity.

Known in Japan as the 'father of bacteriology', Kitasato received his medical degree from the University of Tokyo in 1883. Before entering government, he went to study at the University of Berlin where, as an assistant of Robert Koch, he produced a pure culture of tetanus bacilli.⁸ Kitasato, who revered his mentor throughout his lifetime, based the IID's operational model on that of the Koch Institute.⁹ Like its German counterpart, the IID performed three functions: (1) research, (2) production and sale of sera and vaccines, and (3) treatment. While in Berlin, Kitasato worked alongside Emil von Behring and succeeded in developing serum therapy for the treatment of tetanus.

Kitasato was aided in his efforts to found an institute similar to those in Germany and France by several prominent and politically powerful figures. First and foremost was Nagayo Sensai, the first chief of the Bureau of Hygiene at the Ministry of Home Affairs, the equivalent of today's MHLW (Ministry of Health, Labour and Welfare), followed by two other influential politicians, Gotō Shinpei, Nagayo's successor, and in later years, Hasegawa Tai, who helped Kitasato to obtain state funding. Nagayo felt that Kitasato's leadership was essential to the success of the institute; however, since he knew that Kitasato had a number of powerful enemies, he proceeded with his plans with caution.¹⁰

Kitasato initially founded a small research laboratory in 1892, thanks to financial backing from Fukuzawa Yukichi, a moderniser and the founder of one of Japan's most reputable private institutions, Keio University, Morimura Ichizaemon, an entrepreneur, and the Great Japan Hygiene Society. Like Nagayo, Fukuzawa had studied western science at Tekijuku under Ogata Kōan, the key propagator of the Jennerian vaccination technique in Japan. Fukuzawa provided Kitasato not only with funding but also a plot of land for his activities. The scale of Kitasato's first operation was inadequate, and efforts were made to procure funds from the government to expand production. This move caused the first round of tensions between Kitasato and his academic rival at Tokyo Imperial University (later the University of Tokyo), Ogata Masanori.¹¹ In the end, the IID was awarded the necessary funds, thus ensuring its financial stability. Having been officially placed under the jurisdiction of the Ministry of Home Affairs in 1899 as a national institute, IID became the largest vaccine and sera producer in Japan and the first in the world to employ serum therapy to combat cholera, tetanus and diphtheria.¹²

In 1912 the second round of tensions erupted over the jurisdiction of the IID, this time between Kitasato and the Japanese government led by Prime Minister Ōkuma Shigenobu. According to the government's proposal, the IID was to be situated in Tokyo Imperial University and placed under the jurisdiction of the Ministry of Education. Though it was agreed that Kitasato would remain executive director, he vehemently opposed the new arrangement. Thus shortly after the government's plan was approved, Kitasato resigned along with his entire staff and opened his own private vaccine-producing research institution. Thanks to his foresight in procuring a production licence shortly before his resignation, research activities could be financed through sales of sera and vaccines. The dispute led to the establishment of the Kitasato Institute as a wholly private entity.

In 1947 during the US occupation, IID underwent yet another major organisational change. The end result was the creation of a new national institute of infectious diseases with an organisational model similar to that of the National Institutes of Health (NIH) in the United States. Although the Supreme Commander for Allied Powers (SCAP) in accordance with the recommendation of Brigadier Army General Crawford Sams of the Public Health and Welfare Section (PHW)

officially approved its establishment, key Japanese, in particular, Nanbara Shigeru, law professor and president of Tokyo Imperial University and Tamiya Takeo, head of IID at the end of the war, were also intimately involved with its creation behind the scenes. Based on proposals drawn up by Nanbara, SCAP founded the NIH, later the National Institute of Infectious Diseases (NIID), whose new jurisdiction would become the Ministry of Health and Welfare (MHW). IID (now the Institute of Medical Science, University of Tokyo) remained intact, initially as a research and inspection facility, though many of the staff later migrated to NIID.

NIID's early activities included: (1) research on the causes, treatment, and prevention of infectious diseases, (2) inspections of vaccine quality, (3) development, production and distribution of certain vaccines with limited demand such as the rabies vaccine, and (4) pilot production and distribution of vaccines and sera.

Placed under the MHW (Ministry of Health, Labour and Welfare since 2002), the American and Japanese-inspired institution provided the organisational foundations for post-war research on infectious diseases and vaccines in Japan. In addition to NIID, another entirely new and autonomous institution, the Biologicals Production Association (now the Association of Biological Manufacturers of Japan) was established the same year, 1947.¹³

Foreign influences on Japan's vaccination policy approach

Like the institutions mentioned here, the Preventive Vaccine Law (PVL) was also in a sense a western import, as it was Sams of PHW who officially implemented it. At that time, the need for a new policy framework for disease prevention was great: with the turmoil caused by returning soldiers and citizens from abroad, coupled with unsanitary domestic conditions, infectious diseases were rampant.¹⁴ This was particularly true in Tokyo, where repeated aerial raids in the final days of the war left many destitute and homeless.¹⁵ The measures taken to stop the spread of disease were draconian. According to Watanabe Mikio, PVL, introduced in 1947, was unprecedented anywhere in the world for its severity.¹⁶ Vaccination was made mandatory without exception and onerous fines were imposed on those who violated it.¹⁷

Japan's first routine schedule comprised smallpox, diphtheria, paratyphoid, pertussis, tuberculosis, typhus, plague, scarlet fever, influenza and Weil's disease vaccines. Like the transfer of penicillin production technology from the United States, which was carried out in part to control the spread of sexually transmitted diseases among the troops stationed in Japan, the introduction of mandatory vaccination was also partly motivated by American self-interest.¹⁸ Japanese nationals working directly with SCAP were the first to be vaccinated. Further, according to Watanabe, self-sufficiency in vaccines was encouraged not to promote industrial development in Japan but to respond to criticism in the United States of the financial burden of stationing troops and administrative personnel in Japan.¹⁹

Though SCAP officials' efforts to provide safe and effective vaccines were well intentioned, adverse incidents occurred. The most famous incident was the 1948 Kyoto-Shimane Diphtheria Tragedy, which resulted in an exceptionally high death toll of eighty-three. Despite this, no reports of widespread public dissent vis-à-vis PVL exist and little news of this incident was reported in the media due to stringent censorship. According to Wake Masayoshi, while the issue was discussed in Japanese Diet sessions, SCAP officials hindered the dissemination of such information to the general public.²⁰ Following the incident, Sams halted the sale of all Japanese vaccines and sera and began inspections of some forty-one facilities nationwide. Of these, ten facilities were granted permission to engage in production. It is noteworthy that Sams believed that vaccine production should be carried out solely by the private sector and opted not to allow IID to manufacture vaccines on account of its status as a public entity.

In addition, as was the case for the transfer of penicillin production technology, a specialist from the board of health of the state of Michigan came to Japan to provide direct assistance and supervision in vaccine production at the ten selected facilities. Thanks to these endeavours, the quality of the vaccine produced in Japan improved to the extent that these manufacturers were able to export vaccines to aid in the Korean War (1950–53).²¹

The lessons of the Kyoto-Shimane Diphtheria Tragedy may have left a mark in the collective memories of some public health administrators; however, because the incident received so little mention in

the press, it was never able to serve as a platform for a wider national debate on PVL or the risks associated with vaccination. While responsibility for the tragedy could easily be placed on the severity of SCAP's vaccination policies, evidence suggests a certain degree of complicity on the part of Japanese health policy makers. Indeed, rather than amending the policy of *mandatory* vaccination, it stayed in place until 1994, while the penalty of a fine was not officially removed until 1977.²²

According to Chris Aldous, while Sams and others may have seen their reforms as revolutionary, there was also a certain degree of continuity in Japan's health policy approach. The foundations of some of the institutions of hygiene, particularly those established at the community level, had already been put in place, in some cases since the Meiji period, but had been severely weakened during the war.²³ While PVL has undergone numerous revisions since its introduction during the occupation, it continues to be the bedrock of all Japanese vaccination policy. The following provides another example of foreign influences on Japan's approach to vaccination policy-making in the 1960s and beyond.

The polio vaccine: emergency measures

The history of polio vaccine manufacturing in Japan began in 1958 when an investigating committee for infectious disease prevention recommended domestic production of IPV (inactivated polio vaccine) and research on OPV (oral polio vaccine). This came in the wake of a large-scale polio outbreak in 1960 with some 5,606 reported cases and 317 deaths.²⁴ When the number of cases reported in the first half of 1961 surpassed those of the previous year, health authorities decided to take the emergency measure of importing OPV from the United States and Canada and later also from the Soviet Union, even though domestic clinical trials had not yet commenced. In the meantime, standards for IPV manufacturing were set in October 1960, and six establishments – Biken (Research Foundation for Microbial Diseases of Osaka University), Kaketsuken (Chemo-Sero-Therapeutic Research Institute), Takeda Pharmaceutical Company, Chiba Kessen (no longer in operation today), Kitasato (Kitasato Institute) and Denka Seiken – received production licences. As a result of their efforts, by

1962 the number of new outbreaks dropped to 289 and in 1963 to 131.²⁵ In July 1962, the six private entities joined forces by forming a single producer, Japan Poliomyelitis Research Institute (JPRI), to manufacture OPV domestically. This enabled Japan to meet domestic demand by 1964 and later achieve full self-sufficiency in the polio vaccine.

According to an interview with Abe Shinobu, Executive Director of the JPRI, on 20 February 2014, the idea of having a sole supplier of the polio vaccine was not that of the institute or the government but of Albert Sabin. Sabin based his recommendation on Japan's relatively small geographical size and the need to ensure high quality standards. He personally contributed to Japanese polio production by donating one of his strains to the JPRI in March 1963. The same strain is still in use today.²⁶ Given the risk of OPV-derived paralysis (5.8 million to one for infants), scientists at JPRI began research on IPV production using the Sabin strain in 1976.²⁷ They succeeded in producing the world's first Sabin IPV, known as s-IPV. Because the vaccine had not been tested for use in a combination vaccine, collaborative research began to develop an s-IPV-DTP vaccine.²⁸ Initially, five DTP-producing establishments were involved in the project; however, by 2005 only Biken and Kaketsuken remained.

The polio vaccine example illustrates three characteristic features of Japan's vaccine policy approach. First, unlike in the United States, Japanese health authorities encouraged a sole supplier of the polio (and BCG) vaccine to guarantee a higher safety level since contamination problems could be better dealt with at a single rather than multiple locations. Second, unlike most other developed nations, Japan made no use of combination vaccines using the polio component until late 2012. Third, Japanese health authorities continued to promote the use of OPV due to its good record of safety and superior immunity over IPV, despite over a decade of widespread use of IPV in many countries.²⁹ Also, by using the oral vaccine, regulators were able to avert another risk: injection-associated infections.³⁰

The decision to switch from OPV to IPV in 2012 sparked wide attention in the media and strong public criticism of Japanese regulators for several reasons. First, it left the average Japanese with the impression that Japan was a 'backward nation' in terms of vaccination policies.³¹ Like the Hib vaccine, the decision came much later than

in many other developed countries; the United States had switched to IPV over a decade earlier. Second, the debate over the polio vaccine also brought to light an inconsistency between Japan's domestic stance on vaccination and its global one. Although Japanese representatives had for many years supported WHO's position on promoting the use of IPV in countries where polio had been eradicated, domestic health authorities continued to keep OPV on the domestic routine vaccination schedule.³² Finally, because the switch away from OPV could not be made immediately, some believed that health authorities were jeopardising public health and even took it upon themselves to import IPV directly.³³ Perhaps in response to strong public criticism, the health ministry made the rare move of approving the foreign vaccine, IMOVAX Polio, manufactured by Sanofi Pasteur.

Thus in September 2012, health authorities added a foreign vaccine, cIPV, to Japan's routine vaccination schedule then just two months later, approved the combination vaccine, DTaP+sIPV (Table 8.2). One

Table 8.2 Approvals of Japan's first combination vaccine with a polio component

Name of vaccine	Manufacturer	Type	Application	Date	Launch
IMOVAX Polio	Sanofi Pasteur	cIPV	23 Feb. 2012	26 Apr. 2012	Sept. 2012
Tetrabik Subcutaneous injection syringe	Biken	DTaP+ sIPV	27 Dec. 2012	27 Jul. 2012	Nov. 2012
Quattrovac Subcutaneous injection syringe	Kaketsuken	DTaP+ sIPV	27 Jan. 2012	27 Jul. 2012	Nov. 2012

Source: Based on information provided in an interview with Dr Abe Shinobu, Executive Director, laboratory division at Japan Poliomyelitis Research Institute, Tokyo, 20 February 2014.

can see a similarity in the situation in the 1960s, when the Japanese government resorted to importing the polio vaccine from overseas until a domestic substitute was available.

Current changes in Japan's vaccination policy approach

To clearly elucidate more recent changes, it is useful to divide the period examined in this section into two phases: (1) the closing of the country (*sakoku*) to new vaccines from 1989 to 2006, and (2) the reopening (*kaikoku*) from 2007 to the present. The main catalyst for closing the country was a series of adverse events associated with the MMR combination vaccine, which began shortly after its launch in April 1989. It is of note that commercial production in Japan was only realised in 1986, which is much later than in some other countries, particularly the United States where use commenced more than a decade earlier in 1973. According to Tezuka Yōsuke, the particularly long delay was due to patent ownership issues.³⁴

With grants from the Ministry of Education in 1968, research institutions began developing their own mumps vaccines. Four establishments, Biken (approved in 1981), Kitasato (1981), Takeda (1982) and Kaketsuken (1985), were granted approval, each using a different strain and process.³⁵ By the early 1980s, three establishments, Kitasato, Takeda and Biken, had each developed an MMR vaccine that was ready for launch. Rather than allowing all of the establishments to market different competing MMR products, Japanese health authorities decided to approve a single standardised version, what might be called a 'national MMR vaccine'. Authorities then selected one vaccine from each establishment and combined them. Thus in 1989, Japan's first MMR combination was introduced using Kitasato's measles, Biken's mumps and Takeda's rubella vaccines. Biken took an early lead in mumps research and developed two vaccines using different strains: Urabe AM-9 and Hoshino. According to Okuno Yoshiomi, in 1978, the Urabe strain had already been tested on some 10,000 persons in Japan and South Korea and had an excellent record of safety.³⁶ It is likely that regulators selected Biken's Okabe strain based on this data rather than reports in 1987 and 1988 of a small number of adverse events in Canada, followed by the Canadian health authorities' decision to suspend production.³⁷

From a regulatory standpoint, Japan’s system of routine (mandatory) and non-routine vaccines complicated the provision of the MMR vaccine. According to the 1976 revision PVL, the measles vaccine became part of Japan’s routine vaccination schedule, which meant that patients could receive it free of charge. On the other hand, the rubella vaccine was routine only for adolescent girls, while the mumps vaccine could be administered upon request for an additional fee. Although the parent/guardian could opt to receive both the rubella and mumps vaccines each as a single-dose injection, use of the combination MMR vaccine was initially promoted by the government for its superior coverage and was encouraged by many physicians.³⁸ Indeed, according to Tezuka, after the launch of MMR, some medical institutions *only* offered the MMR vaccine, making it a *de facto* routine vaccination in some parts of the country.³⁹

As shown in Table 8.3, after the 1989 introduction of the MMR vaccine, adverse events soon ensued. MHW officials initially kept information regarding a possible correlation between the mumps vaccine and the incidence of adverse events confidential, a point that would later become a source of public suspicion and mistrust.⁴⁰

Table 8.3 Adverse events following the introduction of MMR in 1989⁴¹

Important dates	Vaccination-related developments
1 April	Start of MMR vaccine
June	Results of survey by Japan Medical Association, Maebashi, Gunma Prefecture showed a high incidence of aseptic meningitis.
19 September	MHW announcement of 1 : 100,000 to 200,000 incidence ratio of aseptic meningitis and decision ‘to continue to promote the use of MMR’ despite the rise in adverse events.
25 October	MHW announcement of 1 : several thousand to 30,000 incidence ratio of aseptic meningitis and decision ‘to proceed with MMR vaccination with caution.’
20 December	MHW announcement of 1: several thousand incidence ratio of aseptic meningitis and decision ‘to administer MMR only when requested by the parent/guardian.’

In September 1989, health authorities received reports of six cases of adverse reactions to the mumps vaccine; however, since the incidents were not life-threatening and caused no long-term harm, they continued to promote its use. In Japan, the central government allots funds to municipal and prefectural governments for the purpose of purchasing and administering vaccinations; however, it is the latter that actually implements and executes vaccination programmes at the local level. Under this system, which provides a certain degree of local autonomy, some municipal and prefectural governments took the decision to suspend the use of MMR based on their own surveys, yet others continued their vaccination programmes using MMR in accordance with the government's recommendation, despite reports of incidents.⁴² Regulators' general reaction to the incidents differed significantly from the DTP vaccine, which was added to the routine schedule of mandatory vaccinations in 1969 but temporarily withdrawn for three months in 1975 following reports of adverse events. In the case of MMR, it was not until April 1993 that officials finally decided to withdraw it completely.

In 1991, MHW officials began an investigation to determine the source of the problem but were unable to obtain any conclusive results. Then in October of the same year, they decided to allow individual vaccine producers to manufacture their own MMR vaccines, a decision that was likely taken due to suspicions regarding Biken's Okabe AM-9 strain.⁴³ In April 1992, health authorities announced a revision of their adverse event ratio to 1:1000, but did not withdraw the MMR vaccine. In April 1993, the results of another investigation provided evidence that the mumps strains of the other establishments were less effective than Biken's Okabe AM-9 strain. With such puzzling and in some cases conflicting results, regulators simply decided to withdraw the MMR vaccine altogether. Several days after the withdrawal of the MMR vaccine, it was revealed that Biken had 'illegally' modified its vaccine production process.⁴⁴ It was also found that Biken had combined its approved mumps vaccine with another one that had been manufactured according to a modified process. According to Ueno Hideo, a plaintiff in the trial that followed, *combining* the two mumps vaccines was the most likely cause of the adverse events.⁴⁵ Whatever the true cause, the revelation shed public doubt on the safety of vaccination in general, and more specifically on Japan's use of combination vaccines in the long term.

Litigation ensued. The court of first instance ruled against the manufacturer and a settlement was made between the victims' families and Biken, a decision that the latter did not appeal. The Tokyo Supreme Court determined that the state was at fault for not fulfilling its obligation to provide proper guidance and supervision, yet no formal government apology was ever issued. According to Ueno, from the perspective of a parent of one of the victims, while justice was in part served, a number of important questions remained unanswered: (1) Was modifying the production process the *only* cause of the problem? (2) Who was responsible for introducing the strain? (3) Who makes the decision to suspend a vaccine when adverse events occur? (4) Why were health authorities so slow in taking action to withdraw the MMR and reinstate vaccination using the single-injection measles vaccine?.⁴⁶

Ueno's fourth question, concerning decision-makers' choice in the type of vaccine administered, is particularly difficult to answer since there are no records available. In an invited commentary, one vaccine expert, Stanley Plotkin, wrote that the Japanese government's motives for not importing the Jeryl Lynn strain, using a strain known to cause a higher incidence of adverse reactions, and completely eliminating the mumps vaccine from the routine schedule despite scientific evidence collected by Japanese scientists of a high incidence of deafness resulting from the mumps, are indicative of 'protectionism in favour of indigenous manufacturers'.⁴⁷ Whatever the real motives, regulators have not changed their stance on the MMR vaccine, although a modified version, the MR vaccine (measles-rubella), was introduced in 2005.

Between 1989 when the first adverse events occurred to 2006, a new *sakoku* began as Japan closed its doors to new vaccines. During this period, policy-makers' approach to new vaccine approval was one of extreme caution. Apart from the hepatitis A vaccine (non-routine), health authorities did not introduce any truly 'new' vaccines. As Table 8.2 shows, until 2012 when health authorities approved vaccines with the IPV polio component, no combination vaccines were in use apart from DTaP and MR. In contrast, from the late 1980s, health authorities in the United States approved and favourably endorsed combination vaccines, which began to proliferate particularly after the launch of the Hib vaccine and the switch to IPV, both in 1987.

Table 8.4 Vaccines approved for use in Japan and the United States (1985–2006)⁴⁸

Approval year	Japan	United States
1985	Hepatitis B (1)	
1987	Live attenuated varicella	Hib IPV
1988	Pneumococcal (2) Recombinant Hepatitis B MMR (3)	
1991		aP (acellular pertussis) (5)
1992		DTaP Japanese encephalitis (6)
1993		DTaP-Hib
1994		Plague
1995	Hepatitis A	Varicella (7)
1996		Hib-Hepatitis B Inactivated Hepatitis A
2000		PCV for children (8)
2001		Hepatitis A/B combination
2002		DTaP-IPV-B
2003		Live intranasal influenza DTP for adults
2005	MR (4)	MMR-Varicella Meningococcal (conjugate)
2006		Rotavirus

(1) Approved in the USA, 1982.

(2) Approved in the USA, 1977.

(3) Approved in the USA, 1971 and launched in Japan in 1989.

(4) MR is MMR without the mumps vaccine. It was reapproved as a two-vaccine combination following adverse reactions to the mumps vaccine.

(5) Approved in Japan in 1981 and exported to the USA.⁴⁹

(6) Developed in Japan and approved in 1976.

(7) Technology transfer from Japan.

(8) 7-Valent Pneumococcal Vaccine for Children.

In the backdrop of the MMR vaccine trial were many others such as those involving the influenza and polio vaccines, which are not covered in this chapter, that called into question government responsibility.⁵⁰ In 1994, PVL underwent a major revision: Japanese health authorities changed their long-standing policy of mandatory mass vaccination. Mandatory vaccination became voluntary, that is, according to the wording of the revised law: all citizens ‘*must* make reasonable efforts to vaccinate’, although vaccination itself would not be mandatory. Mass vaccination programmes that had previously taken place in schools were also discontinued. Thus the revision transferred the burden of choice and responsibility from the state to the individual.⁵¹ Unlike in other countries with a similar system, Japanese health authorities have not implemented any coercive vaccination measures since inoculation rates remain in the 90 per cent range for all the routine vaccines, although they are low – 30–40 per cent – for non-routine vaccinations, many of which are routine in other countries.⁵² Also, since 1994, physicians are obliged to provide information on the risk of vaccine-associated adverse events and obtain informed consent before vaccinating.

The second phase, or opening (*kaikoku*) of the country to vaccines got underway around 2006, with the government’s issuing of the *Vaccine Industry Vision: Supporting Measures to Prevent Infection while Aiming to Respond to Societal Expectations of Industry* (hereafter Vaccine Vision) in 2007. This voluminous six-section policy statement marked the culmination of two years of regular discussion. To build a consensus among all those involved, MHLW officials invited a wide range of participants. Attendees included representatives from academia, regulatory and business organisations such as the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) and the Food and Drug Administration (FDA), physicians, foreign and domestic industry representatives, among others.⁵³ The document clarified the government’s new stance and was symbolic of a larger, more fundamental change in Japan’s health care system. The Vision’s encouragement of vaccination, including what some would consider ‘non-essential’, gives a clear signal that Japanese health authorities have begun incorporating more *preventive* policy measures into a system that had traditionally focused almost exclusively *curative* care. By so doing, regulators have also indirectly addressed other urgent issues,

namely the country's demographic dilemma: a growing elderly population coupled with a shrinking birth rate as well as rising health care expenditures. The dialogue that the Vaccine Vision opened among government, health specialists and industry was a first for Japan, though similar discussions had already begun elsewhere in the 1980s.⁵⁴

The first three chapters of the Vaccine Vision statement provide a general overview of the domestic vaccine industry and outline global growth and consolidation trends. By comparing the evolution of the global industry with the Japanese situation, the document sheds light on two fundamental features of the vaccine supply model: production almost exclusively by small-scale institutes and full vaccine self-sufficiency. According to the document's authors, while there are definite disadvantages to having an industry comprised of small research-based institutes, full self-sufficiency (98.5 per cent) is a beneficial and globally unique feature of Japan's vaccine supply model.⁵⁵ Chapter 4 examines the needs and expectations of society and considers the introduction of evidence-based methodologies such as QALY analyses, which had never before been applied to vaccine policy-making in Japan.⁵⁶

The final two chapters describe the government's plans to foster domestic vaccine industry growth. Chapter 5 contains a section entitled 'Basic Stance on an Industrial Policy for the Vaccine Industry', urging Japanese producers to develop new vaccines, both to bring greater benefits to society and improve international competitiveness. The final chapter posits an 'Action Plan', laying out the new roles of industry and government, including a government pledge to provide financial support for new vaccine development and the expansion or improvement of plants while also encouraging collaborative partnerships with foreign multinationals. The Vaccine Vision defined policy makers' new openness to vaccines on many levels, as illustrated by the new approvals made since its publication and special subsidies allotted to municipal and prefectural governments to encourage their use nationwide.⁵⁷

Japan's decision to approve the Hib vaccine for childhood bacterial meningitis in 2007 is particularly noteworthy since it occurred much later than in most other countries (Table 8.5). WHO representatives have advocated that infants be immunised against the disease, and by

Table 8.5 US–Japan comparison of vaccine approvals (2007–11)

Vaccine	Japanese approval	US approval
Hib (haemophilus influenzae type B)	January 2007	1985
HPV (human papillomavirus)	October 2009	2006 (Gardasil)
PCV (pneumococcal conjugate)	October 2009	2002
Rotavirus	October 2011	1998 (RotaShield)

Source: cdc.gov and mhlw.go.jp.

2006 health authorities in some 100 countries had approved the Hib vaccine, ninety of which listed it in their routine vaccination schedules.⁵⁸ Despite international consensus, most Japanese vaccine experts long maintained that incidence of the disease is much lower in Japan making approval unnecessary. In 1998, Kamiya and others challenged this assumption with the publication of a study showing Hib to be the leading cause of childhood bacterial meningitis in Japan.⁵⁹ After collecting new data in domestic trials, Sanofi Pasteur (then Pasteur, Mérieux Connaught), which established a joint venture with a Japanese firm in 1997, applied for approval and finally succeeded in launching ActHib in 2007 as the first foreign paediatric vaccine ever approved in Japan.

Given Japan's closed stance toward new vaccine approvals and policy of full self-sufficiency, few multinationals such as GSK even attempted to penetrate the domestic vaccine industry. Merck, however, through its fully owned subsidiary Banyu Pharmaceutical Company, has endeavoured to make inroads for many years with limited success. Merck (MSD) succeeded in 1988 in launching Recombivax HB, the world's first recombinant hepatitis B vaccine; however, sales failed to reach the levels seen in other overseas markets. Health authorities approved Merck's application after representatives submitted new trial data collected in Japan, ironically on the same day as another domestic manufacturer, Kaketsuken. Though hepatitis B was once considered a 'national disease' in Japan, the incidence today is low making the

recombinant hepatitis B vaccine (HBV) a type of travel vaccine whose cost is high and demand relatively low. Because HBV was never made routine, sales of the vaccine have never achieved the levels attained by the company in other countries. Other domestic entrants (Mitsubishi Kasei, Meiji Dairies) also launched HBV vaccines but later withdrew due to limited demand.

A major hurdle that foreign multinationals face is costly and time-consuming clinical trials. Both Merck and Sanofi Pasteur were required to conduct new trials in Japan despite a substantial amount of data already collected in other countries and regions. Despite the progress made at the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), since the 1980s, including the implementation of a special measure, ICH-E5 or *Ethnic Factors in the Acceptability of Foreign Clinical Data*, Japanese regulators' reluctance to accept foreign data has remained a contentious issue.⁶⁰

Perhaps more frustrating to foreign vaccine manufacturers, however, is Japan's strict quality control standards. Though Sanofi Pasteur's Hib vaccine received approval in 2007, the first shipments did not reach most medical institutions until December 2008. Even in 2009, there was still a two-month waiting list due to shortages. The delays were not caused by reservations regarding safety. The vaccine had received a favourable endorsement from the Japan Medical Association,⁶¹ and was gaining wider recognition among parents.⁶² According to an article in *Weekly Aera* (the equivalent of *Newsweek* or *Time*), in March 2009, an infant in Kyoto died from meningitis caused by the Hib virus. The infant's parents, a gynaecologist and a paediatrician, were on a waiting list for the vaccine. In the article, the couple endorsed vaccination as the best way to prevent future problems.⁶³ The main reason for the supply shortage was defective packing, specifically the glass vials, which did not present any health risks whatsoever but caused grave suspicions among health authorities.⁶⁴ According to Japanese inspectors, some contained black specks and thus had to be recalled.⁶⁵ Foreign multinationals have automated vial inspections using laser detectors; however, in Japan, personnel manually examine each individual vial before shipment to prevent recalls.⁶⁶ The French were finally able to remedy their defect problems by introducing a similar manual inspection system for all vials exported to Japan.

Conclusion

Foreign influences have played a major role in the formation of Japan's distinctive approach to vaccination policy, including the cornerstone, PVL. The institutional framework, including Japan's mainly institute/laboratory-based vaccine production system, though introduced in the Meiji period by Kitasato, was redefined and reinforced by Sams and others during the occupation period. Other foreign influences include Japan's introduction of the Sabin strain (and BCG), which is still in use today in the s-OPV and s-IPV vaccines. While in many ways influenced by foreign factors, Japan has opted not to follow the global trend of promoting the use of combination vaccines. This decision followed adverse events caused by the MMR vaccine, and until 2012 only two combination vaccines, DtaP and MR were available for use.

Japan's current business model for vaccine production is in many ways closer to the European institutes, whose model Kitasato observed and introduced to Japan in the nineteenth century, than it is to today's multinationals. Another significant difference between the two is that earnings at Japanese institutes are mainly reinvested in research and development activities rather than used as dividends. While healthy competition exists among all of them, there is ample evidence of cooperation to achieve common national goals (the development of a 'national' MMR vaccine), a feature that is rare among the highly competitive multinationals. Tradition has also played an important role in Japan's distinctiveness as a vaccine-producing nation not only in terms of strain selection (Okabe AM-9 versus the Jeryl Lynn strains) but also in the choice of its producers to remain private (Kitasato).

Japan makes an interesting case for its many differences. While parents in many countries have criticised their health authorities for a surfeit of vaccinations, in the more recent past their counterparts in Japan have complained of the opposite. Under pressure to respond to society's demands, policy makers have recently made more 'new-to-Japan' vaccines available. Since Japan's *kaikoku* or opening up to vaccines in 2007, national distinctions have gradually begun to fade as the country's vaccine supply model converges with the mainstream model of other countries. Whether limiting access to vaccines through policy-making by creating a modern-day *sakoku* has been beneficial or detrimental to public health conditions in Japan is unclear, and goes to the

heart of the fundamental debate over vaccination itself and the role that the state should play.

Notes

- 1 J. P. Baker, 'Immunization the American Way: 4 Childhood Vaccines', *American Journal of Public Health*, 90 (February 2000), p. 199.
- 2 M. Akazawa, J. Yongue, S. Ikeda and T. Satō, 'Considering Economic Analyses in the Revision of the Preventive Vaccine Law: A New Direction for Health policy-making in Japan?' *Health Policy*, 118 (2014), pp. 127–34.
- 3 'Japan: Universal Health Care at 50 years', *The Lancet* (11 August 2011), www.thelancet.com/series/japan (accessed 16 September 2015).
- 4 On 22 January 2014, the Centers for Disease Control and Prevention issued a 'Level 2 Alert' for travellers to Japan due to a rubella outbreak (14,357 cases since early 2013, compared to 2,353 cases in 2012). Also see 'Nationwide Rubella Epidemic – Japan, 2013', www.cdc.gov/mmwr/preview/mmwrhtml/mm6223a1.htm (accessed 31 July 2014); www.nc.cdc.gov/travel/notices/alert/rubella-japan (accessed 25 February 2014). See extensive Japanese media coverage of the HPV vaccine due to the increase in adverse events (1,968 cases since approval), which surpassed those of other developed nations. 'Health Ministry Withdraws Recommendation for Cervical Cancer Vaccine', *Asahi Shimbun* (English version) (15 June 2013), https://ajw.asahi.com/article/behind_news/social_affairs/AJ201306150057 (accessed 25 February 2014).
- 5 Y. Kobayashi, 'Discovery of the Causative Organism of Weil's Disease: Historical View', *Journal of Infection Chemotherapy*, 7:1 (2001), pp. 10–15.
- 6 Noguchi did not benefit from a government scholarship as Kitasato and others did, and left to study in the United States under Simon Flexner rather than Germany. Best known for his 1911 discovery of the agent causing syphilis and his extensive work on tropical diseases, Noguchi also directly contributed to the development of new vaccines such as those for snakebite.
- 7 J. R. Bartholomew, *The Formation of Science in Japan: Building a Research Tradition* (New Haven, CT: Yale University Press, 1989), p. 100.
- 8 C. Gradmann (translation by Elborg Forster), *Laboratory Disease: Robert Koch's Medical Bacteriology* (Baltimore, MD: Johns Hopkins University Press, 2009), p. 122.
- 9 For information regarding the close relationship between Kitasato and Koch, see Mariko Ogawa, 'Robert Koch's 74 Days in Japan', *Kleine Reihe* 27

- (Mori Ogai-Gedenkstätte der Humboldt-Universität zu Berlin, 2003). <http://edoc.hu-berlin.de/series/kleine-reihe/27/PDF/27.pdf#search=shrine+kitasato+koch> (accessed 25 February 2014).
- 10 T. Kodaka, *Densenbyō Kenkyūsho: Kindai Igaku Kaitaku no Michinori* (The Institute for Infectious Diseases: Forging a Path to Modern Medicine) (Tokyo: Gakkai Shuppan Sentā, 30 November 1992), p. 43.
 - 11 Bartholomew, *The Formation of Science in Japan*, p. 101.
 - 12 *Ibid.*, p. 122; M. Miyajima, *Kitasato Shibasaburō den* (Biography of Kitasato Shibasaburō) (Tokyo, 1933), p. 115.
 - 13 S. Yamazaki and I. Kurane (eds), *Nihon no Wakuchin Kaihatsu to Hinshitsu Kanri no Rekishiteki Kenshō* (Japanese Vaccine: An Investigation of the History of Development and Quality Control) (Tokyo: Iyaku jyānaru, 2014), pp. 26–8.
 - 14 Editing Committee of the 50-Year History of the Ministry of Health and Welfare (eds), p. 1070. Other examples of Japanese discoveries include the causative agent for tularaemia (by Ohara Hachirō, research published in 1925), scrub typhus (Nagayo Mataro, Tamiya Takeo, 1924) and vibrio parahaemolyticus food-borne infection (Fujino Tsunesaburō, 1950).
 - 15 Supreme Commander for Allied Powers, General Headquarters, *Summation of Non-Military Activities in Japan and Korea, 1945–1948*, no. 1, section 1 (1945), 1–2 (Tokyo: National Diet Library).
 - 16 M. Watanabe, 'Wagakuni no yobōsesshu seido nitsui no rekishiteki ichikōsatsu' (A historical consideration about the Preventive Vaccination Law Constituted in 1948), *Minozoku eisei*, 73–6 (2007), p. 244.
 - 17 Pharmaceutical and Medical Device Regulatory Science Society of Japan (eds), *Drug-Induced Suffering in Japan: A Review from Regulatory and Social Perspectives* (English title of bilingual volume) (Tokyo: Yakuji Nippō, 2013), p. 11. The 3,000-yen fine was costly given that a national civil servants' monthly salary was 13,000 yen.
 - 18 J. Yongue, *The Introduction of American Mass Production Technology to Japan during the Occupation: The case of penicillin*, in P. Donzé and S. Nishimura (eds), *Organizing Global Technology Flows* (New York and London: 2014), pp. 213–29.
 - 19 Watanabe, 'Wagakuni no yobōsesshu seido nitsui no rekishiteki ichikōsatsu', p. 249.
 - 20 M. Wake, 'Cause Analysis of the 1948 Diphtheria Tragedy', *Bulletin of Social Medicine*, 23 (2005). Also see M. Kurokawa and R. Murata, 'On the Toxicity of the "Toxoid" Preparation Responsible for the Kyoto Catastrophe in 1948', *Japanese Journal of Medical Science & Biology*, 14 (1961), pp. 249–56. Both articles were published over a decade after the occupation ended.

- 21 S. Yamazaki and I. Kurane (eds), *Nihon no Wakuchin Kaihatsu to Hinshitsu Kanri no Rekishiteki Kenshō* (Japanese Vaccine: An Investigation of the History of Development and Quality Control) (Tokyo: Iyaku jyānarū, 2014), p. 31.
- 22 The threat of a large fine served as a deterrent as there are no records of actual collection.
- 23 C. Aldous, 'Transforming Public Health?: A Critical Review of Progress Made Against Enteric Diseases During the American-led Occupation of Japan (1945–52)', *Nihon Igaku Zasshi*, 54:1 (March 2008), pp. 9–16.
- 24 M. Hirayama, 'Porio Wakuchin no Kinkyūdōnyū no Keii to sonogono Porio' (Hirayama's English title: 'Progress on Urgent Introduction of Live Polio Vaccine in Japan and Poliomyelitis Thereafter'), *Journal of the Japan Society for Paediatric Infectious Diseases* (in Japanese), 19:2 (2007), pp. 189–96, on p. 193.
- 25 Hirayama, 'Porio Wakuchin no Kinkyūdōnyū no Keii to sonogono Porio', p. 193.
- 26 Interview with Dr Abe Shinobu, Executive Director, laboratory division at Japan Poliomyelitis Research Institute, Tokyo, on 20 February 2014.
- 27 A. Otani, K. Mise and K. Tanaka, *Wakuchin to yobōsesshu nosubete: Minaosareru sono miryoku* (Introduction to Vaccines and Vaccination Remarkable Effects Recently Recognized) (Tokyo: Kanehara Shuppan, 2013), p. 40.
- 28 S. Yamazaki and S. Abe, 'Nihon niokeru fukatsuka porio wakuchin (sIPV) Kaihatsu no keii to genjō' ('Development of Sabin strain-derived inactivated poliovirus in Japan'), *BIO clinica*, 26:13 (2011), pp. 45–51.
- 29 US health authorities switched to IPV over a decade earlier on 1 January 2000.
- 30 Otani, Mise and Tanaka, *Wakuchin to yobōsesshu no subete: Minaosareru sono miroku*, pp. 59–60.
- 31 K. Kobayashi, 'Wakuchin no Kōshinkoku, Nihon' (Japan, Backward Nation for Vaccines), *Journal of the Japan Society for Pediatric Infectious Diseases* (in Japanese), 20:4 (2008), p. 445–6. See also, R. Shimazawa and M. Ikeda, 'The Vaccine Gap between Japan and the UK', *Health Policy*, 107 (2012), pp. 312–7; A. Saitoh and N. Okabe, 'Current Issues with the Immunization Program in Japan: Can we Fill the "Vaccine Gap"?', *Vaccine*, 30:32 (2012), pp. 4752–6.
- 32 M. Hosoda, H. Inoue, Y. Miyazawa, E. Kusumi and K. Shibuya, 'Vaccine-Associated Paralytic Poliomyelitis in Japan', *The Lancet*, 379:9815 (11 February 2012), p. 520.
- 33 *Ibid.*

- 34 Y. Tezuka, *Sengō gyōsei no kōzō to dikenma: Yōbōsesshu gyōsei no hensen* (The Structural Dilemma of Post-war Public Administration: Changes in Preventive Vaccination Policy) (Tokyo: Fujiwara Shoten 2010), p. 238.
- 35 Y. Okuno *et al.*, 'Uirusubyō no yobō chiryō ni kansuru kenkyū no ayumi' (Research on the History of Prevention and Treatment of Viral Diseases), *Virus* 28 (commemorative issue, 1978). www.jstage.jst.go.jp/article/jsv1958/28/Special/28_Special_73/_pdf (accessed 27 October 2015).
- 36 *Ibid.*
- 37 See *Canada Diseases Weekly*, 13–35 (5 September 1987) and 14–46 (11 November 1988).
- 38 According to H. Ueno, whose daughter was vaccinated in 1991, during her hospital visit, the infant's grandmother requested separate inoculations but due to the physician's strong insistence, she reluctantly agreed to use MMR. 'MMR Wakuchin no Jittai' (The actual conditions surrounding the adverse effects of the MMR vaccine), in Pharmaceutical and Medical Device Regulatory Science Society, *Shitte okitai Yakugai no Kyōkun* (Lessons to Learn About the Harmful Effects of Medicines) (Tokyo: Yakuji Nippōsha, 2012).
- 39 Tezuka, *Sengō gyōsei no kōzō to direnma*, p. 238.
- 40 M. C. Andrae, G. L. Freed and S. L. Katz, 'Safety Concern Regarding Combination Vaccines: Experience in Japan', *Vaccine*, 22 (2004), pp. 3911–16, on pp. 3913.
- 41 H. Ueno, 'MMR Wakuchin no Jittai' (The Status of the MMR Vaccine), in Pharmaceutical and Medical Device Regulatory Science Society, *Shitte okitai Yakugai no Kyōkun* (Lessons to Learn About the Harmful Effects of Medicines), (Tokyo: Yakuji Nippōsha, 2012), p. 113.
- 42 The municipality of Kokubunji decided in October to switch from MMR to measles and only administered MMR when there was a 'strong request from the parent/guardian'. Osaka, Shiga Prefecture, Kyoto and Nara Prefectures took measures to discourage the use of MMR, while Wakayama and Hyogo continued administer it.
- 43 Tezuka, *Sengō gyōsei no kōzō to direnma*, p. 243.
- 44 *Ibid.*, p. 244.
- 45 Ueno, *MMR Wakuchin no Jittai* (The Status of the MMR Vaccine), pp. 116–17.
- 46 *Ibid.*, p. 122.
- 47 S. A. Plotkin, 'Commentary: Is Japan Deaf to the Mumps Vaccination?' *Pediatric Infectious Disease Journal*, 28 (2009), p. 176.
- 48 MHLW, *Wakuchin Sangyō Bijon Kanseishō Taisaku wo sasae, shakaiteki kitai ni kotaeru sangyōzō wo mezashite*, p. 23.

- 49 Y. Sato and H. Sato, 'Development of Acellular Pertussis Vaccines', *Biologicals*, 27 (1999), pp. 61–2. Also S. Yakazaki and I. Kurane (eds), 'Nihon no Wakuchin: Kaihatsu to Hinshitsu Kanri no Rekishi Kenshō', pp. 62–7. Based on the findings of Sato Yūji at the Japanese National Institutes of Health, a 'national project' with collaboration by paediatricians, health authorities and scientists at the six production establishments got underway to develop a safer pertussis vaccine. Sato's acellular pertussis vaccine is now administered worldwide and is particularly recognised in China, where it is known as the 'Sato vaccine'. Sato's personal experiences in developing the pertussis vaccine are described in: Y. Sato, 'Nihon de Kaihatsu sareta seisei hakunichi seki wakuchin no kisokenkyū, kaihatsukatei oyobi donyugo no ugoki (Basic Research and Development of Purified Pertussis Vaccine in Japan, the Vaccine and Thereafter)', *Shonikansen Meneki*, 20:3 (2008), on pp. 347–58.
- 50 The following two volumes (1778 pages) contain the proceedings of the influenza and polio vaccine trials. K. Nakadaira, M. Ōno, T. Hirota, Y. Yamakawa, M. Akiyama and T. Kōno (eds), *Nihon saibashorui zenshū, Tokyō yobōsesshukashō* (Complete Collection of Japanese Court Records, Tokyo Preventive Vaccination Trials) (Tokyo: Shinzansha, 2005).
- 51 H. Nakatani, T. Sano and T. Iuchi, 'Development of Vaccination Policy in Japan: Current Issues and Policy Directions', *Japanese Journal of Infectious Diseases*, 55 (2002), pp. 101–11, on p. 103.
- 52 According to T. Nakayama, 'Vaccine Chronicle in Japan', p. 788, rates in 2010 for all routine vaccinations (BCG, DTaP, OPV, MR) were between 90 and 95 percent (80 per cent for JEV), but only 30 to 40 per cent for non-routine vaccinations. For more detailed statistical information, see the WHO website: http://apps.who.int/immunization_monitoring/globalsummary/countries?countrycriteria%5Bcountry%5D%5B%5D=JP&commit=OK (accessed 25 February 2014).
- 53 For a full list of the participants and their affiliations, see Ministry of Health, Labour and Welfare, *Wakuchin Sangyō Bijon Kanseishō Taisaku wo sasae, shakaiteki kitai ni kotaeru sangyōzō wo mezashite* (Vaccine Industry Vision: Supporting Measures to Prevent Infection while Aiming to Respond to Societal Expectations of Industry) (MHLW, March 2007), pp. 2–3.
- 54 Institute of Medicine Division of Health Promotion and Disease Prevention (eds), *Vaccine Supply and Innovation* (Washington DC: National Academy Press, 1985), p. vi.
- 55 Ministry of Health, Labour and Welfare, *Wakuchin Sangyō Bijon Kanseishō Taisaku wo sasae, shakaiteki kitai ni kotaeru sangyōzō wo mezashite*, p. 31; p. 15.

- 56 Akazawa, Yongue, Ikeda and Satō, 'Considering Economic Analyses in the Revision of the Preventive Vaccine Law', pp. 127–34.
- 57 *Ibid.*
- 58 www.who.int/immunization/policy/Immunization_routine_table1.pdf (accessed 25 February 2014).
- 59 H. Kamiya, S. Uehara, T. Kato, K. Shiraki, T. Togashi, T. Morishima, Y. Gotō, O. Satō and S. Standaert, 'Childhood Bacterial Meningitis in Japan', *Pediatric Infectious Disease Journal*, 17:9 (September 1998), pp. 183–5.
- 60 J. Yongue, 'Shin'yaku Kaihatsu wo meguru kigyō to gyōsei' (Corporate Development of New Drugs and Drug Policy) in A. Kudō and M. Ihara (eds), *Kigyō to Gendai no Shihonshugi (Enterprises and Modern Capitalism)* (Kyoto: Minerva Shobō, 2008), pp. 166–91 and W. H. Kuo, 'Japan and Taiwan in the Wake of Bio-Globalization: Drugs, Race and Standards' (PhD dissertation, Massachusetts Institute of Technology, September 2005). See also, www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073120.pdf (accessed on 21 July 2014).
- 61 This has not always been the case. Physicians have been able to influence policy by refusing to administer vaccinations. Tezuka, *Sengyō Gyōsei no Kozō to Direnma*, pp. 178–82.
- 62 www.mhlw.go.jp/shingi/2008/12/dl/s1225-14l.pdf#search=サノフィ国家検定 (accessed on 5 March 2012).
- 63 'The "Two-Month Wait" and Barrier of Having to Bear the Cost Yourself: The Ban on the Hib Vaccine is Finally Lifted' (Nikagetsu machi to jibara no kabe: yatto kaikin sareta hib wakuchin), *Weekly Aera* (9 March 2009), p. 76.
- 64 Interview with former head of Pasteur Mérieux Connaught Daiichi in Lyon, France on 17 June 2011.
- 65 This point was made during numerous interviews with current and previous managers at Sanofi Pasteur. The same problem of black specks is mentioned in Roy Vagelos and Louis Galambos, *Medicine, Science, and Merck*, (Cambridge University Press, 2004), p. 190.
- 66 Interview with Professor Ueda Shigeharu (executive director of Biken or the Institute for Microbial Diseases, Osaka University) and Professor Nojima Hiroshi on 4 August 2011 at the University of Osaka and observations I made during a visit to the Biken factory in Kagawa, Shikoku on 15 November 2011.