TABLE 3. Vaccine efficacy to prevent persistent infections (6-month definition), incident infections, cytological abnormalities, persistent infections (12-month definition), and CIN1+ and CIN2+ associated with 14 oncogenic HPV types*

	Group	N	n	Vaccine Efficacy (95.5% CI), %	P
ATP-E					
Persistent infection (6-mo definition)	Vaccine	424	27	50.6 (19.3–70.5)	0.0022
	Control	422	53		
Incident infection	Vaccine	446	98	31.2 (9.5–47.8)	0.0036
	Control	436	134		
Cytological abnormalities	Vaccine	446	24	43.9 (4.2–67.9)	0.0207
	Control	436	42		
Persistent infection (12-mo definition)	Vaccine	400	8	50.7 (−24.4 to 82.1)	0.1018
	Control	398	16		
CIN1+	Vaccine	446	6	64.9 (4.9–89.0)	0.02
	Control	438	17		
CIN2+	Vaccine	446	2	75.1 (−28.4 to 97.6)	0.0618
	Control	438	8		
TVC-E					
Persistent infection (6-mo definition)	Vaccine	455	52	36.1 (7.4–56.3)	0.0106
	Control	448	78		
Incident infection	Vaccine	470	139	20.7 (−0.4 to 37.4)	0.0713
	Control	478	168		
Cytological abnormalities	Vaccine	460	38	36.6 (2.1–59.3)	0.0243
	Control	458	59		
Persistent infection (12-mo definition)	Vaccine	443	19	50.1 (9.8–73.2)	0.013
	Control	441	37		
CIN1+	Vaccine	460	9	64.2 (19.5–85.6)	0.0051
	Control	458	25		
CIN2+	Vaccine	460	4	66.6 (−12.6 to 92.4)	0.0468
	Control	458	12		

*Fourteen oncogenic HPV types = HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68.

ATP-E: For combined types: subjects DNA negative at months 0 and 6 and seronegative at month 0 for at least 1 HPV type. For single type: subjects DNA negative at months 0 and 6 and seronegative at month 0 for the corresponding HPV type. TVC-E: For combined types: subjects DNA negative seronegative at month 0 for at least 1 HPV type. For single type: subjects DNA negative and seronegative at month 0 for the corresponding HPV type.

n, number of women reporting at least 1 event in each group; N, number of women included in each group.

pregnancies were normal infants (n = 20), followed by elective terminations (n = 14), spontaneous abortions (n = 5), premature birth (n = 1), and lost to follow-up (n = 1); 5 pregnancies were still ongoing at the final analysis. In the control group, pregnancy outcomes were normal infants (n = 19), elective terminations (n = 16), and spontaneous abortions (n = 3); 5 pregnancies were also still ongoing.

DISCUSSION

Two interim analyses of this clinical study were planned: the first (IA-1) to examine immunologic response after 3 doses of the vaccine[16] and the second (IA-2) to demonstrate the efficacy against 6-month persistent infection when 8 events were accrued.[17] Here, we report the final analysis at completion of the study, for a total follow-up of 24 months after the first vaccination. In Japanese women, an efficacy of 100% of the HPV-16/18 AS04–adjuvanted vaccine to prevent 6-month persistent infection with HPV-16/18 was demonstrated. There were no cases of 6-month persistent infection with HPV-16/18 in the HPV vaccine group versus 15 cases in the control vaccine group. The primary objective of the study was thus met. This final analysis therefore confirms the interim results (IA-2), where protection of 100% was already observed (no cases of 6-month persistent infection with HPV-16/18 versus 9 cases in the control vaccine group[17]). The 100% protection against 6-month persistent infection was also demonstrated in a similar scale efficacy trial (HPV-001) conducted in Canada,

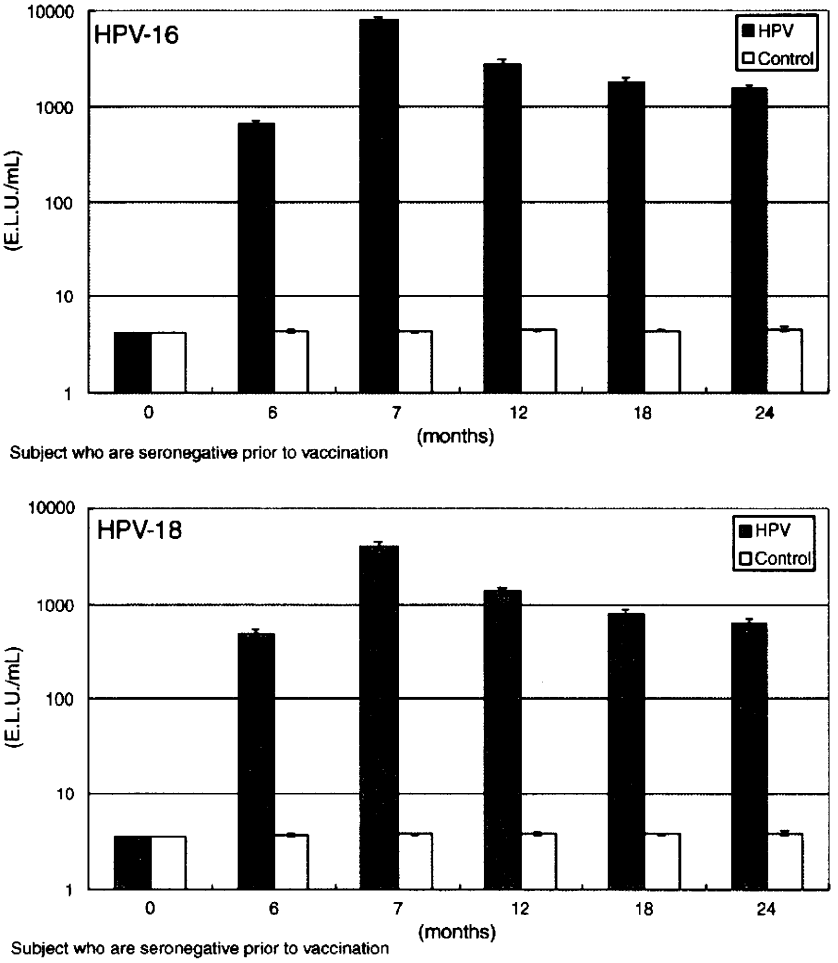

FIGURE 2. Geometric mean titers in the according-to-protocol cohort for immunogenicity.

United States, and Brazil[10]; in a subset of subjects from that study, sustained protection of the cohorts vaccinated with the HPV-16/18 AS04–adjuvanted vaccine was shown up to 7.3 years after the first dose of vaccine (HPV-023).[13,14]

Persistent infection has been recognized as a surrogate marker for cervical cancer and as a valid end point in clinical trials with HPV vaccine.[18,19] The 100% vaccine efficacy to prevent 6-month persistent infection with HPV-16/18 observed in the present clinical study is therefore a solid indication of the vaccine potential to protect against cervical cancers caused by these HPV types. We also observed statistically significant protection against 12-month persistent infection with HPV-16/18, although the number of events was more limited, as expected from the duration of the trial.

Vaccine efficacy to prevent cytological abnormalities associated with HPV-16/18 was 91.7%; in the control vaccine group, 12 subjects were diagnosed with cytological abnormalities, whereas in the HPV vaccine group, 1 subject was diagnosed with an LSIL associated with HPV-18 at month 12. Multiple HPV infections, however, were found in this subject, and HPV-18 was detected only at month 12, whereas HPV-31 was found in all samples taken. Persistent infection with HPV-31 might therefore very well have caused the LSIL.

The vaccine efficacy against virological, cytological, and histopathologic end points associated with any 14 oncogenic HPV types was examined. The overall efficacy of the vaccine to protect against end points associated with all 14 oncogenic HPV types was lower than that calculated for end points associated with the vaccine type HPV-16/18, and certainly for a relatively rare histopathologic end point such as CIN2+, it is difficult to demonstrate significant vaccine efficacy after 24 months of follow-up in the rather small study population. The vaccine efficacy against CIN2+ associated with 14 oncogenic HPV types is of 75.1% (95.5% CI, −28.4% to 97.9%; $P = 0.0618$) in the present study. Although the smaller number of subjects and shorter duration do not allow reaching statistical significance, these results are in line with the high and statistically significant efficacy of 61.9% (96.1% CI, 46.7%–73.2%; $P < 0.0001$) observed in the large-scale pivotal study (PATRICIA), in which 18,644 subjects were vaccinated (with either HPV-16/18 AS04–adjuvanted vaccine or with hepatitis A vaccine).[9]

We have reported previously that the anti–HPV-16 and anti–HPV-18 antibody titers after a 3-dose vaccination course in this study were comparable to those observed in studies conducted in countries outside Japan.[8,10,11,16] Therefore, one could reasonably expect that the protection against CIN lesions in the Japanese population would be similar to that observed in studies conducted elsewhere. Indeed, a similar pattern of antibody persistence as observed in other studies was observed at final analysis in this study with anti–HPV-16 and anti–HPV-18 antibodies at month 24 remaining 51- and 28-fold higher than the level of antibodies elicited by natural infection. High levels of serum antibodies against HPV-16 and HPV-18 are important for protection against cervical dysplasia, and neutralizing antibodies have been shown to be the major defense mechanisms at the site of viral infection. Other studies with this vaccine have demonstrated a high correlation between antibody levels in cervicovaginal secretions and antibody levels in the serum, supporting[20,21] transudation of antibodies to the cervical epithelium to confer specific immune protection at the level of the cervix itself.[20]

Further investigation will be needed to determine the duration of the immune response after 3 doses of vaccine. Current data show antibody response to be sustained for up to 7.3 yeas after the first dose. Mathematical models also indicate that the level of antibodies will remain above natural infection levels for more than 20 years.[15]

The HPV-16/18 AS04–adjuvanted vaccine was generally well tolerated. A higher incidence of local reactions in the vaccine recipients is observed in this study[16] and has been described previously.[8,10] Higher incidences of local symptoms can be attributed to inflammatory reactions accompanying the immune response enhanced by AS04 adjuvant system. The local reactogenicity of the HPV-16/18 AS04–adjuvanted vaccine seemed to be acceptable to the women vaccinated, did not result in a higher rate of dropouts due to adverse events, and did not impact on the compliance with vaccination in the HPV vaccine group. There were no distinctive pregnancy outcomes in the 2 groups. One SAE (0.2%; spontaneous abortion) was reported in the HPV vaccine group by 1 investigator to be possibly related to vaccination because the event appeared 15 days after vaccination, and the temporal relationship of the event to vaccination was considered. Spontaneous abortions are known to be a common complication of gestation, and its incidence is 10% to 14% in Japan.[22] More than 30,000 girls and women older than 10 years have been vaccinated with HPV-16/18 AS04–adjuvanted vaccine in clinical trials. A pooled analysis of those safety data did not show any clinically relevant differences between the HPV vaccine group and the pooled control vaccine groups in terms of rates of SAEs (2.8% vs 3.1%) and rates of spontaneous abortion (9.4% vs 8.6%).[23] This large safety database confirms our observation that the HPV-16/18 AS04–adjuvanted vaccine has a clinically acceptable profile.

In conclusion, the HPV-16/18 AS04–adjuvanted vaccine provided protection against persistent infection with HPV-16/18 associated with oncogenic HPV types in Japanese women. The vaccine had a potent immunogenicity and an acceptable safety profile in Japanese women. These data indicate that HPV-16/18 AS04–adjuvanted vaccine has the potential to decrease the burden of cervical cancer in Japan.

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REFERENCES

1. Parkin D. Global cancer statistics in the year 2000. *Lancet Oncol.* 2001;2:533–543.
2. Cutts FT, Franceschi S, Goldie S, et al. Human papillomavirus and HPV vaccines: a review. *Bull World Health Organ.* 2007;85:719–726.
3. Bosch FX, Qiao YL, Castellsague X. The epidemiology of human papillomavirus infection and its association with cervical cancer. *Int J Gynaecol Obstet.* 2006;94(suppl 1):S8–S21.
4. Stanley M. Prophylactic HPV vaccines: prospects for eliminating ano-genital cancer. *Br J Cancer.* 2007;96: 1320–1323.
5. Ministry of Health, Labour & Walfare. Vital Statistics of Japan. http://ganjoho.ncc.go.jp/professional/statistics/statistics.html. Accessed December 19, 2009.
6. Smith JS, Lindsay L, Hoots B, et al. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update. *Int J Cancer.* 2007;121:621–632.
7. Onuki M, Matsumoto K, Satoh T, et al. Human papillomavirus infections among Japanese women: age-related prevalence and type-specific risk for cervical cancer. *Cancer Sci.* 2009;100:1312–1316.
8. Paavonen J, Jenkins D, Bosch FX, et al. Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial. *Lancet.* 2007;369: 2161–2170.
9. Paavonen J, Naud P, Salmeron J, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04–adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Lancet.* 2009;374:301–314.
10. Harper DM, Franco EL, Wheeler C, et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *Lancet.* 2004;364:1757–1765.
11. Harper DM, Franco EL, Wheeler CM, et al. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. *Lancet.* 2006;367:1247–1255.
12. The GlaxoSmithkline Vaccine HPV-007 Study Group. Sustained efficacy and immunogenicity of the human papillomavirus (HPV)-16/18 AS04–adjuvanted vaccine: analysis of a randomised placebo-controlled trial up to 6.4 years. *Lancet.* 2009;374:1975–1985.
13. Carvalho D, Roteli C, Teixeira J, et al. Immunogenicity and safety of the HPV-16/18 AS04–adjuvanted vaccine up to

7.3 years. Presented at the 25th International Papillomavirus Conference and Clinical Workshop; May 8–14, 2009; Malmö, Sweden.
14. Carvalho D, Roteli C, Teixeira J, et al. Sustained immunogenicity and efficacy of the HPV-16/18 AS04–adjuvanted vaccine (Cervarix™): follow-up to 7.3 years. Presented at the 16th International Meeting of the European Society of Gynaecological Oncology; October 11–14, 2009; Belgrade, Serbia.
15. David MP, Herck KV, Hardt K, et al. Long-term persistence of anti–HPV-16 and -18 antibodies induced by vaccination with the AS04-adjuvanted cervical cancer vaccine: modeling of sustained antibody responses. *Gynecol Oncol.* 2009;115:S1–S6.
16. Konno R, Dobbelaere KO, Godeaux OO, et al. Immunogenicity, reactogenicity and safety of human papillomavirus (HPV)-16/18 AS04–adjuvanted vaccine in Japanese women: interim analysis of a phase II double-blind, randomized controlled trial at Month 7. *Int J Gynecol Cancer.* 2009;19:905–911.
17. Konno R, Tamura S, Dobbelaere KO, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04–adjuvanted vaccine in Japanese women aged 20–25 years: interim analysis of a phase II double-blind, randomized controlled trial. *Int J Gynecol Cancer.* 2010;20:404–410.
18. Koshiol J, Lindsay L, Pimenta JM, et al. Persistent human papillomavirus infection and cervical neoplasia: a systematic review and meta-analysis. *Am J Epidemiol.* 2008;168:123–137.
19. World Health Organization Guidelines. Guidelines to assure the quality, safety and efficacy of recombinant human papillomavirus virus–like particle vaccines. World Health Organization; Geneva, Switzerland, 2006:06.2050.
20. Schwarz TF, Spaczynski M, Schneider A, et al. Immunogenicity and tolerability of an HPV-16/18 AS04–adjuvanted prophylactic cervical cancer vaccine in women aged 15–55 years. *Vaccine.* 2009;27:581–587.
21. Einstein M, Baron M, Levin MJ, et al. Comparison of the immunogenicity and safety of Cervarix™ and Gardasil® human papillomavirus (HPV) cervical cancer vaccines in healthy women aged 18–45 years. *Hum Vaccine.* 2009;5:705–719.
22. Saijo Y, Sata F, Yamada H, et al. Ah receptor, CYP1A2, CYP1A2 and CYP1B1 gene polymorphism are not involved in the risk of recurrent pregnancy loss. *Mol Hum Reprod.* 2004;10:729–733.
23. Descamps D, Hardt K, Spiessens B, et al. Safety of human papillomavirus (HPV)-16/18 AS04 adjuvanted vaccine for cervical cancer prevention: a pooled analysis of 11 clinical trials. *Hum vaccines.* 2009;5:332–340.

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Cervical Cancer Working Group Report

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Disease burden of cervical cancer in Asia was summarized. Human papillomavirus 16 is the most oncogenic human papillomavirus type. Korea's national cervical cancer screening program targets women aged 30 or over, with coverage of almost 80%. Japan has a long history (50 years) of cervical cancer screening, and cytological screening programs have reduced the incidence/mortality of cervical cancer by 70%. But, recent cervical cancer screening coverage is ~24%. Modeling suggested that vaccination of all 12-year-old girls would reduce cervical cancer cases by 73% in Japan. India has no cervical cancer screening program, as well as a serious lack of awareness in the general population, medical professionals and policy-makers. A realistic, affordable approach would be a low-volume, once-in-a-lifetime human papillomavirus-based screening program. In Australia, the national cervical cancer program has been very successful in reducing the incidence and mortality of cervical cancer. Australia was the first country to implement free, national human papillomavirus immunization (April 2007), expected to reduce human papillomavirus 16 infections by 56% in 2010 and 92% in 2050. A comparison of the UK and Japan was demonstrated that in the UK, cervical cancer screening and human papillomavirus vaccination uptakes are high because the government provides adequate education/funding. The Japanese government needs to put more emphasis on women's health and preventative medicine. Our conclusion and recommendations are that heightened public awareness of cervical cancer prevention, focusing on screening and vaccination will lead to improved survival and a better quality of life.

Key words: cervical cancer – human papillomavirus – screening – vaccination – prevention

INTRODUCTION

The Cervical Cancer Working Group report was divided into seven topics: epidemiology of human papillomavirus (HPV) and cervical cancer; cervical cancer in Korea; status of cervical cancer screening and HPV vaccination in Japan; cervical cancer control: Indian perspective; cervical cancer in Australia; public health education for cervical cancer: a comparison of the UK and Japan; and conclusion and recommendations.

EPIDEMIOLOGY OF HPV AND CERVICAL CANCER

Early infection after sexual initiation, continuous new infections into adulthood, related to the sexual behavior patterns of the population etc. are the causes of cervical cancer. A multicentre HPV prevalence survey from 1995 through 2008 found that in Asia, Mongolia has the highest prevalence of cervical HPV DNA in sexually active women, and it is the second highest worldwide. China also shows a

slightly higher prevalence than the other Asian countries. Korea has a prevalence of almost 10%. Hanoi, Vietnam, has a very low prevalence. The prevalence rates of HPV-16 and -18 differ among the continents. In Asia, the prevalence rates were 1.7% for HPV-16, 3.7% for other HPV types and 4.2% for low-risk HPV. China, Japan and Mongolia show different profiles for the most common types of HPV (1). In February 2009, HPV-16, -18, -31 and a number of other types were reclassified as a group of human carcinogens. HPV-16 is the most potent carcinogen, causing cancer at several sites besides the cervix. HPV-18 and ten other types show sufficient evidence of causation of cervical cancer (2).

Cervical cancer epidemiological data from 1988 to 2002 show that the highest incidence of cervical cancer was in South America, followed by Africa and Asia. The lowest incidence was in Western Europe. In Eastern Asia, Thailand had the highest incidence of cervical cancer, followed by Taiwan. Japan showed a low incidence. In Western Asia, the incidence of cervical cancer was low, except in India. As a function of age, the incidence rose from ~25 years old in all East Asia countries, and in Korea, the incidence increased until age 70 and then decreased (3). The global burden of cervical cancer was estimated to be 500 000 cases in 2002. More recent preliminary estimates show the same geographical variation as in 2002, but a lower range of incidence rates compared with 2002. The total number of cases, now estimated to be 487 000, has decreased. With regard to the burden of cervical cancer within Asia, the GLOBOCAN 2008 pooled estimates for China and Japan are based on data from the regional cancer registries and cannot be compared directly. But national estimates were employed for a number of other countries, and the data showed that the incidence has decreased since 2002 in various nations, including Korea, Taiwan, Singapore, Australia and New Zealand. When the cervical cancer burden in Asia was stratified for the Eastern, Southeastern, South-central and Western regions, the 2008 preliminary data showed that the greatest number was in South-central Asia, including India and Pakistan. Eleven percent of all female cancers were cervical cancer, and 9% of deaths were due to this malignancy (4) (caution: it will be available in the mid of May 2010). For the prevention of cervical cancer, the most important factor is public health awareness, through healthy and safe sexual behavior, followed by early detection and screening (Fig. 1).

CERVICAL CANCER IN KOREA

In Korea, cervical cancer is the sixth most common female cancer, after breast, thyroid, stomach, colorectal and lung cancers. The standardized incidence rate is 12.8. The National Cancer Registry data revealed that invasive cervical cancer is decreasing, whereas carcinoma *in situ* is increasing, perhaps due to screening and early detection. The mortality rate due to cervical cancer is also showing a decreasing trend. The age-specific incidence of cervical cancer has decreased for women in the 60–64-year-old group, but increased in elderly women, whereas the incidence of carcinoma *in situ* has increased in middle-aged Korean women (5). Pooled analysis of published data for HPV involvement in cervical cancer shows that less than 70% of cases have HPV-16 or -18 DNA.

Korea has a national cervical cancer screening program based on Pap smears for women aged 30 or more, but the Korean Society of Obstetrics and Gynecology recommends screening of all women after first intercourse or 20 years of age. Cervical screening by Pap smear was started in 1989 for health insurance beneficiaries and in 1999 for Medicaid women. The percentage of women who have been screened has increased rapidly and is now slightly a bit below 80% (Fig. 2).

With regard to HPV vaccination, the Korean Food and Drug Administration approved Gardasil™ in 2007 and Cervariax™ in 2008, but there are no guidelines for HPV vaccination at the national level. A subcommittee of the National Advisory Committee on Immunization Practices began developing HPV immunization guidelines in 2006, but they are not yet finalized. Two surveys of HPV awareness and acceptability of vaccination were conducted in 2002 and 2007 and found that awareness was very low. However, in the 2002 survey, the acceptability of vaccination was ~55% even before the introduction of vaccination, and in the 2007 survey, ~58% of females found vaccination acceptable (6,7). A National Cancer Incidence Data Base, Site-specific Cancer Registry and a Cervical Cancer Registry have been established in Korea, but a vaccination registry remains under consideration.

In summary, in Korea, the cervical cancer burden has gradually decreased in recent years in terms of the incidence and mortality due to early detection (CIS represented 40% of cervical malignancies and is increasing). The burden due to HPV-related diseases is still high and rising. The HPV vaccination program will depend on the cost-effectiveness of the HPV vaccine in Korea.

STATUS OF CERVICAL CANCER SCREENING AND HPV VACCINATION IN JAPAN

Cervical cancer screening was started in Japan in the late 1950s, and a national screening program was enacted in 1982 (8). Cytological screening programs have been shown to reduce the incidence and mortality of cervical cancer by 70%. Prior to the national screening program, the pattern for the age-specific rate of cervical cancer in Japan was that of a developing country. After the screening was introduced, the age-specific rate pattern has become that of a developed country, with the rate decreasing after 35 years of age (8). OECD data show high rates of cervical cancer screening coverage in the USA and Europe, while increasing coverage in Korea and very low (23.4%) coverage in Japan (9).

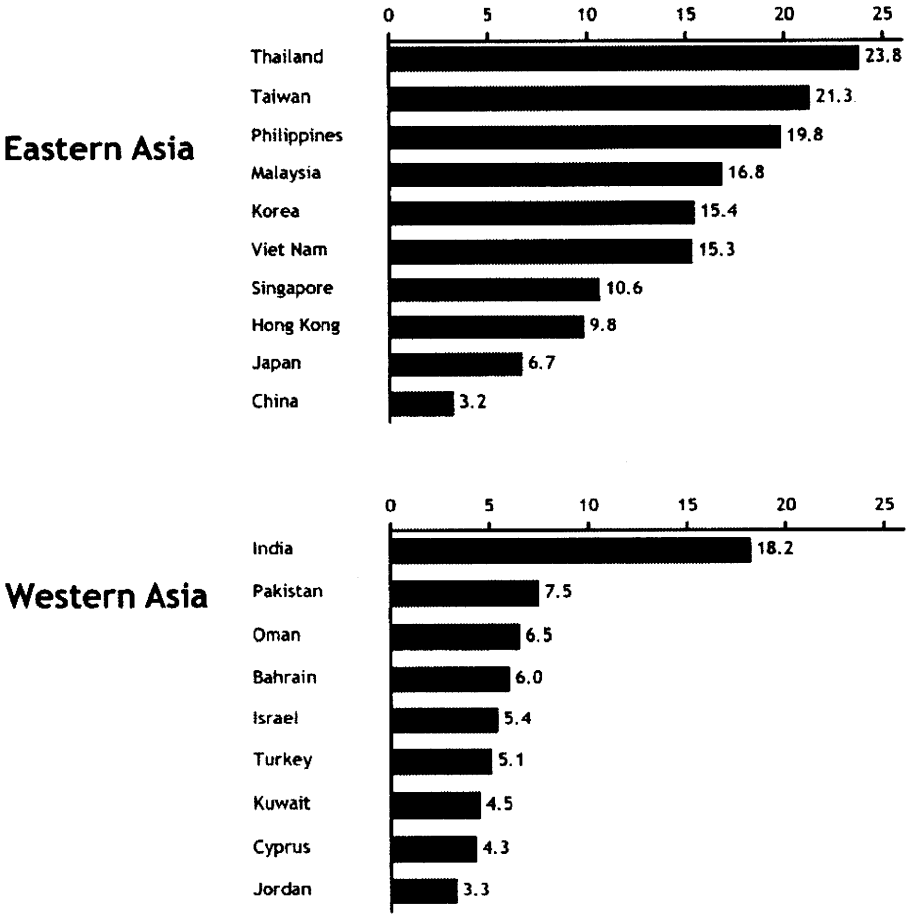

Figure 1. Cervical cancer incidence in Asia.

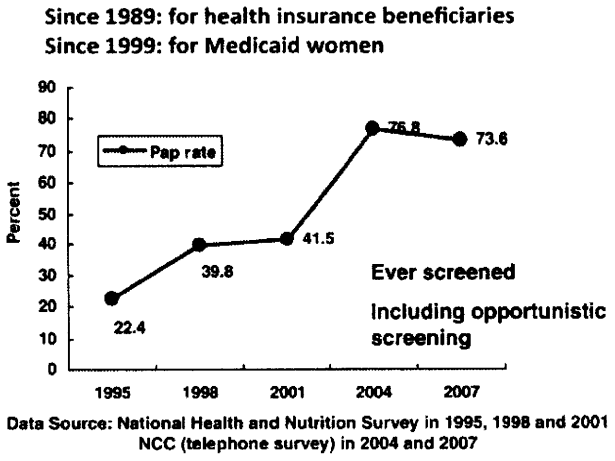

Figure 2. Cervical cancer screening in Korea.

The age-standardized mortality of cervical cancer in Japanese women has been less stable in the last 15 years. Mortality rates fell in all birth cohorts, up to those born around 1940–1945, but thereafter there has been a progressive rise in mortality in each successive generation due to the recent low coverage of cervical screening. With regard to cervical cancer prevention in Japan, in 1983, the government passed a Health and Medical Service Law for the Aged, but that law was later changed in 1998, leaving screening up to the regional governments (8).

Recently, University of Tsukuba data show that the prevalence of HPV-16/18 in cervical cancer in Japan is 67% (10). As in other countries, the percentage of adenocarcinoma or adenosquamous carcinoma in cervical cancer has been increasing in Japan. Modeling of the effect of introduction of HPV vaccination indicated that the number of cervical cancer cases could be reduced by 73% if all 12-year-old girls in Japan were vaccinated. In addition, simulation of the cost-effectiveness when vaccinating single cohorts from 10 to 45 years of age found that vaccination up to 29-year olds would generate savings to the Japanese society. Vaccination of 30-year olds would generate costs while still preventing cervical cancer cases and generating QALY over a screening program only (11) (Fig. 3). An HPV vaccine was licensed in 2009. Japan has a long history of cervical cancer screening

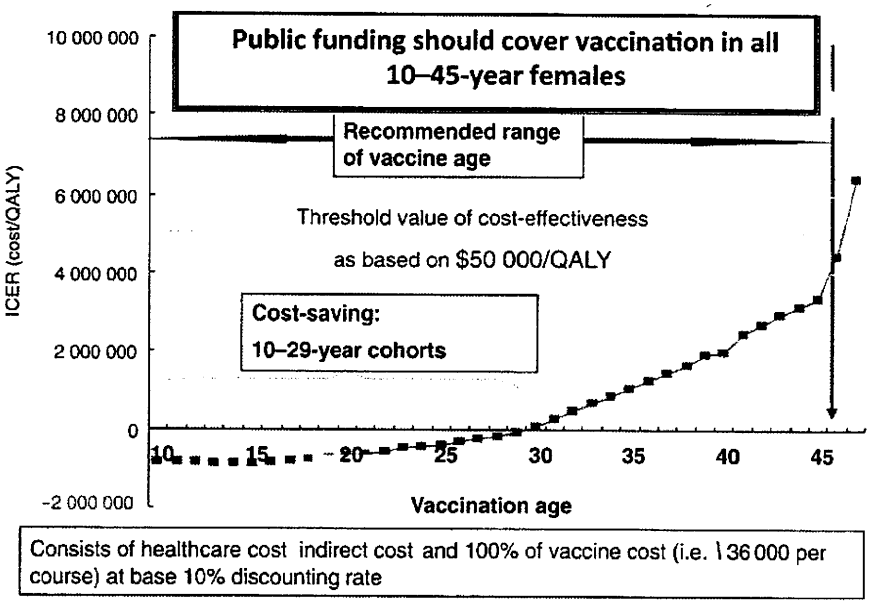

Figure 3. Public funding should cover vaccination in all 10–45-year females. Simulation of the cost-effectiveness of cervix cancer vaccination when vaccinating single cohorts from 10- to 45-year old was performed. Vaccination up to 29-year olds generates savings to the Japan society. However, vaccinating as of 30-year old will generate costs while still preventing cervical cancer cases and generating QALY over screening program only. In addition, the ICERs (incremental cost per incremental effectiveness) for 30–45-year-old single cohorts were well below the generally accepted threshold value of $50 000/QALY gained in the USA.

but a lack of long-term vision with acceptance of logical scientific evidence (12).

CERVICAL CANCER CONTROL: INDIAN PERSPECTIVE

Asia-Pacific countries are very heterogeneous in terms of their cervical cancer control activities. At one end of the spectrum is Korea, which has a good, well-organized cervical cancer screening program and vaccination program, and Japan, which has a screening program that is effective in reducing mortality. At the other end of the spectrum is India, which has no cervical cancer screening program, as a result of which no asymptomatic women are advised to undergo a Pap smear. Availability of Pap testing is very limited, and there is hardly any infrastructure for performance of colposcopy or management of cervical precancerous lesions. Thus, in the case of an abnormal Pap smear, doctors either put the patient on antibiotics or antioxidants while following her up or go straight to hysterectomy.

There is a serious lack of awareness not only in the general population but also in the medical fraternity and policy–makers in India. Women's perceptions regarding cervical cancer screening are also a problem. A small demonstration program offering free cervical cancer screening in the community attracted only 60% of the target population for testing. Interview of the 40% no-shows revealed that the main reason given was that a test was not needed because the women had no symptoms. That was followed by the burden of housework and the absence of permission from the husband or in-laws.

India thus needs a national program, but the approach must be realistic. What can be afforded at present is probably a low-volume screening program, a once-in-a-lifetime test. An HPV-based test would probably be best because of its sensitivity. Two HPV vaccines have been approved, but their high cost restricts their use to wealthier citizens. Their inclusion in a national program within the next 5 years cannot be expected, and a huge number of women in need will go unscreened and untreated. A questionnaire survey of the attitudes of the wealthy urban and educated class in the Calcutta area revealed that even in that population nearly 70% of the men and women had never heard of cervical cancer. After reading a fact sheet, nearly 75% of both sexes agreed to having their daughters vaccinated. Nearly half of parents who refused the vaccine for their daughters said the reason was that the vaccine was new and its safety unknown (Table 1).

Table 1. Assessment of cervical screening services in India

Dabash et al., Reproductive Health 2005
Screening of asymptomatic women almost absent
Pap smear available in tertiary centers only
Limited opportunities for provider training
Gap in provider knowledge and practices

CERVICAL CANCER IN AUSTRALIA

The National Cervical Screening Program (NCSP) was started in Australia in 1991 (13). It recommends screening every 2 years by Pap smear, starting at age 18 and continuing to 70 years. The program is responsible for the recruitment of women for Pap smear, educating the smear takers (such as nurses), ensuring quality assurance for laboratory reading Pap smears and for smear takers and maintenance of registries for Pap smear results. Two-year participation in 2006–07 was 61.5% for women aged 20–69 and the 3-year participation rate was 74.0%. The number of new cases of cervical cancer in Australia has continued to decline and the age-standardized incidence rate of all cervical cancer is 6.9 per 100 000 women (14). The risk of cervical cancer increases with age and 20% of new cervical cancer cases occur at an age above 70 years (15). The age-standardized mortality rate from cervical cancer has more than halved since the start of the program, from 4.0 deaths per 100 000 women in 1991 to 1.9 deaths per 100 000 women in 2006. However, this program has not reduced the incidence of adenocarcinoma. The NCSP costs around $90 million annually. Australia was the first country in the world to introduce HPV vaccination to a national immunization program, starting in April 2007 (16). It is a free, school-based program for girls in the first year of high school (aged 12–13 years old) using quadrivalent vaccine. There was also a 2-year catch-up program from July 2007 for women aged 14–26 years which ended in 2009 (Table 2). An interim report (17) indicated coverage of 70% or more among almost all school cohorts vaccinated in the program. Both quadrivalent and bivalent vaccines are also available for females up to 45 years on a self-funded basis, as well as quadrivalent for males aged 9–15 years. The next most important aspect of the program is the HPV Register, which is supported by the Australian government. All girls vaccinated in the school-based program and the catch-up program are reported to the Registry. In order to keep the Registry as complete and accurate as possible, family physicians are paid to report the vaccinations. The HPV Register will facilitate cross-referencing of the vaccination data with Pap smear results and cervical cancer registries, allowing an evaluation of the impact of vaccination (18). It is estimated that in 2010, HPV vaccination will reduce HPV-16 infections by 56% and by 92% in 2050 (19).

Table 2. HPV vaccination in Australia

Government Funded	
Since April 2007	School-based HPV vaccination program for 12-13yo girls. (Gardasil®) [Catch up program for females 14-26yo. Started in July 2007 and ceased in December 2009.]
Self-Funded	
Since June 2006	Gardasil® for males 9-15yo.
Since March 2007	Cervarix® for women and girls aged 10 to 45 years.
Since August 2009	Gardasil® for women and girls aged 14 to 45 years.

PUBLIC HEALTH EDUCATION FOR CERVICAL CANCER: A COMPARISON OF THE UK AND JAPAN

Mass screening for cervical cancer began in the UK in 1988, liquid-based cytology (LBC) was introduced in 2003, the HPV vaccine was licensed in 2006 and a school-based, free HPV vaccination program was started in 2008. Since all screening is now done by LBC, HPV DNA testing was introduced in 2009 on a triage basis (20). All of these programs are free to the patient.

Japan also had a nationally funded cervical cancer screening program until 1998, when responsibility was transferred to the regional governments. The screening age was lowered from 30 to 20 years in 2004, and the interval was increased from 1 to 2 years. Since 2009, free screening coupons have been offered to women aged 20–40 every 5 years. The bivalent HPV vaccine was approved in October 2009 and available for use in December of the same year. Regional governments subsidize 70–90% of Pap smears, but HPV DNA testing and HPV vaccination are not covered by insurance. Unfortunately, less than 25% of the target population undergoes regular Pap smears and this figure is even lower in younger women (21).

The UK's mass screening program has been successful in reducing the incidence and mortality rates of cervical cancer by 60–70%, and Scotland's HPV vaccination rates are perhaps the world's highest: the uptake rate for the first year of the school-based program which included girls aged 12–13 years and those aged 16–18 years was 94.2, 93.1 and 89.8% for the first, second and third dose, respectively (22).

To understand the differences in attitudes to cervical cancer prevention in both the UK and Japan, we must first consider what makes public health measures effective? With regard to cervical cancer prevention programs, education, environment and enforcement are very important.

Concerning education, in the UK, schools, female family members, doctors, newspapers/magazines and TV inform girls about HPV, screening and vaccination (Fig. 4). In Japan, the 'educators'—mothers, teachers and nurses—themselves have not been educated and thus do not know about or have Pap smears. Some information is spread via health magazines, but little in teen magazines.

Regarding the environment, in the UK, Pap smears are performed at the GP surgery and girls have the right to request a female doctor or nurse. The majority of smear takers are nurses, who take the smear in a private room, after a detailed explanation has been given. In this case, the patient feels she is in control. In Japan, screening takes place in an OBGYN clinic or hospital department,

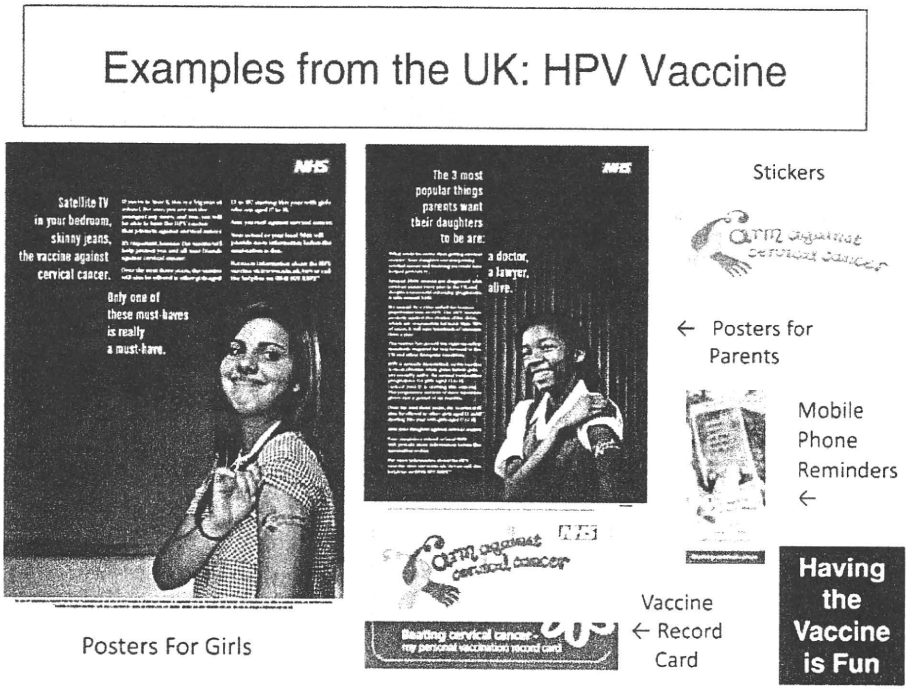

Figure 4. Examples from the UK: HPV vaccine.

where women only usually go if they are pregnant. All smear takers are OBGYN doctors, most of whom are men. Explanation is limited, a curtain separates the patient from the doctor, and the patient has no control and often no privacy.

With regard to the enforcement of cervical cancer prevention measures, in the UK, the government funds research to make programs successful and produces educational campaigns/materials, and all medical care is free. HPV vaccination is promoted using posters etc., and stickers are given to girls to make the vaccination fun and fashionable. Mobile phones give reminders about the next vaccination. A homepage also provides information for girls and mothers, and even celebrities give their views on why the HPV vaccine is important (23). In Japan, volunteer groups, NPOs and drug companies do the promoting, preventative medicine is not covered by health insurance, and women's health is not a high priority. The low-dose contraceptive pill has only been licensed for 10 years, and national health insurance coverage for the treatment of conditions such as endometriosis using the Pill only started in 2009.

In summary, in the UK, there are high cervical cancer screening rates and high HPV vaccination rates, because the government provides adequate education and funding. Japan also has a good infrastructure for screening and vaccination and the necessary financial means. If the government put more emphasis on women's health and preventative medicine, then the cervical cancer prevention program could be like that of the UK.

CONCLUSION AND RECOMMENDATIONS

The WHO position paper on HPV vaccines states that these vaccines should be introduced as part of a coordinated prevention strategy for cervical cancer and other HPV-related diseases, and the strategy should include education on risk-reducing behaviors as well as diagnosis and treatment of precancerous lesions and cancer (24).

For instance, the HPV vaccine is primarily recommended for girls aged 11–14 years in Japan, since it is most effective in women who have not been exposed to HPV. Public funding is critical to achieve high coverage of HPV vaccination in this age group. HPV vaccination in older women (15–45 years), the second target (or catch-up), is also recommended, since it is highly cost-effective and it should also be publicly funded (11). Since boys do not get cervical cancer and herd immunity can be achieved if 70% of girls are vaccinated, vaccinating boys is not thought to be cost-effective. Pregnant women should avoid HPV vaccination because of limited data. HPV vaccination of HIV-infected female patients may be highly beneficial due to their compromised immune system, making it more difficult for these women to get rid of the virus naturally.

Special programs are needed to educate schoolteachers, opinion leaders, healthcare professionals and policy-makers about cervical cancer and HPV at the regional level in order to strengthen the acceptability of vaccination (12). It is increasingly clear that HPV vaccination is essential for cervical cancer prevention. Persistent infection with one of the 15 high-risk HPV types is considered a basic cause of cervical

cancer. Worldwide, meta-analyses have estimated that HPV-16 and -18 account for 70% of all cervical cancers. Any cross-protection of HPV-16/18 vaccines against disease related to other HPV types would be a bonus (25). Cervical cancer screening should continue in the future with effective modification (26).

Heightened public awareness regarding healthy and safe sexual behavior together with early detection by screening are essential for the prevention of cervical cancer, whereas advanced treatments will lead to improved survival and a better quality of life.

Conflict of interest statement

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References

1. Vaccarella S, Franceschi S, Snijders PJF, Herrero R, Meijer CJLM, Plummer M, IARC HPV Prevalence Surveys Study Group. Concurrent infection with multiple human papillomavirus types: pooled analysis of the IARC HPV prevalence surveys. *Cancer Epidemiol Biomarkers Prev* 2010;19:503–10.
2. Bouvard V, Baan R, Straif K, Freeman C, Galichet L, Cogliano V, et al., WHO International Agency for Research on Cancer Monograph Working Group. A review of human carcinogens—Part B: biological agents. *Lancet Oncol* 2009;10:321–2.
3. Shin HR, Masuyer E, Ferlay J, Maria-Paula Curado MP, on behalf of the Asian Contributors to CI5 IX. Cancer in Asia - incidence rates based on data in cancer incidence in five continents IX (1998–2002). *Asian Pac J Cancer Prev* 2010;11(Suppl. 2):11–16.
4. http://www-dep.iarc.fr/GLOBOCAN/2008.
5. Chung HH, Jang MJ, Jung KW, Shin HR, Kim JW, Lee HP, et al., Members for Gynecologic Oncology Committee of Korean Society of Obstetrics and Gynecology. Cervical cancer incidence and survival in Korea: 1993–2002. *Int J Gynecol Cancer* 2006;16:1833–8.
6. Shin HR, Franceschi S, Vaccarella S, Roh JW, Ju YH, Oh JK, et al. Prevalence and determinants of genital infection with papillomavirus, in female and male university students in Busan, South Korea. *J Infect Dis* 2004;190:468–76.
7. Oh JK, Lim MK, Yun EH, Lee EH, Shin HR. Awareness of and attitude towards human papillomavirus infection and vaccination for cervical cancer prevention among adult males and females in Korea: a nationwide interview survey. *Vaccine* 2010;28:1854–60.
8. Konno R, Shin HR, Kim YT, Song YS, Sasagawa T, Inoue M, et al. Human papillomavirus infection and cervical cancer prevention in Japan and Korea. *Vaccine* 2008;26(Suppl 12):M30–42.
9. Armesto Garcia S, Lapetra Gil ML, Wei L, Kelley E, Members of the Health Care Quality Indicators (HCQI) Expert Group. Health Care Quality Indicators Project 2006 Data Collection Update Report. OECD HealthWorking Papers No. 29, DELSA/HEA/WD/HWP. Paris: Organization for Economic Co-operation and Development; 2007.
10. Onuki M, Matsumoto K, Satoh T, Yamada N, Hamada H, Yoshikawa H, et al. Human papillomavirus infections among Japanese women: age-related prevalence and type-specific risk for cervical cancer. *Cancer Sci* 2009;100:1312–6.
11. Konno R, Sasagawa T, Fukuda T, Van-Kriekinge G, Demarteau N. Cost-effectiveness analysis of prophylactic cervical cancer vaccination in Japanese women. *Int J Gynecol Cancer* 2010;20:385–92.
12. Garland SM, Cuzick J, Domingo EJ, Goldie SJ, Kim YT, Konno R, et al. Recommendations for cervical cancer prevention in Asia Pacific. *Vaccine* 2008;26(Suppl 12):M89–98.
13. http://www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/cervical-about.
14. http://www.aihw.gov.au/publications/can/can-43-10676/can-43-10676.pdf.
15. http://www.cancervic.org.au/images/research/CEC/CervicalCancer/CervicalCancer2006.pdf.
16. http://www.aph.gov.au/library/pubs/BD/2007-08/08bd007.htm.
17. Brotherton JM, Deeks SL, Campbell-Lloyd S, Misrachi A, Passaris I, Peterson K, et al. Interim estimates of human papillomavirus vaccination coverage in the school-based program in Australia. *Commun Dis Intell* 2008;32:457–61.
18. http://www.hpvregister.org.au/.
19. Smith MA, Canfell K, Brotherton JM, Lew JB, Barnabas RV. The predicted impact of vaccination on human papillomavirus infections in Australia. *Int J Cancer* 2008;123:1854–63.
20. http://www.cancerscreening.nhs.uk/cervical/ (30 October 2009, date last accessed).
21. http://ganjoho.ncc.go.jp/professional/statistics/statistics.html (1 November 2009, date last accessed).
22. http://www.isdscotland.org/isd/6153.html (2 November 2009, date last accessed).
23. http://www.fightcervicalcancer.org.uk/ (5 November 2009, date last accessed).
24. World Health Organization. WHO position on HPV vaccines. *Vaccine* 2009;27:7236–7.
25. Paavonen J, Naud P, Salmerón J, Struyf F, Lehtinen M, Dubin G, et al., HPV PATRICIA Study Group, Greenacre M. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Lancet* 2009;374:301–14.
26. Cuzick J, Arbyn M, Sankaranarayanan R, Tsu V, Ronco G, Mayrand M-H, et al. Overview of the evidence from cervical cancer screening studies. *Vaccine* 2008;26(Suppl 10):K29–41.

新時代のワクチン戦略について考える

総論

11. 予防接種の費用対効果分析

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予防接種の費用対効果分析

大日康史[1)]

SUMMARY
予防接種の費用対効果分析について，まずその概説を踏まえたうえで，Hib，HPV，PCV7ワクチンを具体例として検討する．その結果，Hibワクチンは費用対効果に優れていないかもしれない可能性が指摘されるが，これは諸外国での検討結果と大きく異なる．また，HPV，PCV7ワクチンは費用対効果は優れているが，水痘，ムンプスワクチンよりは劣る．したがって，費用対効果分析は医療制度や環境に強く依存しており，直接的に結果を輸入できず，日本での検討の重要性が示唆される．最後に諸外国での予防接種に関する政策意思決定の方式について概観し，日本においても政策意思決定機関として，公平で透明，かつ専門性の高い組織が望まれる．
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KEYWORDS
予防接種，費用対効果分析，定期接種化

なぜ費用対効果分析が必要か

日本におけるワクチンの定期接種化においては，感染症対策に熱心な医師および患者団体がその推進を願う一方で，ワクチン全般に対する反対，限られた予算の配分あるいは接種事故などに伴う訴訟を懸念する国との間での綱引きが行われているが，声が大きいほうが勝つ，つまりより有力な政治家を巻き込んだほうの意見が採用される，というのではあまりにお粗末である．患者団体の圧力が弱いことはワクチン導入の利益が低いことを必ずしも意味しないし，また，副反応で損なわれる健康や生命が尊く，病気により損なわれる健康や生命は価値が低いわけではない．健康や生命の価値は，その原因が何であれ同じ価値を有する．そうした価値判断に関しては中立的な立場が求められる．もちろん，感情的には自己の意思として行ったことによる被害のほうが，知らずに被った被害よりも大きく感じるのは自然である．これがワクチン反対派の根拠になるわけである．また，国においても定期予防接種による副反応が生じた場合には，時には訴訟になるが，逆にワクチン導入の意思決定が遅れることは，たとえそれによって自然流行により健康や生命のうえでの被害が生じたとしても訴訟にはならない．その非対称性から国の意思決定は中立ではありえなくなる．

また，全く自明なことであるが，健康や生命は無限の価値をもちえない．人の命は地球より重いことはない．もし本当に地球より重いのであれば，すべての予算や資源を医療に費やせばそれでよいわけで，話は簡単である．しかし現実は財政緊迫の折，また，国民医療費の増加が常に潜在的な危機をもって捉えられている以上，健康や生命は有限の価値しかもちえない．予防接種においても当然に費用が発生し，また，定期予防接種では税金が用いられるために，費用以上の効果が上がっているかが常に問われ，それを証明する必要がある．したがって中立的な価値判断に立って，あくまで科学的に副反応も自然感染による健康被害も，また，接種費用に関しても同じ土俵で評価する必要がある．それを行うのが費用対効果分析である．

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ワクチンの定期接種化に向けての判断基準は，しばしば安全性，有効性，費用対効果と称されるが，その意味において費用対効果分析は安全性と有効性，さらには費用を天秤にかける最も総合的な判断基準であると言えよう．

ここで言う費用対効果分析は，日常的な用語としての意味ではない．分析が科学的に行われるためには，合理性はもちろんのこと，透明性や再現性が常に担保されなければならない．したがって，一定のルールに従って分析が進められなければならない．本稿ではそれについての概説を行い，具体例としてHibワクチンにおける費用対効果分析を紹介する．最後に諸外国では，どのような形で費用対効果分析が予防接種行政に組み込まれているかについてレビューする．

費用対効果分析の概説

費用対効果分析は予防接種に限定されず，医療や公衆衛生，あるいは道路建設や環境といった政策全般に用いられる．ここではそれらに共通する構成要素を紹介しながら，特に予防接種における費用対効果分析での特徴について述べる．一般に費用対効果分析は，主に①評価者，②費用概念，③効果概念，④時間軸で構成される．

1．評価者

評価者とは誰の視点で評価するかである．これには，個人や病院，保険者，企業から自治体，社会まであり得る．評価者によって，費用や効果の概念が異なる．例えば病院，保険者，企業，自治体からの視点では，主に自己の金銭的収支が主要な関心である．予防接種においても，任意接種やあるいは高齢者のインフルエンザへの公費補助など，自治体の裁量がある場合には公費補助額とそれによって削減される医療費(より正確には国民保険財政の改善)が大きな関心事になる．つまり，そこには住民の健康や生命は効果としては認識されていない．一方，個人が評価者であれば健康や生命こそが効果であるが，自己負担額以外の税金や保険料で賄われる部分については費用としては認識されない．

そのように考えると社会的な視点が最も望ましい．社会的な視点では，効果は住民の健康や生命である一方で，費用はその負担が税金であれ被接種者であれその総額になる．したがって，予防接種の費用対効果分析においては社会的な視点が用いることが良いとされる．ただここで問題なのは，しばしば日本において国は社会的な視点というよりもむしろ，自治体の視点に立っている点である．先の訴訟の例を出すまでもなく，国民の健康や生命というよりもむしろ自己の業務上の負担が優先され判断されているのが現状である．また，予算の関係で金銭的な費用あるいは収支のみに着目し，本来的には最も重要な国民の健康や生命が適切に評価されていない．これは行政を執行する機関としてはやむを得ない判断かもしれない．むしろ意思決定を行う組織を執行機関から独立させる必要がある．日本では残念ながら現時点ではそのような組織はないが，諸外国での取り組みについて後で述べる．

2．費用概念

費用と一口に言ってもその定義は様々である．ワクチン接種費用や医療費のように直接的に金銭の授受が発生する費用は直接費用と呼び，これは非常にわかりやすいために議論から外れることはまずない．むしろわかりやすすぎて，直接費用のみに着目する弊害は大きい．

逆に金銭の授受を伴わない費用，あるいは負担は間接費用と呼ばれる．あるいは，経済学では本来得られたであろう便益を失ったという意味で機会費用と呼ばれている．例えば家族看護の負担である．自宅療養での看護を，訪問看護に頼れば医療費として計上されるが，家族が行えばそれは医療費ではない．しかしそこに負担が発生し，費用が発生していることは間違いない．これを考慮しないと，自宅での療養を促進することが医療費を抑制し(これは間違いない)，費用を下げる，といった誤った結論を導く．

では，例えば家族看護の負担をどのように計上すべきであろうか．この点については，医療経済学上2つの考え方があった．1つは摩擦費用で，その家族看護によって国民総生産が低下した分が費用であるとする考え，言い方を換えれば国民総生産が低下しなければ間接費用が発生していない，とする考え方である．これは非常に奇妙である．例えば失業率が高く，罹患した従業員の代わ

りがすぐに見つかるような状況では，その疾患によって国民総生産が低下しないので間接費用は発生せずに，失業率が低く代わりが見つからず，それによって生産が停滞するような場合にのみ間接費用が発生することになる．たとえ，その疾患による患者数が全く同じであっても，失業率で間接費用が異なるのは非常に奇妙である．実は医療経済学上では，1995年までにこの考え方は完全に否定されており，現在では認められていない．

もう1つのより適切な考え方は人的資本アプローチと呼ばれ，その人の生産性が本来の仕事や家事，育児などを中断して家族看護に振り向かざるをえなかったそのこと自身が，既に費用であるとする考えである．また，その人の生産性は，その人が就業しているか否かを問わない．つまり，金銭を得る仕事に就いていないからといって生産性がないことを意味していない．例えばいわゆる“専業主婦”は，家事労働や育児に従事しているわけであるが，それはその方の生産性がないから仕方なく家事労働や育児を行っているからではなく，“家族”という単位で考えた際に家事労働や育児に専念したほうがより“家族”の満足が高まると判断された結果である，と考えるべきである．つまり，金銭を得る就業機会を放棄して家事労働や育児に専念しているわけであるが，その家事労働や育児に専念する価値は，就業していた場合に得られたであろう賃金以上であることは明らかである．したがって，そうした家事や育児が看病によって行うことができなくなれば，そこに費用が発生することは疑いがない．

こうした医療経済学的には決着した議論も，一般には誤解が根強い．医療経済学の論理を習熟していないほうの議論は，こうした誤りに陥りやすい．したがって，予防接種の費用対効果分析に当たっては，医療経済学の教育，訓練を受けた者が当たらなければならない．

3．効果概念

一般的な費用対効果分析における効果は金銭で評価される．例えば高速道路の建設における費用対効果分析では，渋滞緩和やアクセスの向上を金銭評価して行われる．しかしながら予防接種を含め，医療や公衆衛生の費用対効果分析は，健康や生命を扱っているために金銭評価になじまないと感じる人も少なくない．

そこで，医療や公衆衛生の費用対効果分析では，ほかの分野とは異なり，金銭以外の効果軸も金銭単位と合わせて用いられている．金銭以外の効果軸には，余命，生存率や検査値などの物理単位と，QOLを時間軸に関して足し合わせたQALY(quality adjusted life years：質調整生存年)が用いられている．特に後者は，患者の感じている満足に基づいているために望ましいとされている．ちなみに効果を金銭単位で評価した分析を費用対便益分析(cost benefit anlysis；CBA)，物理単位で評価した分析を費用対効果分析(cost effective anlysis；CEA)，QALY単位で評価した分析を費用対効用分析(cost utility anlysis；CUA)と呼ばれている．また，この3種類の効果概念を総括して，あるいはより一般的に費用対効果分析(cost effective anlysis；CEA)と呼んでいるために，それが広義か狭義かを文脈上判断する必要がある．ただし，たとえ混乱しても弊害は大きくない．

物理単位やQALYで予防接種などの効果を評価したとしても，比較する費用は金銭単位であるために，最終的な採択か却下を判断する際には何らかの基準を政策意思決定者はもたなければならない．つまり，QALYを使って健康や生命の金銭評価を回避できるのは研究者のレベルまでであって，政策意思決定においてそれは避けられない．最終的には費用と比較する以上は健康や生命も金銭評価する必要がある．したがって効果を金銭評価であろうが，物理単位であろうが，QALYであろうが，経由が異なるだけで最終的な意思決定においては本質的な差はない．また，QALYの元になるQOLの測定は実際には困難な場合が少なくなく，習熟を要する．

では，QALYをいかに金銭評価しているのであろうか．国によって公表か非公開かは分かれるが，例えばアメリカの予防接種政策では，1QALYを改善する(つまり完全に健康な状態であれば1年余命を伸ばす)費用(incremental cost effectiveness ratio；ICER)が5万ドル未満であればその予防接種は推奨，5万ドル以上10万ドル未満であれば留保，10万ドル以上であれば推奨しない，とされている．日本においては，予防

接種も含め医療や公衆衛生において公式に費用対効果分析が用いられたことがないために，QALYの金銭評価も公式に決められたことはない．ただし，研究レベルでは進められており，一般市民からのアンケート調査から600万円程度とされている[1]．

逆に1QALYの金銭評価を5万ドル，あるいは600万円とするのであれば，健康や生命も金銭評価されているために，同じ金銭単位である費用と直接的な比較ができる．例えば，定期接種化によってQOLの改善や医療費の削減，家族看護負担の軽減といった効果の合計の金銭評価を，ワクチンの接種費用や副反応，あるいは接種に伴う家族看護負担の増加といった費用・負担の金銭評価で除することによって，いわばその定期接種化による収益率を求めることができ，便益費用比(benefit cost ratio；BCR)と呼ばれている．これが1を上回れば定期接種化の効果が費用を上回り，定期接種化が費用対効果的に推奨される．また，効果の金銭評価から費用を引くことによって，いわばその施策によるもうけ，つまりどの程度社会が豊かになったかを金銭単位で評価できる．これは純便益(net benefit；NB)と呼ばれている．もちろんBCRが1を上回るときに，NBは正となる．これらの指標は日常的にもなじみやすく，また，予防接種と高速道路建設とを比較することも可能である．したがって，単に医療や公衆衛生にとどまらず，公共サービス全体の中で比較，評価することができる．ICERではそれができない．

ところで，分析手法あるいは研究によって費用と効果の概念が大きく異なることに留意が必要である．例えば予防接種プログラムに関するCBAでの費用とは，そのプログラム実施にかかわるワクチン代，技術料，事務費，接種に伴う家族看護，副反応に伴う医療費，機会費用や家族看護を指すが，CEA，CUAにおけるICERでは，罹患時の医療費や機会費用，家族看護費用も費用に含まれる．逆にCBAでは罹患時の医療費や機会費用，家族看護費用はプログラムの結果であるために，その削減という意味で効果として計上される．そのために単純な比較はできないし，その研究での定義を踏まえたうえで判断する必要がある．また，二重の計上をしないような留意が必要である．

4．時間軸

効果や費用の検討期間は一般的に長期が望ましいが，その分結論を出すのが遅れ，また，検討対象の感染症とは無関係な医療費やQOLの低下の影響を排除する必要が生じる．小児の感染症の多くは急性で患者の多くは比較的短期間で回復するが，成人の感染症では長期間の潜伏期を経て発症する場合や，発症後の経過も長期にわたる場合，あるいは死亡に至る場合も少なくない．検討期間が長期にわたる場合には現在の100万円と10年後の100万円は利子率分だけ価値が異なるために，その調整を行う必要がある．これは割引と呼ばれ，利子率相当分(割引率)として3%が一般的に用いられている．QOLの効果のほうも割り引くべきかどうか議論が分かれるところであるが，費用との兼ね合いから割り引かれるのが一般的である．なお，日本では利子率が3%より非常に低い水準で推移しているために，3%が妥当であるかの議論は残る．また，先の理由から小児の急性感染症では割り引かれないこともある．

費用対効果分析の具体例(Hib)

より精密な議論は別稿[2]に譲るとして，具体例として，ここでは2008年に任意接種が始まったインフルエンザ菌b型(Hib)の定期接種化について検討してみよう．

Hibの疾病負担は，本人の機会費用で93～806億円，家族看護で24.3～207億円，医療費2.1～8.1億円，計120～1,021億円とされている[3]．また，414億円とする報告もある[4]．出生コホートを110万人とすると，それぞれ110億円，936億円，405億円となる．以後それぞれ低位，高位，中位推定と呼ぶことにする．

予防接種費用は，4回でワクチン代が3万円とする．家族看護負担は先行研究[5,6]をならって約5,000円とすると2万円となる．今回はDPTとの同時接種を想定し，その半額とする．有効率は98%とする[4]．また，予防接種によってHib流行そのものが抑制されるという外部効果を考慮しな

表1　諸外国でのHibの費用対効果分析

国	年	ワクチン単価（1回当たり米ドル）	便益費用比	文献
スペイン	1999	11.3	1.49	7
チリ	1993	1.0	1.66	8
スウェーデン	1998	18.6	1以上	9
イスラエル	1993	7.7	1.16	10
アメリカ	1985	3.0	1以上	11
日本	2008	70.0	0.25～2.08	3

いこととする．換言すればワクチンの効果は接種を受けたもの個人防御に限定する．そのために，接種率は費用対効果分析に影響を及ぼさない．

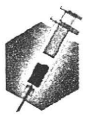
ワクチン接種費用は440億円なので，疾病負担の低位，中位，高位推定でのBCRはそれぞれ0.25，0.90，2.08となる．またNBは，−332.2，−42.8，477.20億円となる．したがって，高位推定のみで費用対効果的である．この場合Hibの疾病負担は，水痘[5]やムンプス[6]と比較して高位で約2倍，中位でほぼ同程度，低位だと1/4に相当する．

しかしながらHibワクチン予防接種の費用対効果分析における問題点はむしろ，高いワクチン代と接種回数にある．それによって，費用対効果が著しく低下する．つまり，疾病負担を低位と取るか高位と取るかで結論が異なるが，定期接種として推奨できるほど費用対効果が優れているわけではない．

諸外国での費用対効果分析との比較（Hib）

では，諸外国ではどうであろうか．前述したように，様々な効果概念があるので直接的な比較が難しい．効果概念が同じBCRを用いている研究だけに限定してまとめたのが**表1**である[3,7~11]．**表1**では全般的に1以上であり有効である．したがって一見したところ，諸外国の研究ではHibワクチンが優れていることを示している．これらを根拠として諸外国ではHibワクチンの定期接種化，推奨が進められたわけである．

しかしながら，具体的な数字が入っている研究では便益費用比は2以下であり，それほど高くない．また，注目すべきはワクチンの費用である．日本では1回当たり7,500円程度でドル換算では75ドルとなるが，これらの研究では最高でもスウェーデンでの18.9ドルと1/3にも満たない．単純に考えればワクチンの単価が高ければ費用がかさみ，その分便益費用比は低下する．ワクチン単価が日本では3倍以上とすると，便益費用比は1/3以下にならざるをえない．したがって，ここで挙げた研究において日本での75ドルという単価で，便益費用比が1を上回ることはありえないと考えられる．したがって，先の日本での検討と諸外国の検討は一見して矛盾しているように思えるが，実はワクチンの単価の違いによるもので，本質的な傾向には齟齬はない．



費用対効果分析の具体例（HPV）

次に，やはり最近認可され任意接種が始まったHPV（human papillomavirus）ワクチンを検討してみよう．日本での研究では，12歳女子全員への接種の場合には便益費用比は1.95とされている[12]．ただ任意接種開始前の分析であったためにワクチン代も低く見積もられており，開始後の平均的な接種料5.5万円/コースに上げると1.25に低下するものの，なお1を上回っており，費用対効果的であるとする結論には影響しない．他方で死亡時の機会費用が低く見積もられていたので，それを日本でのQALY当たりの金銭評価600万円/QALYとし（他方で死亡時以外の機会費用は省略），便益費用比は4.90まで向上する．ただ，HPVは小児の感染症とは異なり，10年あるいはそれより先での発症，死亡の抑制が目的であり，また，アウトカムも死亡が想定されるので割引が非常に重要になる．そこで諸外国の一般的な割引率である3%を用いると便益費用比は1.94まで低下するものの，なお1を上回る．ICERでの評価は256万円/QALYとなる．諸外国ではすべてICERによる評価である（**表2**）[12~18]が，便益費用比が計算できる研究[14]では便益費用比は1.22であり，日本のほうが若干高い．

表2　諸外国でのHPVの費用対効果分析

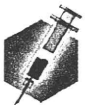
国	年	費用	ICER	文献
オーストラリア	2007	AU$115/dose(豪州$)	AU$18,735/QALY	13
アメリカ	2007	$360	$2,964/QAL	14
アメリカ	2008	$360	$10,294/QALY	15
イギリス	2008	£60/dose	£22,500/QALY	16
アメリカ	2008	$120/dose	$43,600/QALY	17
アイルランド	2008	€100	€17,383/LYG	18
日本	2008	3.6万円/コース	便益費用比：1.95*	12
日本	2010	5.5万円/コース	便益費用比：1.94	本稿

*：論文資料から筆者計算.

表3　諸外国でのPCV7の費用対効果分析

国	年	ワクチン費用	接種回数	結果	文献
ドイツ	2009	€62.42/dose (事務費€6.86/dose)	4	便益費用比：2.29	20
ブラジル	2009	$26.35/dose 廃棄率：10%	4	ICER：$2756/QALY	21
イタリア	2005	€39	3	ICER：€26449/QALY	22
日本	2008	7,000円/dose	4	便益費用比：2.31*	19
日本	2010	10,000円/dose	4	便益費用比：1.08	本稿

*：論文資料から筆者計算.



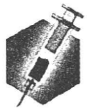
費用対効果分析の具体例(PCV7)

こちらも近年認可され任意接種が始まった小児用7価肺炎球菌結合型ワクチン(7-valent pneumococcal conjugate vaccine；PCV7)を検討してみる．日本での研究では，便益費用比は2.31とされているが[19]，やはり任意接種開始前の分析であったためにワクチン代も低く見積もられており，開始後の平均的な接種料4万円/コースおよび0，1歳児であるために接種に伴う家族看護費用を4回計で2万円と見積もると1.08と低くなるものの，なお1を上回っている．

諸外国での検討事例を**表3**[19~22]にまとめた．文献20)では便益費用比は2.29と日本より高いが，これは集団免疫効果を考慮しているためである．日本での検討は文献19)でも，本稿でもここまでは集団免疫効果を考慮していない．集団免疫効果をアメリカ並み[23]とすると3.69まで増加し，文献20)よりも高い．しかし，日本とアメリカでは高齢者での肺炎球菌ワクチン接種率も大きく異なるために，単純な置き換えは危険であり，精査が必要である．

他のワクチンとの比較

では，ほかの定期接種化が求められているワクチンにおける費用対効果分析はどのようなものであろうか．日本における水痘についての便益費用比は4以上[5]，ムンプスについては5.2[6]とされておりHibやPCV7よりもかなり高い．したがって，(高位推定に依拠して)HibやPCV7の定期接種化を推進するにしても，それらよりも水痘やムンプスが優先して実施されるべきである．HPVは割引率の影響を強く受けるが，1%とすると水痘やムンプスとほぼ同じ程度の費用対効果となるので，1%に依拠する場合には水痘やムンプスと同じ程度に定期接種化が進められるべきである．3%に依拠する場合には水痘やムンプスより費用対効果的に劣る．



おわりに

Hib，HPV，PCV7を例に，特にほかのワクチンとの比較しながらその定期接種化の妥当性について議論した．これらに限らず，今後定期接種化が求められるワクチンに関しては上記のような

費用対効果分析に関しての検討が不可欠である．また，前述したように，その検討に際して公平性，中立性，また，高い専門性が求められる．そのために最終的には政府が定めるとしても，独立した専門的な機関による検討，政府への助言が必要になる．また，具体例として指摘したように諸外国での結果をそのまま日本に輸入することは非常に危険である．したがって，日本の制度や環境に合わせた評価を行う必要がある．

では，諸外国ではどのように行っているのであろうか．国によって，ワクチンに対してのみの費用対効果分析を行っている国もあれば，医薬品全般に対して行っている費用対効果分析の一部としてワクチンの費用対効果分析を行っている国もあるが，オーストラリア，ベルギー，イギリス，フィンランド，オランダ，スウェーデン，アメリカではワクチンの費用対効果分析が政策意思決定のために公式に行われている[24]．他方で香港，ニュージーランド，シンガポールでは公式には位置付けられていない．特にアメリカではCDCを事務局としてACIP(Advisory Committee on Immunization Practice)が組織され，年3回定期的に費用対効果分析を含めた，疫学，有効性，安全性の検討が行われている．1つのワクチンに対して相当の時間をかけて専門家が検討した結果が報告され，それが一般国民，患者団体も含めた公開の場で討議されている．

残念ながらACIPのような組織は日本には存在しない．厚生労働省が必要に応じて諮問会議などを開催して安全性，有効性の議論を行い決定してきたのが現状である．日本においても中立的，専門的な組織が安全性，有効性に加えて最終的な判断基準としての費用対効果分析を行い，ワクチンの定期予防接種の意思決定に科学的な根拠を常に与え続ける態勢が求められる．

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文　献

1) 大日康史，菅原民枝：1 QALY獲得に対する最大支払い意思額に関する研究．医療と社会　16：157-165，2006
2) 大日康史，菅原民枝：Hibワクチン予防接種の費用対効果分析．平成19年度厚生労働科学研究費補助金新興・再興感染症研究事業「予防接種で予防可能疾患の今後の感染症対策に必要な予防接種に関する研究」(研究代表者：岡部信彦)，2008
3) 大日康史，西村龍夫：Hibワクチン導入の医療経済学．外来小児　8：198-200，2005
4) 神谷齊，宮崎千明，中野貴司，他：インフルエンザ菌b型髄膜炎の疾病負担とHibワクチンの費用対効果分析．日小児会誌　110：1214-1221，2006
5) 菅原民枝，大日康史，及川馨，他：水痘ワクチン定期接種化の費用対効果分析．感染症誌　80：212-219，2006
6) 菅原民枝，大日康史，多屋馨子，他：ムンプスワクチンの定期接種化の費用対効果分析．感染症誌　81：555-561，2007
7) Jiménez FJ, Guallar-Castillón P, Rubio Terrés C, et al : Cost-benefit analysis of Haemophilus influenzae type b vaccination in children in Spain. Pharmacoeconomics　15：75-83，1999
8) Levine OS, Ortiz E, Contreras R, et al : Cost-benefit analysis for the use of Haemophilus influenzae type b conjugate vaccine in Santiago, Chile. Am J Epidemiol　137：1221-1228，1993
9) Garpenholt O, Silfverdal SA, Levin LA : Economic evaluation of general childhood vaccination against Haemophilus influenzae type b in Sweden. Scand J Infect Dis　30：5-10，1998
10) Ginsberg GM, Kassis I, Dagan R : Cost benefit analysis of Haemophilus influenzae type b vaccination programme in Israel. J Epidemiol Community Health　47：485-490，1993
11) Cochi SL, Broome CV, Hightower AW : Immunization of US children with Hemophilus influenzae type b polysaccharide vaccine. A cost-effectiveness model of strategy assessment. JAMA　253：521-529，1985
12) 今野良，笹川寿之，福田敬：日本人女性における子宮頸癌予防ワクチンの費用効果分析．産婦治療　97：530-542，2008
13) Kulasingam S, Connelly L, Connay E, et al : A cost-effectiveness analysis of adding a human papillomavirus vaccine to the Australian National Cervical Cancer Screening Program. Sex Health　4：165-175，2007
14) Elbasha EH, Dasbach EJ, Insinga RP, et al : Model for assessing human papillomavirus vaccination strategies. Emerg Infect Dis　13：28-41，2007
15) Chesson HW, Ekwueme DU, Saraiya M, et al :

Cost-effectiveness of human papillomavirus vaccination in the United States. Emerg Infect Dis 14：244-251，2008
16) Jit M, Choi YH, Edmunds WJ, et al : Economic evaluation of human papillomavirus vaccination in the United Kingdom. BMJ 17：a 769，2008
17) Kim JJ, Goldie SJ : Health and economic implications of HPV vaccination in the United States. N Engl J Med 359：821-832，2008
18) Usher C, Tilson L, Oisen J, et al : Cost-effectiveness of human papillomavirus vaccine in reducing the risk of cervical cancer in Ireland due to HPV types 16 and 18 using a transmission dynamic model. Vaccine 26：5654-5661，2008
19) 神谷斎，岩田敏，石和田稔彦，他：小児用7価肺炎球菌結合型ワクチンの医療経済効果．小児臨 61：2233-2241，2008
20) Claes C, Reinert RR, von der Schulenburg JM : Cost effectiveness analysis of heptavalent pneumococcal conjugate vaccine in Germany considering herd immunity effects. Eur J Health Econ 10：25-38，2009
21) Vespa G, Constenla DO, Pepe C, et al : Estimating the cost-effectiveness of pneumococcal conjugate vaccination in Brazil. Rev Panam Salud Publica 26：518-528，2009
22) Marchetti M, Colombo GL. Cost-effectiveness of universal pneumococcal vaccination for infants in Italy. Vaccine 23：4565-4576，2005
23) Ray GT, Whitney CG, Fireman BH, et al : Cost-effectiveness of pneumococcal conjugate vaccine : evidence from the first 5 years of use in the United State incorporating herd effects. Pediat Infect Dis J 25：494-501，2006
24) Jacobs P, Ohinmaa A : A comparison of the use of economics in vaccine expert reviews. Vaccine 28：2841-2845，2010

Summary

Cost-effectiveness analysis on vaccine policy

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After an overview of cost-effectiveness analysis of vaccines, we examine the Hib HPV, PCV7 vaccine as an example. Though we concluded that it may not be cost-effective, it differs a great deal from studies in other countries. Moreover, though HPV and PCV7 vaccines show cost-effetiveness, they are more expensive than varicella or Mups vaccine. Therefore, cost-effectiveness analysis heavily depends on the medical system or the acceptance atmosphere, and thus we cannot directly import results from the other countries, so it is important to evaluate our vaccines in Japan. Finally we summarize briefly the policy decision system for vaccines in other countries, and we hope that fair, transparent and highly specialized institutions will make policy decisions concerning vaccines in Japan.

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