A Review of Factors Affecting Vaccine Preventable Disease in Japan

Norimitsu Kuwabara MD and Michael S.L. Ching MD, MPH

Abstract

Japan is well known as a country with a strong health record. However its incidence rates of vaccine preventable diseases (VPD) such as hepatitis B, measles, mumps, rubella, and varicella remain higher than other developed countries. This article reviews the factors that contribute to the high rates of VPD in Japan. These include historical and political factors that delayed the introduction of several important vaccines until recently. Access has also been affected by vaccines being divided into government-funded "routine" (eg, polio, pertussis) and self-pay "voluntary" groups (eg, hepatitis A and B). Routine vaccines have higher rates of administration than voluntary vaccines. Administration factors include differences in well child care schedules, the approach to simultaneous vaccination, vaccination contraindication due to fever, and vaccination spacing. Parental factors include low intention to fully vaccinate their children and misperceptions about side effects and efficacy. There are also provider knowledge gaps regarding indications, adverse effects, interval, and simultaneous vaccination. These multifactorial issues combine to produce lower population immunization rates and a higher incidence of VPD than other developed countries. This article will provide insight into the current situation of Japanese vaccinations, the issues to be addressed and suggestions for public health promotion.

Keywords

immunization, Japan, vaccination rates, voluntary vaccines, vaccine preventable disease

Introduction

Japan ranks among the world leaders in the health of its citizens. The Japanese have the longest life expectancy and number of years lived in full health.[1] Japan is among the leaders in the developed world in low obesity rates and low infant and cardiovascular disease mortality.[2–4] The World Health Organization (WHO) ranked Japan first in overall health goal attainment among 191 countries in its most recent rankings in 2000.[5]

In stark contrast to these positive health indicators, Japan is also well known as a country with persistently high rates of vaccine preventable diseases (VPD) such as hepatitis B, measles, rubella, mumps, and varicella.[6–8] The 2012-2013 rubella outbreak in Japan caused about 15,000 cases of rubella and 43 cases of congenital rubella syndrome.[9] In June 2013, the US Centers for Disease Control (CDC) released an advisory against travel to Japan for expectant mothers who are not rubella-immune because of the risk of congenital rubella syndrome.[10]

People traveling from Japan have also repeatedly brought VPD overseas with them.[11,12] Japan accounted for more measles importation to the United States than any other single country between 1993 and 2001.[13] Between 1994 and 2013 there were 32 cases of measles, 156 cases of mumps and 16 cases of rubella imported to Hawai'i from Japan.[14]

Why are VPD so common in Japan? Japan is among the wealthiest countries in the world, has universal health care, and has access to the same vaccines as other developed countries. This paper seeks to review the historical and systemic factors that have affected the rates of VPD in Japan and offers suggestions for public health intervention.

Recent Historical Context

The Japanese Preventive Immunization Law enacted in 1948 made vaccination a duty of parents and physicians. In 1970, because of public concern in part due to smallpox vaccine adverse events, the Japanese government organized a compensation system for injuries for vaccinations carried out under the vaccine law.[15] This led to increased scrutiny of adverse events associated with other vaccines such as the pertussis vaccine.

In the 1940s, the estimated mortality rate by pertussis in Japan was more than 10,000 per year.[16] Whole cell pertussis vaccination was initially introduced in 1950. Combined diphtheria, tetanus, and pertussis vaccination, with whole cell pertussis component (DTwP) was introduced in Japan in 1968. Pertussis mortality dramatically decreased to 206 deaths in 1971, and no deaths by pertussis were reported by 1974. Nevertheless there were concerns about adverse effects because more than half of vaccinated patients complained of local redness, swelling, and fever.[17]

When two infants died within 24 hours of receiving DTwP in the winter of 1974-1975, the government suspended licensure of DTwP. Licensure was reinstated two months later with a change in the minimum recommended age from 3 months to 2 years as a precaution.[15] Vaccination rates in young children fell dramatically, and the incidence of pertussis increased to 13,105 cases with 41 deaths by 1979.[15] Japanese researchers then developed the first acellular pertussis vaccine, and it was added to the routine vaccination program as combined DTaP in 1981. In the subsequent decade, the incidence of pertussis fell back to nearly the same rates as before 1975.

The next major vaccine issue began in 1987 when the measles, mumps, rubella (MMR) vaccine was approved for use in Japan. Shortly after its introduction this version of MMR was linked to aseptic meningitis due to the *urabe* strain of the mumps vaccine.[18] Subsequently, in 1993, the combination MMR vaccine was discontinued and replaced with separate measles, mumps, and rubella vaccines.[19,20] This incident caused significant public scrutiny of all vaccinations and swayed the prevailing political attitude towards a more cautious approach.

In addition to the pertussis and MMR events, the Japanese government was sued several times in the 1980s and 1990s due to vaccine adverse events.[19] Pressure by citizens and medical professionals led to the 1994 modification of the Preventive

Immunization Law to make vaccination an individual responsibility instead of a mandatory act.[17] Mass vaccination in regional Public Health Centers was replaced by vaccination by private physicians.

Adoption Rate of New Vaccines

After the discontinuation of MMR and the change in the Preventive Immunization Law, new vaccines were introduced in Japan at much slower rates than in other developed countries. Between 1993 and 2007 there was a "vaccine gap", and only two new vaccines were brought to the Japanese market (hepatitis A and a combination measles and rubella vaccine).[19] In contrast, 17 new vaccines were introduced over the same time frame in the United States.[19]

Several important vaccines were delayed by years during this time including *Haemophilus influenzae* type b (Hib) vaccine, pneumococcal conjugate vaccine (PCV7) and inactivated polio vaccine (IPV). Japan began using Hib and PCV7 in 2009 while the United States licensed these in 1985 and 2000 respectively.[19,21,22] Because of the relatively recent introduction of these important vaccines, Hib meningitis and epiglottitis, and invasive pneumococcal diseases have only recently seen decreases in incidence rates.[23–26]

Live, attenuated oral polio vaccine (OPV) was introduced in Japan in 1960 when there were 5800 cases of paralytic polio reported. By 1980 there were no cases of paralytic polio caused by wild poliovirus; all cases were due to vaccination.[17] The United States replaced OPV with IPV in 2000 because of this concern and the overall low rates of disease. However, this decision occurred during the "vaccine gap" in Japan. IPV was only introduced in Japan in 2012 despite numerous cases of vaccine-associated paralysis and five unvaccinated individuals contracting poliomyelitis from OPV between 2004 to 2008.[27,28]

Despite recent introductions of new vaccines, the Japanese Ministry of Health, Labor, and Welfare (MHLW) has been quick to suspend vaccines. Both Hib and PCV7 were suspended for a month in 2011 because of seven deaths of children that were ultimately found to be unrelated to the vaccines.[17,29] One recent vaccine to enter the Japanese market is the quadrivalent human papillomavirus virus (HPV) vaccine Gardasil. This was added in April 2013 following US licensure of Gardasil in 2006. However only two months after becoming available in Japan, the government ordered providers to cease active promotion of this vaccine and Cervarix (human papillomavirus bivalent vaccine) because of fears of complex regional pain syndrome.[30] HPV vaccination is under further investigation in Japan and may be withdrawn from the market despite ongoing use in the United States and other countries, drawing parallels to the DTwP and MMR events decades earlier.[30]

Multiple Vaccine Systems

Japan has a universal health care system that provides access to health for all citizens. However there are two kinds of vaccine systems in Japan, routine vaccination and voluntary vaccination (Table 2). The government pays for routine vaccinations while families must pay for voluntary vaccinations. Costs vary by vaccine (Table 3). In Japan the list of voluntary vaccinations includes hepatitis A, hepatitis B, influenza, and mumps.

Japanese rates of routine vaccinations are among the highest in the world. For example, in 2013, the rate of vaccination with three doses of DTP in Japan was estimated to be >99.5%, compared with 94% in the United States.[31] Despite prior challenges with rubella coverage, in 2013, 95% of eligible Japanese children reportedly received one dose of rubella vaccine compared with 91% in the United States.[31]

On the other hand, voluntary vaccines have lower rates of administration than routine vaccinations.[32,33] In a Japanese survey conducted in the second half of 2011, only 53% of 18 month old children were reported to be vaccinated against Hib, 43% against pneumococcus, and 1.3% against hepatitis B.[33] This compares with rates of 90%, 92% and 92% respectively for these vaccinations in the United States.[31] At the time of that

Table 1. Reported Incidence of Vaccine Preventable Diseases in the United States and Japan in 2011.

Disease	United States		Japan	
	2011 reported cases[a]	Incidence/100,000 population[b]	2011 reported cases[31]	Incidence/100,000 population[b]
Measles	220	0.06	434	0.34
Diphtheria	0	0	0	0
Pertussis	18,719	6.0	4,395	3.44
Rubella	4	0.0013	369[c]	0.29
Polio (paralytic)	0	0	0	0
Tetanus	36	0.012	116	0.091
Mumps	404	0.13	137,060	107

[a] Adams DA, Gallagher KM, Jajosky RA, et al. Summary of Notifiable Diseases - United States, 2011. *MMWR Morb. Mortal. Wkly. Rep.* 2013;60(53):1-117.

[b] Projections for 2011, estimated using US Census* and Japan National Institute of Population and Social Security Research.**

[c] This number does not reflect the ongoing rubella epidemic in Japan. There were 3,936 laboratory confirmed cases of rubella in January-May 2013 in Japan including 10 cases of congenital rubella syndrome.[6]

* Population Clock. Available at: http://www.census.gov/popclock/. Accessed February 10, 2014.

** Department of Population Dynamics Research. *Population Projections for Japan (January 2012): 2011 to 2060.* National Institute of Population and Social Security Research; 2012:45. Available at: http://www.ipss.go.jp/site-ad/index_english/esuikei/ppfj2012.pdf. Accessed February 10, 2014.

Table 2. Comparison of Vaccines Between Japan and United States		
	Japan	United States
H. influenzae type b (Hib)	○	○
Pneumococcus (PCV)	○	○
Diphtheria	○	○
Pertussis	○	○
Tetanus	○	○
Polio (inactivated)	○	○
Human papillomavirus (HPV)	○	○
Measles	○	○
Rubella	○	○
Mumps	▲	○
Varicella	Δ	○
Hepatitis A	▲	○
Hepatitis B	▲	○
Rotavirus (oral)	▲	○
Influenza	▲	○
Tuberculosis (BCG)	○	×
Japanese encephalitis	○	×
Meningococcus	×	○

○ = Routine vaccine ; ▲ = Voluntary vaccine (Δ = Varicella will become a routine vaccine in October 2014); × = Vaccine not ordinarily available.

Table 3. Approximate Costs for Voluntary Vaccines in Japan			
	Cost per vaccination (varies by area, these examples are provided for illustration[a])	**Number of Doses**	**Cost for the vaccine series ($'s only)**
Mumps	¥6,000 (US $60)	2	$120
Varicella	¥8,000 (US $80)	2	$160
Hepatitis A	¥6,800 (US $68)	2	$136
Hepatitis B	¥5,000 (US $50)	3	$150
Rotavirus Rotarix	¥15,000 (US $150)	2	$300
RotaTeq	¥10,000 (US $100)	3	$300
Influenza	¥2,500 (US $25)	1 (annual)	$25
Human papilloma virus (Cervarix or Gardasil)	¥16,000 (US $160)	3	$480
		Total Out of Pocket Costs	$1371

[a]Aozora Children's Hospital. Vaccinations (in Japanese). Available at: http://aozora-chiho.jp/vaccination/. Accessed September 2, 2014.

study, Hib and pneumococcal vaccines were voluntary vaccines and did not become routine until April 2013.

Part of the lower rate of vaccination with voluntary vaccines may be cost. Vaccine expense was cited as the most common discouraging factor among families not receiving voluntary vaccinations.[33] In one study on HPV vaccine, 93% of mothers reported that they would accept the vaccine if it were free but only 1.5% would accept it at the recommended price of 40,000 yen (~US $390).[34] In another study 20% of adults reported that they were unable to afford the influenza vaccine.[35] Having free and non-free sets of vaccinations affects access and also communicates explicit government endorsement and prioritization of routine vaccinations.

A result of the lower rates of vaccination for voluntary vaccines is ongoing outbreaks of vaccine preventable diseases. Rotavirus has experienced significant declines in countries adopting universal vaccination programs, while Japan experiences ongoing seasonal outbreaks of this disease.[36,37] Annual acute hepatitis B incidence in Japan was estimated to be 1.7-1.9 per 100,000 in 2007-2008.[38] In the United States where hepatitis B vaccination rates exceed 90%,[31] the incidence has fallen from 11.5 per 100,000 to about 1.5 per 100,000 in 2007 and has continued to fall to about 0.9 per 100,000 in 2011.[39–41]

Schedule of Well Child Care and Vaccination Issues

The schedule for well child care may also present barriers to vaccination. In Japan, children are usually seen at 1 month of age, 4 months, 10 months, 18 months, and 3 years. This frequency may be insufficient to cover every vaccine. Parents may not bring their children for vaccines between well visits because they are busy working even when pediatricians open "immunization clinic" hours for patients.

The Japanese approach to vaccination in children with mild fevers may also contribute to missed opportunities for vaccination. The Japanese Immunization Vaccination Law does not allow vaccination if patients have a body temperature more than 37.5° C (99.5° F).[42] This contrasts with the recommended practice in the United States, where there is not a specific threshold for body temperature. The US Advisory Committee on Immunization Practices (ACIP) recommends basing a decision to vaccinate on the overall clinical impression of the physician instead of a predetermined body temperature.[43] Delaying vaccination of children who have mild fevers at well child visits increases the risk of missed vaccinations.[43,44]

Recommendations about vaccine intervals also vary between the United States and Japan. If an inactivated vaccine or oral live vaccine is given, United States patients can return at any time to receive additional vaccinations if needed.[43] If a parenteral live vaccine is administered, patients should wait at least 28 days before receiving another parenteral live vaccine. In Japan, patients need to wait at least one week for the next vaccination after any inactivated vaccine as well as 28 days for live vaccines.[45]

A waiting period does not typically present an issue if multiple vaccines are given simultaneously, but in Japan multiple vaccines are less often given simultaneously than in the United States. In Japan, there has not historically been a need for simultaneous vaccination because many of the vaccines delivered in early childhood were not available until recently (eg, Hib, PCV) or not on the routine schedule (HBV).[19] Only since the licensure of Hib and PCV has there been an opportunity to deliver multiple routine vaccines on the same day, but there are still reports of hesitation among families and providers to do so.[46] Providing a combination vaccine might ameliorate this issue, but such vaccines are limited to Japanese-produced DTaP, diphtheria-tetanus (DT), and measles-rubella at this time.[19] A diphtheria-tetanus-acellular pertussis plus Sabin derived injectable poliovirus vaccine (DTaP-sIPV) was introduced in November 2012, and may improve coverage but this will not eliminate the need for simultaneous vaccination.[47]

In Japan, vaccinations also must be given within a pre-determined schedule to be covered by the government. If parents do not return within this window, the routine vaccination fee may not be reimbursed.[48] In this situation, patients who miss the window must pay for routine vaccinations themselves, producing a further barrier toward even routine vaccination.

School Requirements

While no federal vaccination laws exist in the United States, all 50 states require certain vaccinations prior to the entry of children into public schools. However, there is no domestic legislation to enforce vaccination for children entering school in Japan. This may result in a missed opportunity for vaccination. Studies following the introduction of varicella vaccine in the United States have shown that school entry requirements increased rates of this vaccination by an estimated 8%-28% within the first year of the mandate.[49,50]

Vaccine Administration Route

Another issue that may affect vaccine effectiveness is the administration route. Japanese law requires subcutaneous administration of most vaccines except HPV.[19] This contrasts to the intramuscular route for many vaccines in other countries. For many vaccinations, intramuscular shots are associated with decreased pain, lower adverse effect rates, and improved efficacy compared to the subcutaneous route.[51,52]

The reason for this preference for subcutaneous vaccination is also rooted in history. The intramuscular route was popular in Japan until the 1970s. The anterior femoral site was the preferred injection location. However, multiple cases of quadriceps contractures were reported around this time.[53] Despite the fact that the main medicines administered intramuscularly in this area were analgesics and antibiotics, not vaccines, these events became a significant social issue. Subsequently, the government changed the Preventive Immunization Law and adopted a cautious stance toward intramuscular administration. This aspect of the law has not been changed in the past 40 years.

Parent and Provider Attitudes toward Vaccination

Lower vaccination rates among voluntary vaccinations may also be driven by parent and provider attitudes. Japanese parents appear to have low intention to vaccinate their children against voluntary vaccines. In one study 33% of mothers reported an intent to fully vaccinate their children with 50% reporting a desire to vaccinate only for specific vaccines.[54] In another study of parents who did not choose voluntary vaccinations, 39% worried about side effects, and 12.9% doubted the vaccine's positive effects.[33] Ten percent were motivated to acquire natural resistance to some voluntary vaccine pathogens (eg, varicella) despite the low likelihood of developing natural immunity to other voluntary vaccine pathogens (eg, hepatitis B).

Health professionals may also have misperceptions of vaccines.[55] Japanese medical providers do not always have a basic knowledge of vaccines such as the adverse effects, indication of vaccination, interval, or possibility of giving multiple vaccines on the same day.[46] A qualitative study of Japanese resident physicians demonstrated low personal vaccination rates for measles and themes of lack of awareness of disease severity and fear of adverse effects.[46] Additionally large numbers of healthcare workers have been shown to be susceptible to VPD.[56]

Discussion

While there are ongoing issues with vaccine adoption in Japan, there is great hope for progress. Recent changes in vaccine policy have led to licensing of Hib and pneumococcal conjugate vaccines. These vaccines have resulted in significant decreases in invasive *H. influenzae* and pneumococcal disease. The incidence rates of *H. influenzae* meningitis and non-meningitis infections were reduced by 92% and 82% respectively between 2008 and 2012.[26] There have been similar decreases in pneumococcal meningitis (71% decrease) and non-meningitis invasive pneumococcal disease (52% decrease).[57]

Nevertheless, despite the introduction of new vaccines, there are still large numbers of susceptible adults who may serve as a reservoir for ongoing infection. Adults constituted 92% of cases in the 2012-2013 rubella outbreak, and eighty percent of 20-39 year olds who developed rubella had not received the rubella vaccine.[58] Because of prioritization of prior immunization efforts towards women to prevent congenital rubella syndrome, only 73%-86% of adult males demonstrated seropositivity to rubella.[59] To interrupt natural transmission of disease, it is estimated that 87%-99% vaccination rates with rubella vaccine and 95%-99% with measles vaccine are required.[60–62] Because of Japan's high population density, even higher coverage may be required, particularly during an outbreak.

There has been progress towards improving population immunity rates. For example, in 2006, Japan increased the recommended frequency of measles and rubella (MR) vaccine from once to twice due to measles outbreaks in 2001-2002. Because the efficacy of a single dose of measles containing vaccine is estimated at 95%, a two dose schedule is critical for

ensuring that the herd immunity threshold is reached.[63] Other changes such as catch up immunization with MR in 13 and 18 year olds, and public awareness campaigns were started after the development of the National Measles Elimination Plan in 2007.[64] This has resulted in improved protection of children as only 5.6% of rubella cases in the recent outbreak were among children under 15 years old.[6] However, until adult immunization levels increase, herd immunity effects may be limited.

On a political level, there has also been progress. In the United States**,** the ACIP is a federal committee that is mainly composed of specialists who have no interest in pharmaceutical companies. The ACIP evaluates evidence of vaccine efficacy and provides recommendations for their use.[65] The Japanese government recently founded a similar vaccine subcommittee of its MHLW in April 2013.[17,66] The purpose of this subcommittee is to evaluate the efficacy of vaccines and monitor their adverse effects. The MHLW appoints the committee members, and they provide only recommendations rather than set actual policy. Consumer representatives and patients provide only limited input on recommendations. Final policy decisions continue to be made by the MHLW.

Nevertheless the actions of this committee may be able to promote uptake of new and existing vaccines. Since the founding of this subcommittee, the MHLW has decided to shift varicella vaccine from the voluntary to the routine vaccine list starting in October 2014. The remaining voluntary vaccines (eg, mumps, hepatitis B, and rotavirus) will be discussed for inclusion in the list of routine vaccines after the 2015 vaccine subcommittee meetings.[67]

While the number of vaccines has been increasing, there are still barriers to increasing vaccination effectiveness such as rules regarding the route, interval, and payment systems. Increasing the number of government subsidized vaccines, improving the knowledge of physicians and parents, and reforming policies on subcutaneous injection and interval of vaccination may all contribute to improvements in Japanese VPD rates. In addition, public and practice-based vaccine recall strategies, monitoring of voluntary as well as routine vaccine delivery and safety systems, public health campaigns promoting catch-up vaccine coverage for adults, and creating quality or financial incentives for primary care providers to vaccinate children and adults are all strategies that have been recommended in the United States for enhancing vaccination and may be beneficial in Japan.[68,69]

One example for improving parent and provider knowledge would be to standardize vaccination information efforts. In contrast to the national Vaccine Information Statements provided by the CDC in the United States, each municipal government in Japan provides its own vaccination information to citizens based on their own interpretation.[70] This information is not standardized between municipalities. It may be beneficial for the Japanese government to standardize this information and make it widely available to improve parent and provider knowledge.

Another possible area for improvement would be to institute mandatory vaccination requirements for children attending school in Japan. While vaccination rates with the routine vaccines are already high, this would provide an opportunity for reviewing the vaccination status of all children. However, this would constitute a very significant change in public policy, and instituting such a policy, would require the unified support of many stakeholders.

Conclusion

Providers who may see Japanese nationals or their children should be aware of differences in rates of vaccinations. It will be important to carefully review vaccine records as the adults and their children may be missing vaccinations that would be important for disease prevention and school entry. In addition there should be a higher index of suspicion for VPD when these children present with febrile illnesses, especially among tourists or new arrivals to the country. Finally, Japanese parents may have attitudes towards vaccination that differ from many American parents, and providers should be prepared to address potential barriers to vaccination with cultural sensitivity. They should be ready to explain the differences in the vaccine systems in America and Japan.

The views expressed in this manuscript are those of the authors and do not reflect the official policy or position of the Department of the Army, Department of Defense, or the US Government.

Conflict of Interest

None of the authors identify a conflict of interest.

Acknowledgement

The authors wish to thank Mark W. Burnett MD, for his constructive comments and manuscript review.

Authors' Affiliations:
- Pediatric Residency Program, John A. Burns School of Medicine, University of Hawai'i, Honolulu, HI (NK)
- Department of Pediatrics, Tripler Army Medical Center, Honolulu, HI (MSLC)

Correspondence to:
Norimitsu Kuwabara MD; University of Hawai'i Pediatric Residency Program, Kapi'olani Medical Center for Women and Children, 1319 Punahou St., 7th Fl., Honolulu, HI 96826; Ph: (808) 369-1200; Email: nkuwa@hawaii.edu

References

1. World Health Organization. *World Health Statistics 2014*. Geneva, Switzerland: World Health Organization; 2014. Available at: http://apps.who.int/iris/bitstream/10665/112738/1/9789240692671_eng.pdf?ua=1. Accessed August 28, 2014.
2. OECD. Infant Mortality. In: *Health at a Glance 2013: OECD Indicators*. OECD Publishing. Available at: http://dx.doi.org/10.1787/health_glance-2013-11-en. Accessed November 21, 2013.
3. OECD. Overweight and obesity. In: *OECD Factbook 2013: Economic, Environmental and Social Statistics*. OECD Publishing. Available at: http://dx.doi.org/10.1787/factbook-2013-100-en. Accessed November 21, 2013.
4. OECD. Mortality from cardiovascular diseases. In: *Health at a Glance 2013: OECD Indicators*. OECD Publishing. Available at: http://dx.doi.org/10.1787/health_glance-2013-11-en. Accessed November 21, 2013.
5. World Health Organization. *The World Health Report 2000 - Health Systems: Improving Performance*. Geneva, Switzerland; 2000. Available at: http://www.who.int/whr/2000/en/. Accessed November 6, 2013.
6. Centers for Disease Control and Prevention (CDC). Nationwide rubella epidemic--Japan, 2013. *MMWR Morb. Mortal. Wkly. Rep.* 2013;62(23):457-462.
7. Eshima N, Tokumaru O, Hara S, et al. Age-specific sex-related differences in infections: a statistical analysis of national surveillance data in Japan. *PLoS ONE* 2012;7(7):e42261. doi:10.1371/journal.pone.0042261.
8. Hashimoto S, Murakami Y, Taniguchi K, et al. Annual incidence rate of infectious diseases estimated from sentinel surveillance data in Japan. *J. Epidemiol.* 2003;13(3):136-141.

9. Infectious Disease Surveillance Center. *Isolation/detection of Rubella Virus in Japan, 2012-2014 (as of August 26, 2014)*. National Institute of Infectious Diseases; 2014. Available at: http://www.nih.go.jp/niid/en/2013-03-15-04-55-59/2266-disease-based/ha/rubella/idsc/iasr-rubella-e/4945-iasr-rubella-e-140826.html. Accessed September 4, 2014.
10. Rubella (German Measles) in Japan - Alert - Level 2, Practice Enhanced Precautions - Travel Health Notices | Travelers' Health | CDC. 2013. Available at: http://wwwnc.cdc.gov/travel/notices/alert/rubella-japan. Accessed November 6, 2013.
11. Katz SL, Hinman AR. Summary and conclusions: measles elimination meeting, 16-17 March 2000. *J. Infect. Dis.* 2004;189 Suppl 1:S43-47. doi:10.1086/377696.
12. Centers for Disease Control and Prevention (CDC). Measles--United States, 2000. *MMWR Morb. Mortal. Wkly. Rep.* 2002;51(6):120-123.
13. Vukshich Oster N, Harpaz R, Redd SB, Papania MJ. International Importation of Measles Virus—United States, 1993–2001. *J. Infect. Dis.* 2004;189(s1):S48-S53. doi:10.1086/374854.
14. He H. *Personal Communication: Imported Cases from Japan (1994-2013): Measles, Mumps, Rubella*. Disease Outbreak Control Division, Disease Investigation Branch, State of Hawai'i Department of Health; 2014.
15. Noble GR, Bernier RH, Esber EC, et al. Acellular and whole-cell pertussis vaccines in Japan. Report of a visit by US scientists. *JAMA J. Am. Med. Assoc.* 1987;257(10):1351-1356.
16. Sato Y, Sato H. Development of acellular pertussis vaccines. *Biologicals* 1999;27(2):61-69. doi:10.1006/biol.1999.0181.
17. Nakayama T. Vaccine chronicle in Japan. *J. Infect. Chemother.* 2013;19(5):787-798. doi:10.1007/s10156-013-0641-6.
18. Kimura M, Kuno-Sakai H, Yamazaki S, et al. Adverse events associated with MMR vaccines in Japan. *Acta Paediatr. Jpn. Overseas Ed.* 1996;38(3):205-211.
19. Saitoh A, Okabe N. Current issues with the immunization program in Japan: Can we fill the "vaccine gap"? *Vaccine* 2012;30(32):4752-4756. doi:10.1016/j.vaccine.2012.04.026.
20. Why Japan banned MMR vaccine. *Dly. Mail Online*. Available at: http://www.dailymail.co.uk/health/article-17509/Why-Japan-banned-MMR-vaccine.html. Accessed November 21, 2013.
21. College of Physicians of Philadelphia. Haemophilus influenzae type b (Hib) — History of Vaccines. *Hist. Vaccines*. Available at: http://www.historyofvaccines.org/content/articles/haemophilus-influenzae-type-b-hib. Accessed November 21, 2013.
22. Advisory Committee on Immunization Practices. Preventing pneumococcal disease among infants and young children. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm. Rep.* 2000;49(RR-9):1-35.
23. Takeuchi M, Yasunaga H, Horiguchi H, Fushimi K. The burden of epiglottitis among Japanese children before the Haemophilus influenzae type b vaccination era: an analysis using a nationwide administrative database. *J. Infect. Chemother.* 2013;19(5):876-879. doi:10.1007/s10156-013-0585-x.
24. Shinjoh M, Iwata S, Sato Y, Akita H, Sunakawa K. Childhood bacterial meningitis trends in Japan from 2009 to 2010 [in Japanese]. *Kansenshōgaku Zasshi J. Jpn. Assoc. Infect. Dis.* 2012;86(5):582-591.
25. Ubukata K, Chiba N, Morozumi M, Iwata S, Sunakawa K, Working Group of Nationwide Surveillance for Bacterial Meningitis. Longitudinal surveillance of Haemophilus influenzae isolates from pediatric patients with meningitis throughout Japan, 2000-2011. *J. Infect. Chemother.* 2013;19(1):34-41. doi:10.1007/s10156-012-0448-x.
26. National Institute of Infectious Diseases. Invasive Haemophilus influenzae infections in Japan [in Japanese]. *Infect. Agents Surveill. Rep.* 2013;34(7):195-186.
27. Hosoda M, Inoue H, Miyazawa Y, Kusumi E, Shibuya K. Vaccine-associated paralytic poliomyelitis in Japan. *Lancet* 11;379(9815):520. doi:10.1016/S0140-6736(12)60232-3.
28. Murashige N, Matsumura T, Masahiro K. Disseminating Japan's immunisation policy to the world. *Lancet* 2011;377(9762):299. doi:10.1016/S0140-6736(11)60091-3.
29. Rockoff JD. Japan Clears Suspended Vaccines. *Wall Street Journal*. http://online.wsj.com/news/articles/SB10001424052748704604704576221623126167378. Published March 25, 2011. Accessed January 15, 2014.
30. Gilmour S, Kanda M, Kusumi E, Tanimoto T, Kami M, Shibuya K. HPV vaccination programme in Japan. *Lancet* 2013;382(9894):768. doi:10.1016/S0140-6736(13)61831-0.
31. World Health Organization. WHO vaccine-preventable diseases: monitoring system. 2014 global summary. 2014. Available at: http://apps.who.int/immunization_monitoring/globalsummary/. Accessed August 26, 2014.
32. Baba K, Okuno Y, Tanaka-Taya K, Okabe N. Immunization coverage and natural infection rates of vaccine-preventable diseases among children by questionnaire survey in 2005 in Japan. *Vaccine* 2011;29(16):3089-3092. doi:10.1016/j.vaccine.2010.09.022.
33. Tsuda Y, Watanabe M, Tanimoto Y, et al. The Current Situation of Voluntary Vaccination and the Factors Influencing Its Coverage Among Children in Takatsuki, Japan: Focus on Hib and Pneumococcal Vaccines. *Asia. Pac. J. Public Health* 2013. doi:10.1177/1010539513487013.
34. Hanley SJB, Yoshioka E, Ito Y, et al. Acceptance of and attitudes towards human papillomavirus vaccination in Japanese mothers of adolescent girls. *Vaccine* 2012;30(39):5740-5747. doi:10.1016/j.vaccine.2012.07.003.
35. Iwasa T, Wada K. Reasons for and against receiving influenza vaccination in a working age population in Japan: a national cross-sectional study. *BMC Public Health* 2013;13(1):647. doi:10.1186/1471-2458-13-647.
36. Tate JE, Mutuc JD, Panozzo CA, et al. Sustained Decline in Rotavirus Detections in the United States Following the Introduction of Rotavirus Vaccine in 2006: *Pediatr. Infect. Dis. J.* 2011;30:S30-S34. doi:10.1097/INF.0b013e3181ffe3eb.
37. Rotavirus, 2005-2010, Japan. *Infect. Agents Surveill. Rep.* 2011;32(3):61-62.
38. Sako A, Yasunaga H, Horiguchi H, Hashimoto H, Masaki N, Matsuda S. Acute hepatitis B in Japan: Incidence, clinical practices and health policy. *Hepatol. Res.* 2011;41(1):39-45. doi:10.1111/j.1872-034X.2010.00745.x.
39. Centers for Disease Control. Viral Hepatitis Statistics & Surveillance - Surveillance Data for Acute Viral Hepatitis – United States, 2008. Available at: http://www.cdc.gov/hepatitis/Statistics/2008Surveillance/index.htm. Accessed September 4, 2014.
40. Daniels D, Grytdal S, Wasley A, Centers for Disease Control and Prevention (CDC). Surveillance for acute viral hepatitis - United States, 2007. *Morb. Mortal. Wkly. Rep. Surveill. Summ. Wash. DC 2002* 2009;58(3):1-27.
41. Centers for Disease Control. CDC DVH - Viral Hepatitis Statistics & Surveillance - Surveillance for Viral Hepatitis – United States, 2011. 2013. Available at: http://www.cdc.gov/hepatitis/Statistics/2011Surveillance/. Accessed August 27, 2014.
42. Ministry of Health, Labor and Welfare. The implementation guideline for immunizations [in Japanese]. Available at: http://www.mhlw.go.jp/bunya/kenkou/teiki-yobou/07.html. Accessed January 21, 2014.
43. National Center for Immunization and Respiratory Diseases. General recommendations on immunization --- recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm. Rep.* 2011;60(2):1-64.
44. Szilagyi PG, Rodewald LE. Missed opportunities for immunizations: a review of the evidence. *J. Public Health Manag. Pract.* 1996;2(1):18-25.
45. Vaccination Guideline 2013 [in Japanese]. *Found. Vaccin. Res. Cent.* Available at: http://www.yoboseshu-rc.com/index.php. Accessed January 14, 2014.
46. Okamoto S, Slingsby BT, Nakayama T, et al. Barriers to vaccination among Japanese medical students: focus group interviews. *Pediatr. Int.* 2008;50(3):300-305. doi:10.1111/j.1442-200X.2008.02576.x.
47. Okada K, Miyazaki C, Kino Y, Ozaki T, Hirose M, Ueda K. Phase II and III Clinical Studies of Diphtheria-Tetanus-Acellular Pertussis Vaccine Containing Inactivated Polio Vaccine Derived from Sabin Strains (DTaP-sIPV). *J. Infect. Dis.* 2013;208(2):275-283. doi:10.1093/infdis/jit155.
48. Ministry of Health, Labor and Welfare. The immunization act [in Japanese]. Available at: http://www.mhlw.go.jp/topics/bcg/hourei/1.html. Accessed December 22, 2013.
49. Davis MM, Gaglia MA. Associations of daycare and school entry vaccination requirements with varicella immunization rates. *Vaccine* 2005;23(23):3053-3060. doi:10.1016/j.vaccine.2004.10.047.
50. Abrevaya J, Mulligan K. Effectiveness of state-level vaccination mandates: evidence from the varicella vaccine. *J. Health Econ.* 2011;30(5):966-976. doi:10.1016/j.jhealeco.2011.06.003.
51. Cook IF, Barr I, Hartel G, Pond D, Hampson AW. Reactogenicity and immunogenicity of an inactivated influenza vaccine administered by intramuscular or subcutaneous injection in elderly adults. *Vaccine* 2006;24(13):2395-2402. doi:10.1016/j.vaccine.2005.11.057.
52. Wahl M, Hermodsson S. Intradermal, subcutaneous or intramuscular administration of hepatitis B vaccine: side effects and antibody response. *Scand. J. Infect. Dis.* 1987;19(6):617-621.
53. Takara H, Ooki K. Quadriceps Contracture: Case Reports and its Problems [in Japanese]. *Chiba Med. J.* 1975;51(3):151-155.
54. Saitoh A, Nagata S, Saitoh A, et al. Perinatal immunization education improves immunization rates and knowledge: a randomized controlled trial. *Prev. Med.* 2013;56(6):398-405. doi:10.1016/j.ypmed.2013.03.003.
55. Gomi H, Takahashi H. Why is measles still endemic in Japan? *Lancet* 2004;364(9431):328-329. doi:10.1016/S0140-6736(04)16715-9.
56. Hatakeyama S, Moriya K, Itoyama S, et al. Prevalence of measles, rubella, mumps, and varicella antibodies among healthcare workers in Japan. *Infect. Control Hosp. Epidemiol.* 2004;25(7):591-594. doi:10.1086/502444.
57. National Institute of Infectious Diseases. Pneumococcal infections as of March 2013 [in Japanese]. *Infect. Agents Surveill. Rep.* 2013;34(3):55-56.
58. Kato H, Imamura A, Sekiya N, Yanagisawa N, Suganuma A, Ajisawa A. Medical study of cases diagnosed as rubella in adults [in Japanese]. *Kansenshōgaku Zasshi J. Jpn. Assoc. Infect. Dis.* 2013;87(5):603-607.
59. National Institute of Infectious Diseases. Rubella and Congenital Rubella Syndrome in Japan, as of March 2013. *IASR* 2013;34(4):87-89.
60. Gay NJ. The theory of measles elimination: implications for the design of elimination strategies. *J. Infect. Dis.* 2004;189 Suppl 1:S27-35. doi:10.1086/381592.
61. Orenstein WA, Strebel PM, Papania M, Sutter RW, Bellini WJ, Cochi SL. Measles eradication: is it in our future? *Am. J. Public Health* 2000;90(10):1521-1525.
62. Plans-Rubió P. Evaluation of the establishment of herd immunity in the population by means of serological surveys and vaccination coverage. *Hum. Vaccines Immunother.* 2012;8(2):184-188. doi:10.4161/hv.18444.
63. Watson JC, Hadler SC, Dykewicz CA, Reef S, Phillips L. Measles, mumps, and rubella--vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm. Rep. Morb. Mortal. Wkly. Rep. Recomm. Rep. Cent. Dis. Control* 1998;47(RR-8):1-57.
64. Centers for Disease Control and Prevention (CDC). Progress toward measles elimination--Japan, 1999-2008. *MMWR Morb. Mortal. Wkly. Rep.* 2008;57(38):1049-1052.
65. Kamiya H, Okabe N. Leadership in Immunization: the relevance to Japan of the U.S.A. experience of the Centers for Disease Control and Prevention (CDC) and the Advisory Committee on Immunization Practices (ACIP). *Vaccine* 2009;27(11):1724-1728. doi:10.1016/j.vaccine.2009.01.030.
66. Ministry of Health, Labor and Welfare. The minutes at vaccine subcommittee meeting [in Japanese]. Available at: http://www.mhlw.go.jp/stf/shingi/2r98520000008f2q.html#shingi127713. Accessed November 17, 2013.
67. Ministry of Health, Labor and Welfare. The 4th vaccine subcommittee meeting [in Japanese]. 2014. Available at: http://nk.jiho.jp/servlet/nk/related/pdf/1226642404647.pdf. Accessed August 28, 2014.
68. Centers for Disease Control. Immunization Strategies. In: *Epidemiology and Prevention of Vaccine-Preventable Diseases*. 12th ed. Centers for Disease Control; 2012. Available at: http://www.cdc.gov/vaccines/pubs/pinkbook/index.html. Accessed August 28, 2014.
69. Immunization Work Group of the National and Global Public Health Committee of the Infectious Diseases Society of America. Actions to strengthen adult and adolescent immunization coverage in the United States: policy principles of the Infectious Diseases Society of America. *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* 2007;44(12):e104-108. doi:10.1086/519541.
70. Gomi H. Japanese vaccination politics [in Japanese]. *Shukan Igakukai Shimbun Wkly. Med. Community Newsp.* 2003. Available at: http://www.igaku-shoin.co.jp/nwsppr/n2003dir/n2547dir/n2547_03.htm. Accessed November 17, 2013.