J Infect Chemother
DOI 10.1007/s10156-013-0641-6

REVIEW ARTICLE

Vaccine chronicle in Japan

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Received: 2 May 2013

Abstract The concept of immunization was started in Japan in 1849 when Jenner's cowpox vaccine seed was introduced, and the current immunization law was stipulated in 1948. There have been two turning points for amendments to the immunization law: the compensation remedy for vaccine-associated adverse events in 1976, and the concept of private vaccination in 1994. In 1992, the regional Court of Tokyo, not the Supreme Court, decided the governmental responsibility on vaccine-associated adverse events, which caused the stagnation of vaccine development. In 2010, many universal vaccines became available as the recommended vaccines, but several vaccines, including mumps, zoster, hepatitis B, and rota vaccines, are still voluntary vaccines, not universal routine applications. In this report, immunization strategies and vaccine development are reviewed for each vaccine item and future vaccine concerns are discussed.

Keywords Vaccine · Surveillance · MMR · DPT · Voluntary vaccines · Recommended vaccines

Abbreviations

ACIP	Advisory Committee on Immunization Practices
BCG	Bacillus Calmette–Guérin
DTaP	Acellular pertussis vaccine combined with diphtheria and tetanus toxoids
DTwP	Whole cell pertussis vaccine combined with diphtheria and tetanus toxoids
FHA	Filamentous hemagglutinin
HA	Hemagglutinin
HBV	Hepatitis B virus vaccine
Hib	*Haemophilus influenzae* type b conjugated with tetanus toxoid
HPV	Human papilloma virus vaccine
JEV	Japanese encephalitis vaccine
IPV	Inactivated polio vaccine
LAMP	Loop-mediated isothermal amplification
MMR	Measles, mumps, and rubella-combined vaccine
MR	Measles and rubella-combined vaccine
NA	Neuraminidase
NT	Neutralization test
OPV	Live oral polio vaccine
PCV7	7-valent *Streptococcus pneumoniae* conjugated vaccine with recombinant diphtheria toxoid
PT	Pertussis toxin
Tdap	Tetanus toxoid combined with a reduced concentration of diphtheria toxoid and acellular pertussis
VAP	Vaccine-associated paralytic polio
VZV	Varicella zoster virus vaccine

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Dawn of vaccines in Japan

The dawn of vaccinology was the first scientific systematic investigation of the cowpox vaccination by Edward Jenner in 1796, although several variations in approach were performed using dried pus from smallpox skin lesions in Central Asia, China, and Turkey [1]. Jenner's cowpox vaccination procedure was introduced into Japan in the Edo era by Philipp F.B. von Siebold. Sporadic nationwide outbreaks occurred at that time, which caused social, economic, and political stagnation, and doctors of herbal traditional medicine, studying Western modern medicine, wanted to use Jenner's cowpox vaccine as a preventive

Published online: 09 July 2013

procedure for smallpox. Many attempts were made to import the cowpox seed, but these did not succeed because Jenner's cowpox vaccine is a live vaccine: it was inactivated during long-term transportation or if the inoculation chain in children was interrupted. It was finally introduced to Nagasaki in 1849, bringing the vaccination scar through the idea proposed by Dr. Souken Narabayashi, who was the chief doctor of Nabeshima-Han (Saga Prefecture). The vaccination procedure became available at the Shutousyo (Vaccination Institute) in Osaka and Edo cities, which was the origin of the School of Medicine of Osaka and Tokyo Universities [2]. Jenner's cowpox vaccine gained in popularity because of its distinct effectiveness against smallpox. However, some opinions were against vaccination because of misunderstanding involving unreasonable and nonscientific rumors, as has recently been observed.

The Japanese government in the Meiji era decided that all Japanese people should be immunized with the vaccine for smallpox, which was stipulated in 1876, and a vaccination law against smallpox started in 1910. The present immunization law was implemented in 1948 under occupation by the United States (US). Issues related to vaccine development and immunization policies are summarized in Table 1. There have been two turning points for amendments to the immunization law: the compensation remedy for vaccine-associated adverse events in 1976, and the concept of private vaccination in 1994. These two turning points were attributed to vaccine-associated adverse events or accidents and lawsuits against serious neurological adverse events after immunization with vaccinia and the measles, mumps, and rubella-combined vaccine (MMR) [3]. In 1992, the regional Court of Tokyo, not the Supreme Court, set the governmental responsibility for vaccine-associated adverse events because the government did not make an effort to enlighten the public and doctors by explaining the possible adverse events associated with vaccinations, even though immunization was recommended to be compulsory [3]. This lack of information was a major reason why the government was reluctant to take active immunization strategic action, leading to the so-called long-term vaccine gap after the discontinuation, in 1993, of MMR, which had been introduced in 1989, because of the unexpectedly high incidence of aseptic meningitis caused by mumps vaccine components [4, 5]. The mechanisms behind the higher incidence of aseptic meningitis with the combined live MMR vaccine than with monovalent mumps vaccines were not clearly identified. Thereafter, new vaccines were not introduced, but many pediatric vaccines have been approved in developed countries, with the implementation of recommended vaccines, which shows that vaccine-preventable diseases should be controlled with available vaccines

Table 1 History of immunization and vaccine development in Japan

1948: Immunization Law [Smallpox, Diphtheria, Typhoid fever, Salmonella Paratyphi, Pertussis, Tuberculosis, Typhus, Plague, Cholera, Scarlet fever, Influenza, Leptospirosis]	
1951: Preventive law against tuberculosis.	
1961: The polio vaccine was recommended.	
1962: School immunization with the influenza vaccine	Adverse events after the smallpox vaccination 1968–1970
1968: DPwT was recommended vaccination 1968–1970	
1976: Amendment of the immunization law for a compensation remedy for adverse events: Recommended obligatory [Smallpox, Diphtheria, Tetanus, Pertussis, Polio]; Temporarily [influenza, JEV]	DPT accidents 1974–1975
1977: The rubella vaccine was recommended.	
1978: The measles vaccine was recommended.	
1980: Eradication of smallpox and stopped being used.	
1981: The mumps vaccine was licensed.	MMR scandal 1989–1993
1985: The hepatitis B vaccine was licensed for the prevention of vertical transmission in1986.	
1994: Ammendment for private vaccination: Recommended [DPT, Polio, Measles, Rubella, JEV] Voluntary [influenza, VZV, Mumps]	
1995: The hepatitis A vaccine was licensed,	
2001: The influenza vaccine was recommended for the elderly >65 years.	
2005: BCG was recommended for infants 0–6 months of age.	JEV ADEM 2005
2005: The JEV vaccination was interrupted until 2009 and a booster at 14 years was stopped.	
2006: The two-dose schedule was started, using the MR combined vaccine.	
2009: Pandemic 2009 vaccines were imported from GSK and Novartis.	
2010: Hib, PCV7, and HPV were temporarily recommended.	

DPwP Whole cell pertussis vaccine combined with diphtheria and tetanus toxoids, *JEV* Japanese encephalitis virus vaccine, *MMR* Measles, mumps and rubella-combined vaccine, *VZV* Varicella zoster virus vaccine, *ADEM* Acute disseminated encephalomyelitis, *Hib* Haemophilus influenzae type b vaccine, *PCV7* 7-valent Str. pneumoniae vaccine, *HPV* Human Papilloma virus vaccine