Efficacy, immunogenisity and safety of HPV-16/18 AS04 adjuvanted vaccine and Evaluation of cost-effectiveness in Japan

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Cervical Cancer Prevention in Japan

- **1950's Start of cervical cancer mass screening**
- **1982 Health and Medical Service Law for the Aged Passed (Cervical Screening Program Implemented Nationally)**
- **1998 Health and Medical Service Law for the Aged Nullified**
  - **National Funding Stopped**
  - **Screening left to Regional Government**
- **2009 Free screening coupons every 5 years to women 20-40 yr**
- **2009 HPV Vaccine Licensed (Oct 16th), available in Dec.**

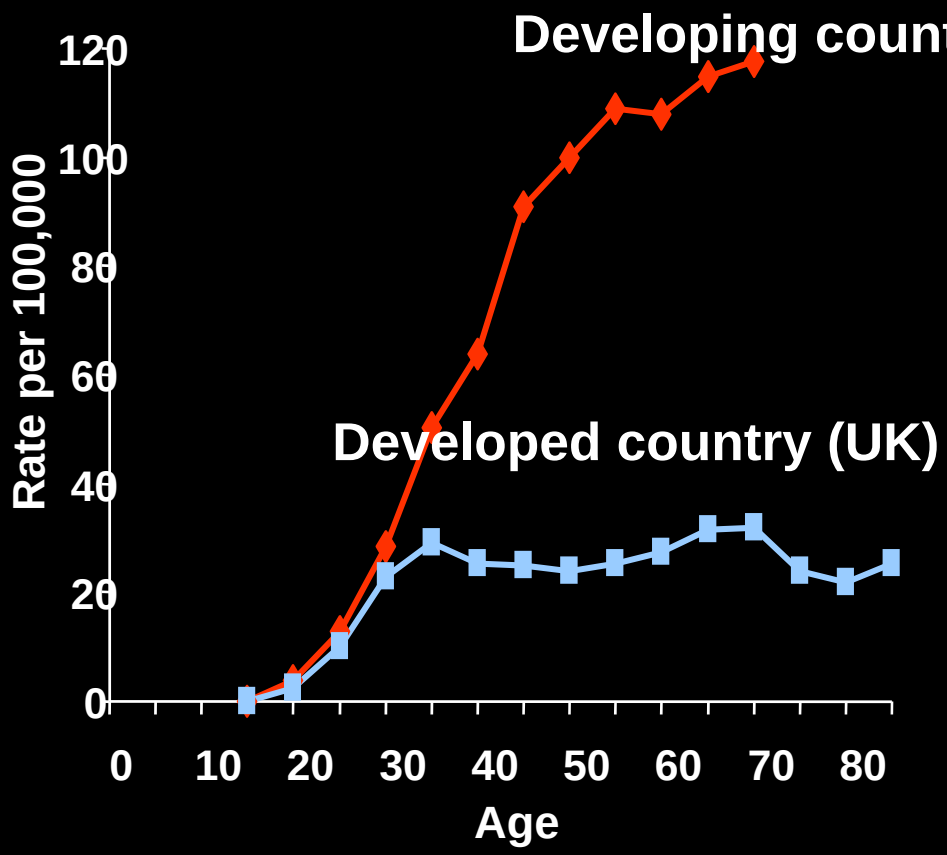
Time trends of cervical cancer

Mortality rates and cervical screening coverage in the Miyagi prefecture, Japan (1962–1994).

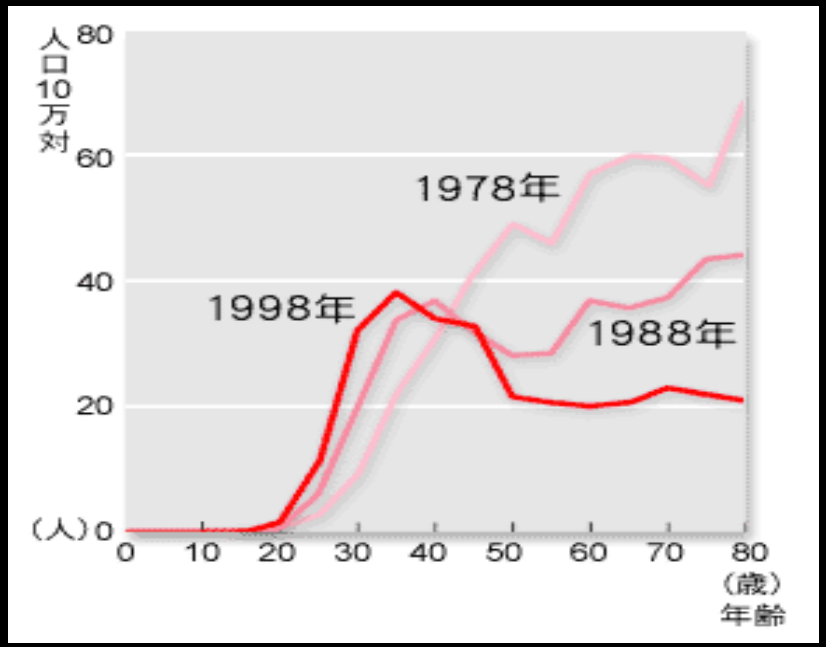
- In Japan, cervical cancer screening started in the end of 1950's. National screening program was enacted in 1982.
- Cytological screening programs have been shown to reduce incidence and mortality by 70% of cervical cancer.

Konno R, Shin HR et al. Vaccine 26S: M30-M42, 2008

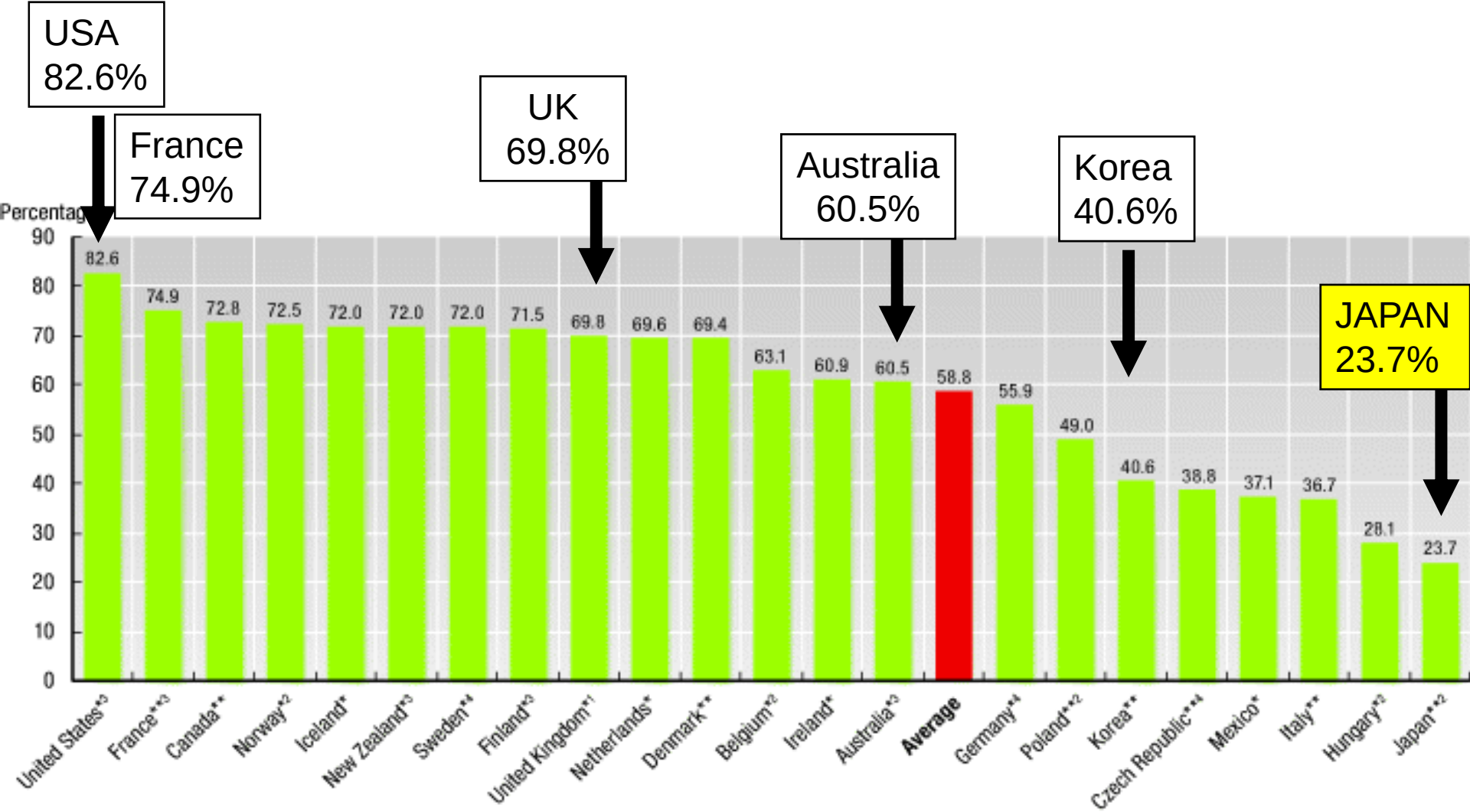
Reduction of incidence of cervical cancer due to screening



Japan



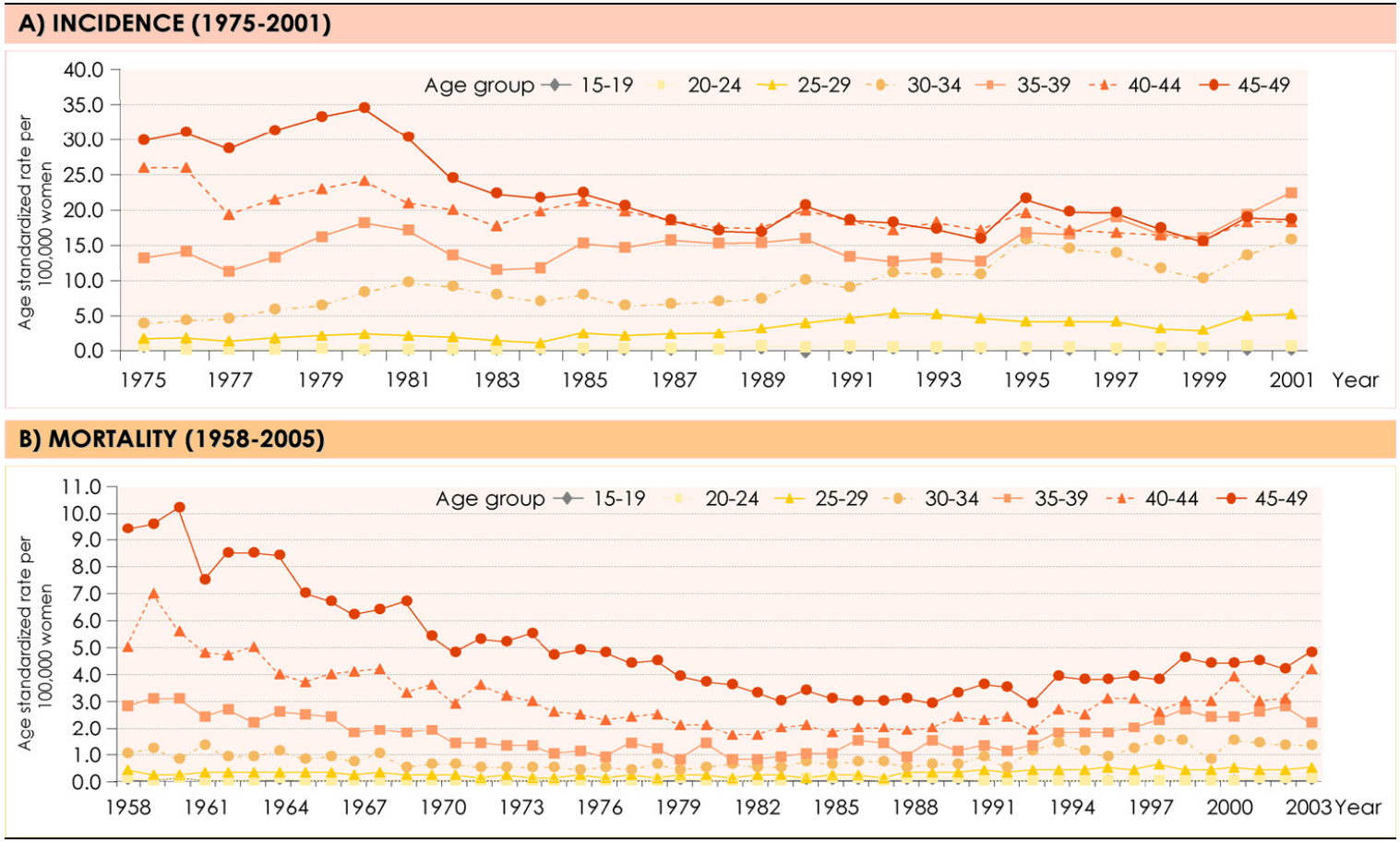
1. Ferlay J et al. Globocan 2002. IARCPress 2004.



OECD: Coverage of cervical cancer screening

Health Care Quality Indicators Project - 2006 data collection update report (OECD Health Working Paper No. 29) 05-Oct-2007

Age-standardized incidence (1975–2001) and mortality (1958–2005) of cervical cancer in women aged 15-49 years in Japan



In Japan, age-standardized incidence and mortality has decreased until 1990. However, there were interesting age-specific trends. Since the middle of 1990's, there has been a progressive increase in incidence and mortality. These changes should depend on the situation with recent low coverage of cervical screening, especially in younger generation.

Konno R, Shin HR et al. Vaccine 26S: M30-M42, 2008

Disease burden:
Prevalence of HPV in women with normal cytology and coverage of cervical cancer screening

Country	Incidence (ASRW)	Mortality (ASRW)	HPV prevalence in women with normal cytology (%)		Screening coverage (%)
			20-29 yr	30-49 yr	
Japan	6.8	2.8	23.1	7.9	24
Korea	17.9	4.7	12.7	9.3	33
India	30.7	17.8	13.2	14.4	ND
Thailand	19.8	8.4	8.7	7	<5%
China	6.8	3.8	6.5	8.6	ND
Australia	6.9	1.7	30.1	13.9	62

Modified form Garland S, Konno R, FX Bocsh et al. Vaccine 26S: M89-M98, 2008

In Australia, HPV is prevalent but screening coverage is high. Incidence and mortality are low . In China, HPV prevalence is low, then incidence and mortality are low. Japan has long history of cervical cancer screening, but prevalence of HPV is relatively high. Low coverage of screening caused recent increase of cervical cancer in younger females.

Considering disease burden of cervical cancer, screening as secondary prevention has been effective even though in HPV prevalent areas. Effort to increase the coverage of screening should continue in developed country. HPV vaccine will be powerful tool as a primary prevention for cervical cancer even though in the areas without sufficient resources for screening.

Cervical cancer – preventable disease

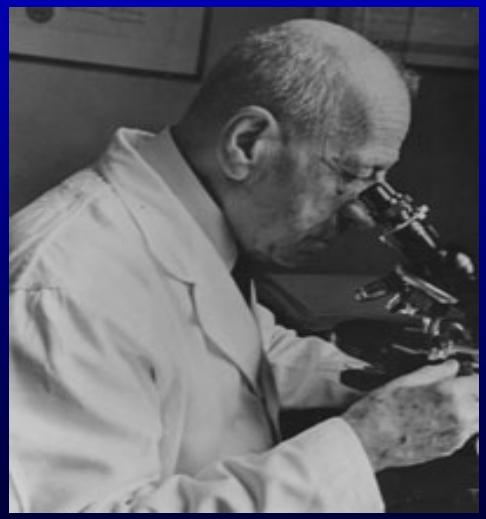
Primary prevention

HPV vaccine

Secondary prevention

Cervical cancer screening

= precursor screening



Dr. Papanicolaou

Dr. zur Hausen

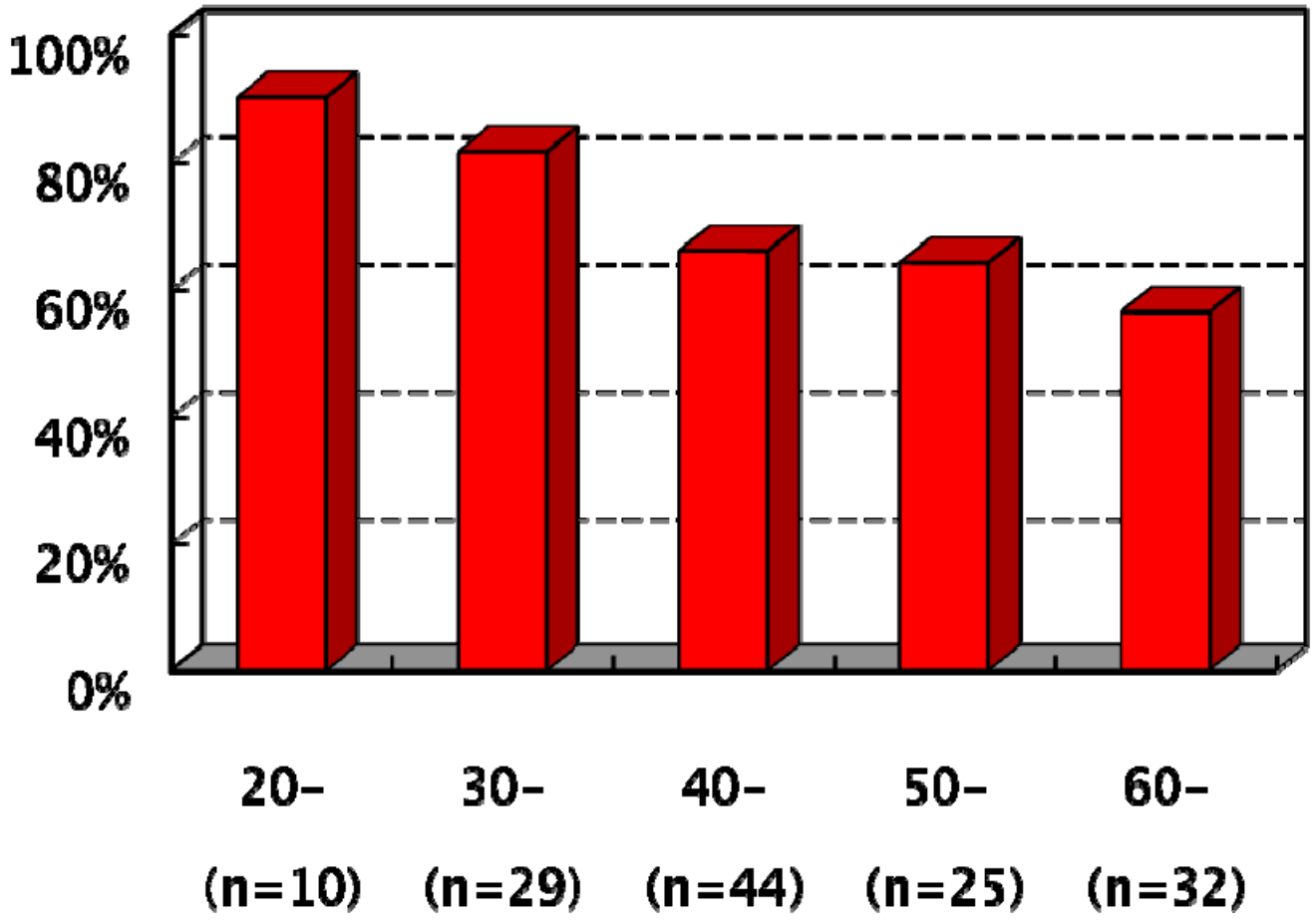
Dr. Frazer
Honda prize, 17th, November, 2009

Human papillomavirus vaccines
WHO position paper

- HPV vaccines should be introduced as part of a coordinated cervical cancer and other HPV-related diseases prevention strategy, including
  - Education on risk reducing behaviours
  - diagnosis and treatment of precancerous lesions and cancer
- HPV vaccine introduction
  - should not undermine or divert funding from effective cervical cancer screening programmes
  - should not replace cervical cancer screening (30% of cervical cancer caused by HPV types other than 16 and 18)
- Programmes to introduce HPV vaccines should seek opportunities to link with other adolescent health services
- HPV vaccination should not be deferred in countries because one or more of these interventions cannot be implemented at the time when vaccination could be introduced

Prevalence of HPV16/18 in Cervical Cancer in Japan
-University of Tsukuba-

67%



Onuki M et al. Cancer Science, 2009

Women's age

Clinical Study of HPV-16/18 AS04 adjuvanted vaccine in Japanese healthy women (HPV 032 study)

◆ Participants:

- Japanese healthy women aged 20-25 years at primary study entry
- Women with a history of CIN or abnormal cervical cytology were excluded (intact cervix).

◆ Subjects for Analysis

●ATP cohort

- received all 3 doses of vaccine according to protocol
- had no HPV-16 or HPV-18 infection at study entry and at month 6
- DNA negative for oncogenic HPV 16/18 at study entry and at month 6

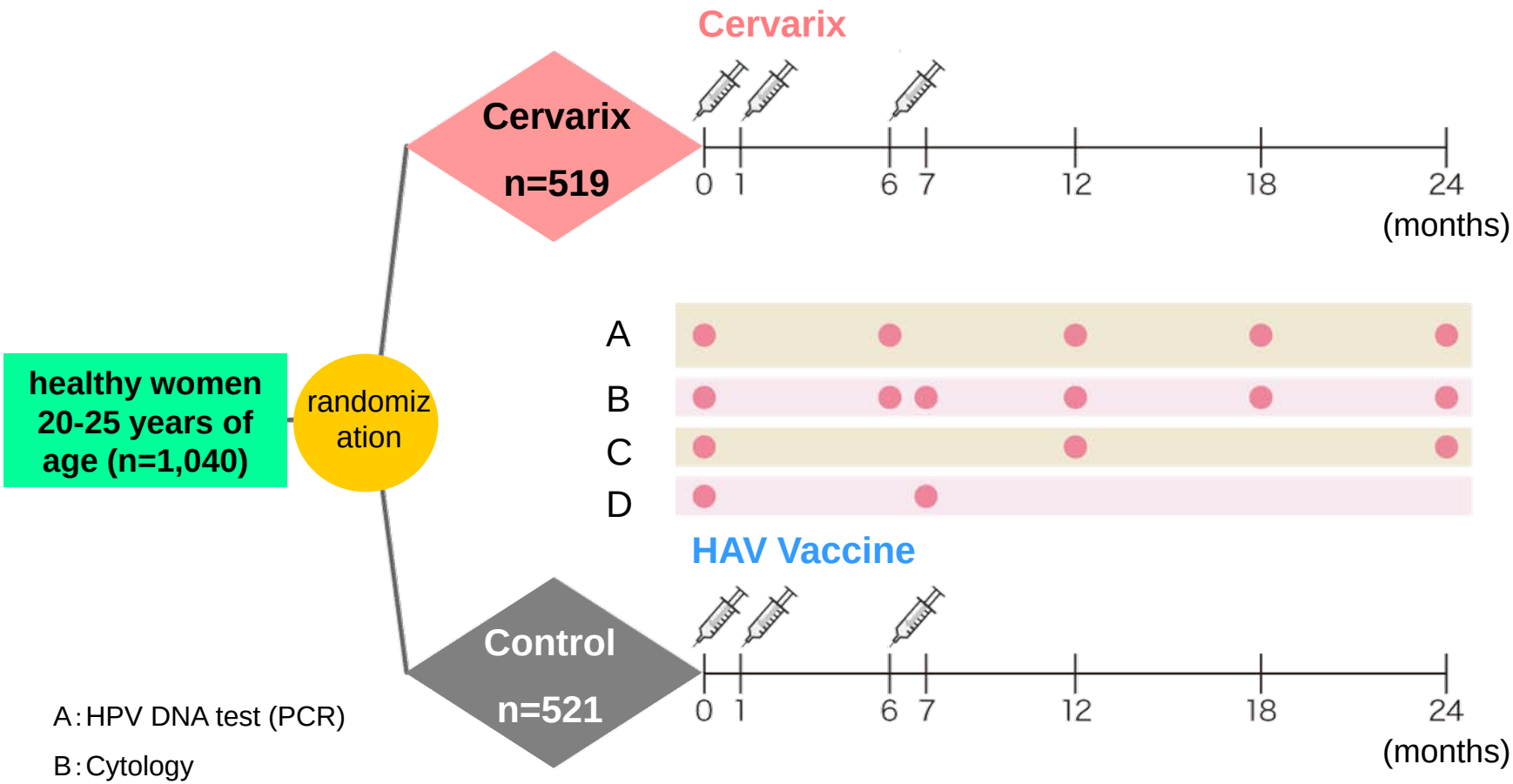
●TVC cohort

- women who received at least 1 vaccine dose

◆ Methods

the phase II, double-blind (observed-blind), controlled randomized multicenter study. Women were received Cervarix or Control Vaccine (licensed HAV Vaccine “Aimmugen”) according to a 0-,1-, and 6-month schedule.

Study schedule (HPV 032 study)



A : HPV DNA test (PCR)

B : Cytology

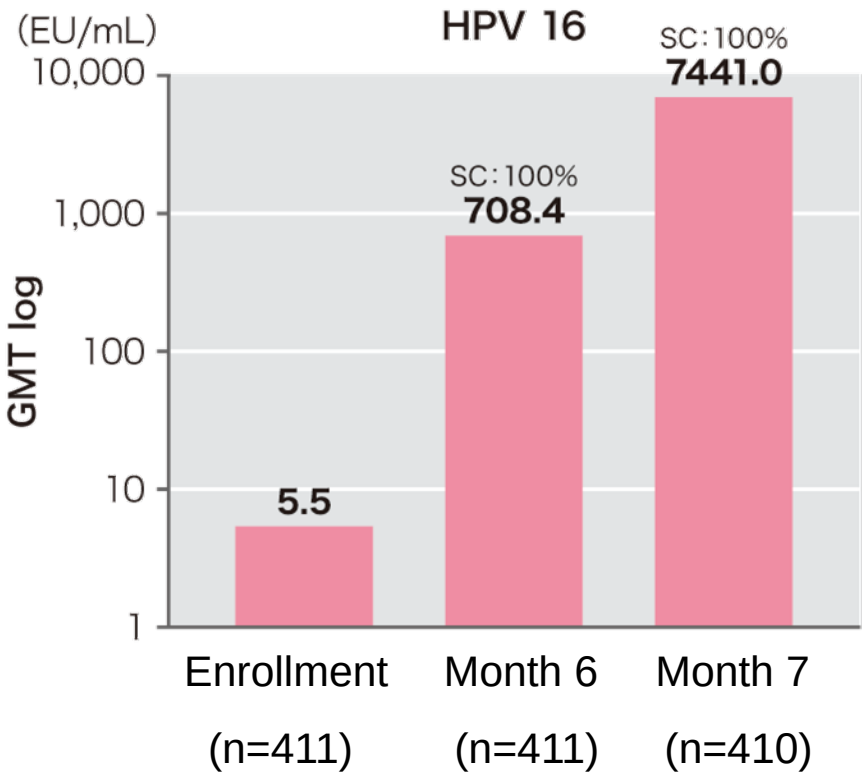
C : Immunogenicity test

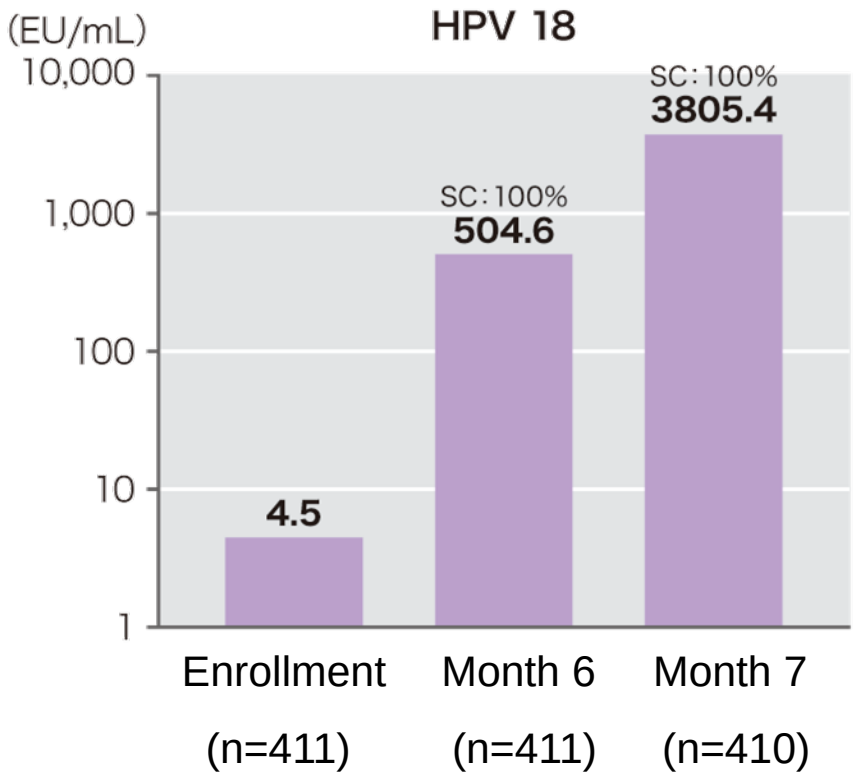
D : Blood samples test

Konno R et al: Int J Gynecol Cancer 19(5): 905-911, 2009

Strong immunogenicity was obtained from 3 doses of administration

HPV032 Study (interim analysis) : Seropositivity rate and GMTs after immunization





SC : seroconversion rates

Participants : 1040 Japanese healthy woman aged 20 to 25 years

Methods : the phase II, doubleblind(observed-blind), controlled randomized multicenter study. Women were received Cervarix or Control Vaccine (licensed HAV Vaccine “Aimmugen”) according to a 0-,1-, and 6-month schedule. The primary objective was to assess the effi cacy and immunogenicity, safety.(The mean duration of follow-up was 13.5 months).

Safety : 6 women in the HPV group reported 7serious adverse events (SAEs) and 8 women in the HAV group reported 9 SAEs. All 16 events are Brain contusion, Skull fracture, Gastritis, Abortion spontaneous, 2 Acute tonsillitis, Hepatitis acute, Chemical abortion, Automobile accident injury, Acute pyelonephritis, Avulsion fracture of posterior cruciate ligament attachment of right knee, Contusion of right lower leg, Appendicitis, Pneumothorax spontaneous, Spontaneous abortion, Pneumonia.

Konno R et al: Int J Gynecol Cancer 19(5): 905-911, 2009

Vaccine efficacy against 6-month persistent infection associated with HPV 16/18 in Japanese women (HPV 032 study)

Vaccine efficacy against 6-month persistent infections with HPV 16/18

End point	Number of evaluable women reporting event (number of evaluable women)		Vaccine efficacy	p value
	cervarix	control		
Persistent infections with HPV 16/18	0 (n=387)	15 (n=392)	100%	＜0.0001
Persistent infections with HPV 16	0 (n=332)	11 (n=340)	100%	0.0009
Persistent infections with HPV 18	0 (n=346)	5 (n=343)	100%	0.0301

Fisher's

Participants：1040 Japanese healthy woman aged 20 to 25 years

Methods：the phase II, doubleblind(observed-blind), controlled randomized multicenter study. Women were received Cervarix or Control Vaccine (licensed HAV Vaccine "Aimmugen") according to a 0-,1-, and 6-month schedule.

Safety：16 women in the HPV group reported 20serious adverse events (SAEs) and 15 women in the HAV group reported 17 SAEs.

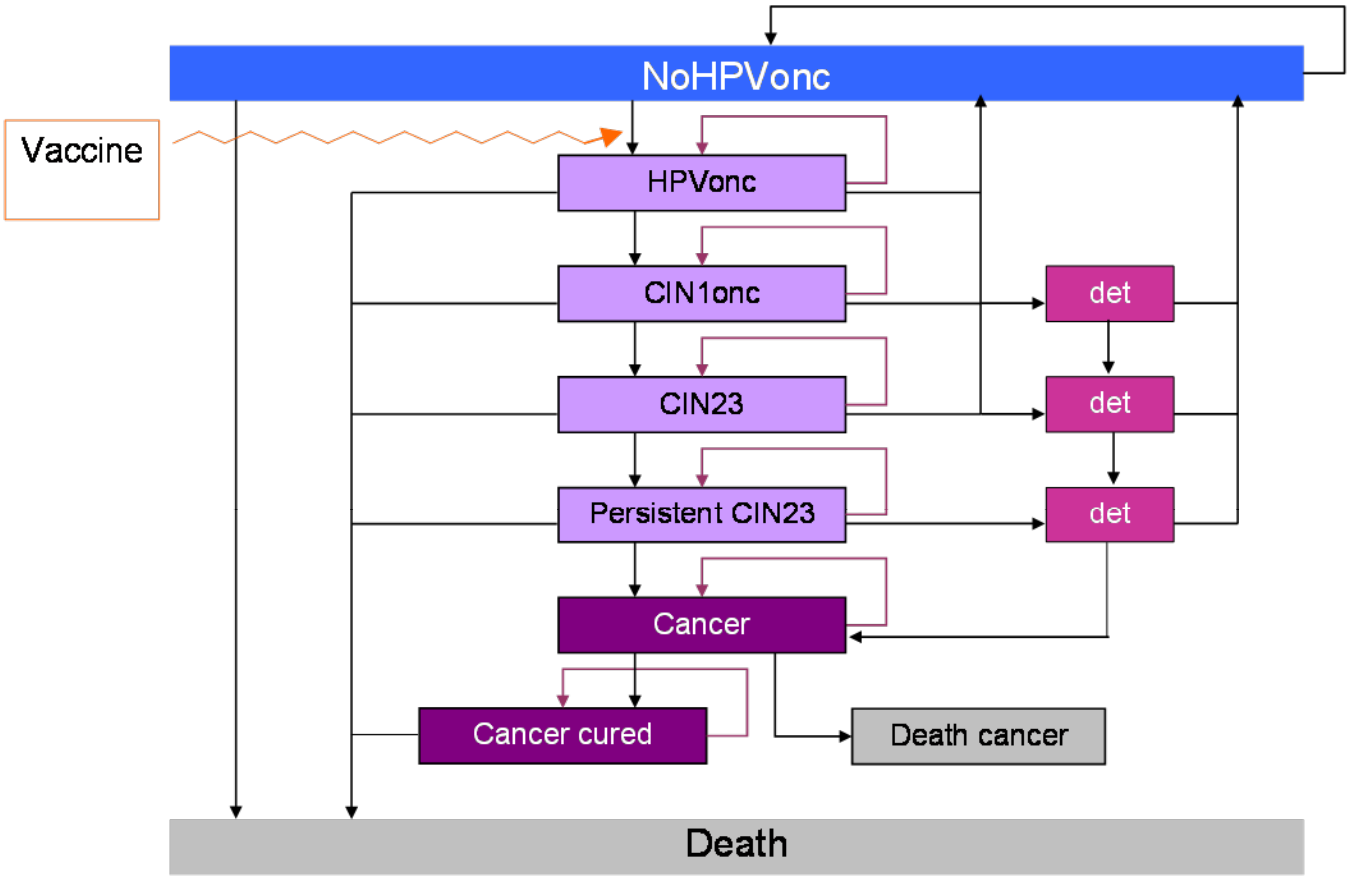
- All HPV vaccine recipients were still seropositive at Month 24, with sustained antibody response.
- Vaccine safety was similar in both treatment groups.
- In the study population of 20-25 year old Japanese females, the HPV-16/18 vaccine showed 100% protection against persistent infection with HPV-16/18 (6-month definition), high immune response and a favorable safety profile.

Cost-Effective Analysis of HPV vaccine for the Prevention of Cervical Cancer in Japan

Overlook of this study

- Intervention: HPV 16/18 vaccine (12-yr girls or 10 to 45-yr females)
- Alternative: screening program only (unvaccinated)
- Methods: cost-utility and benefit analysis
- Perspective: societal and healthcare body
- Health outcome measure: QALY
- Cost components: Vaccine, treatment, diagnosis, morbidity & mortality due to cervical cancer and CIN
- Model structure: Markov model

Markov model for economic evaluation of HPV vaccine



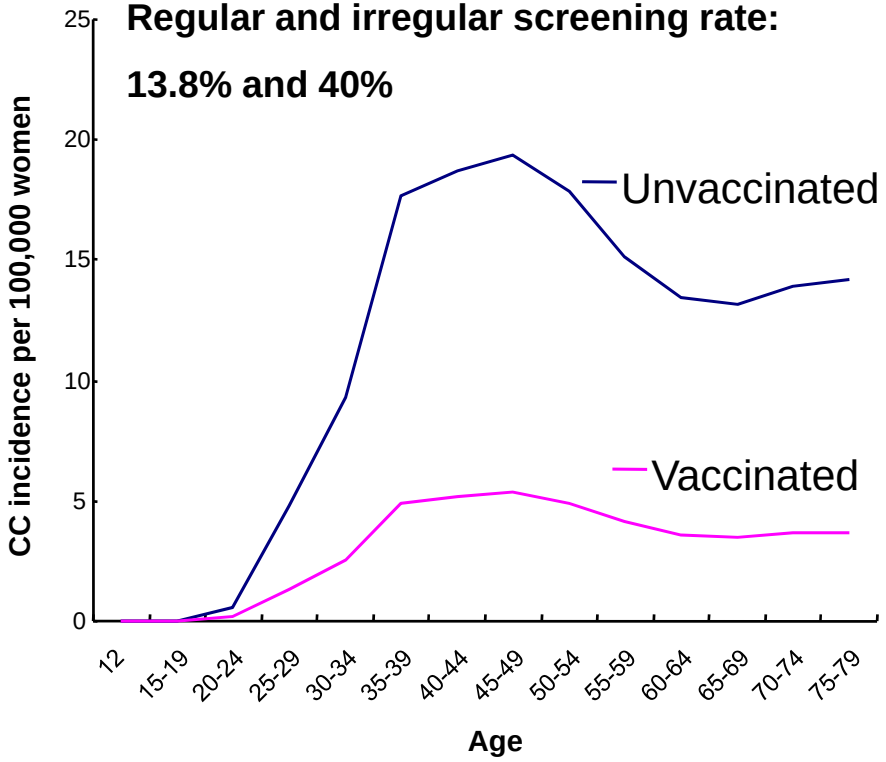
det: subjects with disease detected through screening: same pathways but different probabilities

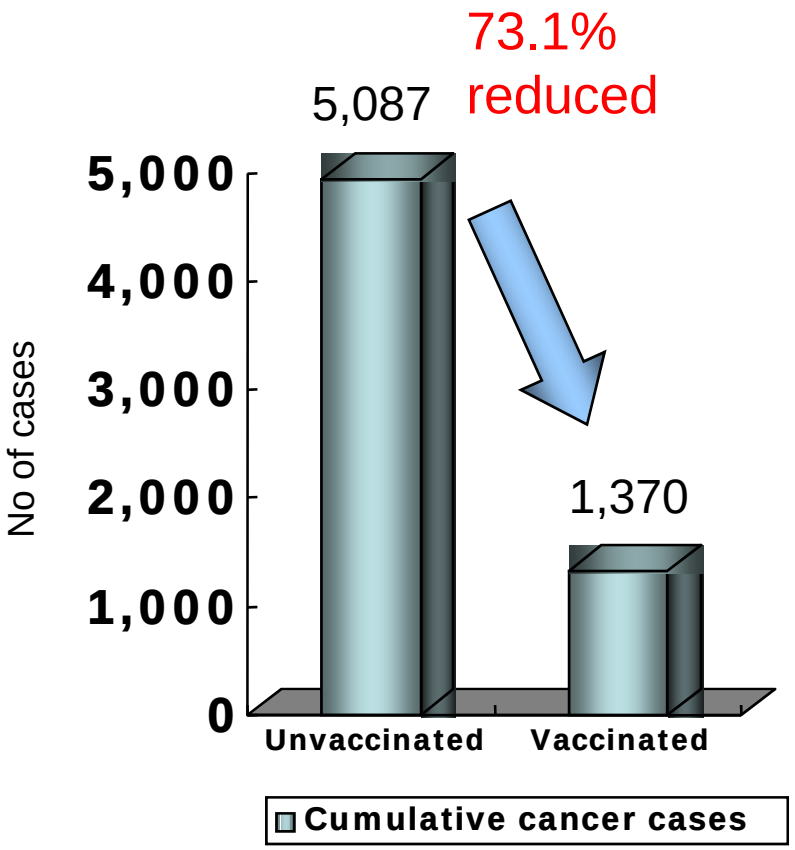
[Condition]

HPV prevalence: 71%

Regular and irregular screening rate:

13.8% and 40%





The figure shows the decrease in the projected number of cancer cases per 100,000 women per age group.

Vaccination of 100% of a single cohort would reduce the number of cancer cases by 73.1% from unvaccination to vaccination.

The cervical cancer vaccine can reduce the number of cervical cancer cases by 73.1% (about 4,000) and also deaths by 73.2% when vaccinating all 12-yr females in Japan.

Cost	Unvaccinated	Vaccinated	Difference	%Diff
Total costs	\81,550,056,836	¥62,560,369,505	-\18,989,687,331	-23.3%
Vaccine costs#	*¥ 0*	*¥21,204,000,000*	*¥21,204,000,000*	-
*Healthcare costs**	*¥49,383,935,935*	*¥32,558,513,234*	*-¥16,825,422,701*	*-34.1%*
*Indirect costs***	*\32,166,120,901*	*\8,797,856,271*	*-\23,368,264,630*	*-72.6%*

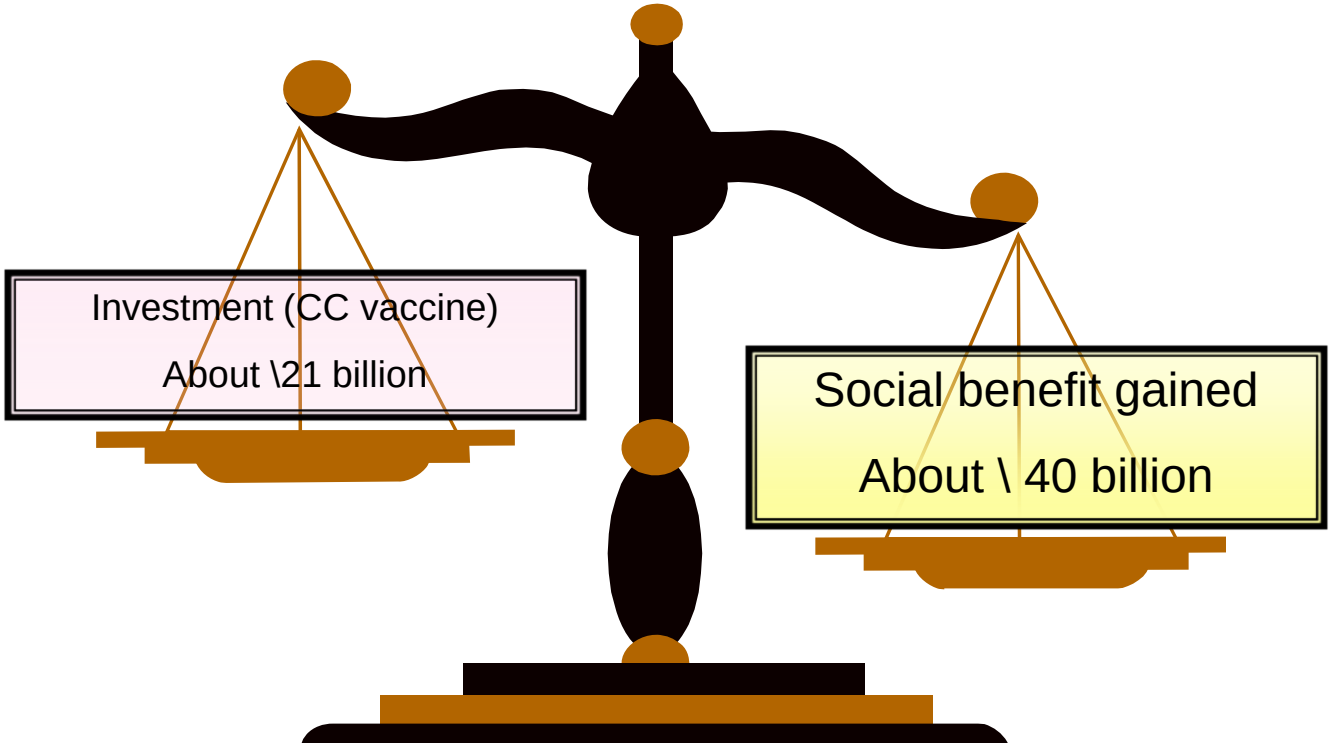
This analysis based on a cohort of 598,000 12 year old girls followed for 90 years.

#It is assumed that price of vaccine is \36,000 per course (100% coverage by public funding).

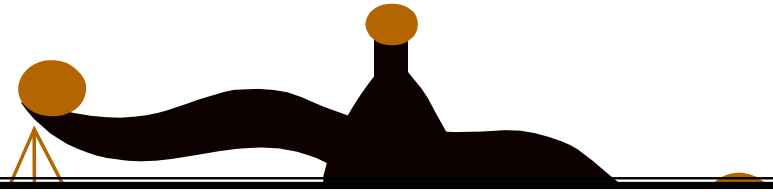
***direct medical cost (1.0% discounting rate), included co-payment**

****productivity loss due to hospitalisation/physician visit and death caused by cervical cancer**

HPV vaccine to all 12-yr females saves \19 billion to Japan society.



HPV vaccination to all 12-yr females has about 2-fold higher cost-performance than threshold value (CBR: 1.0) for efficiency.



Note: CBR (cost-benefit ratio)

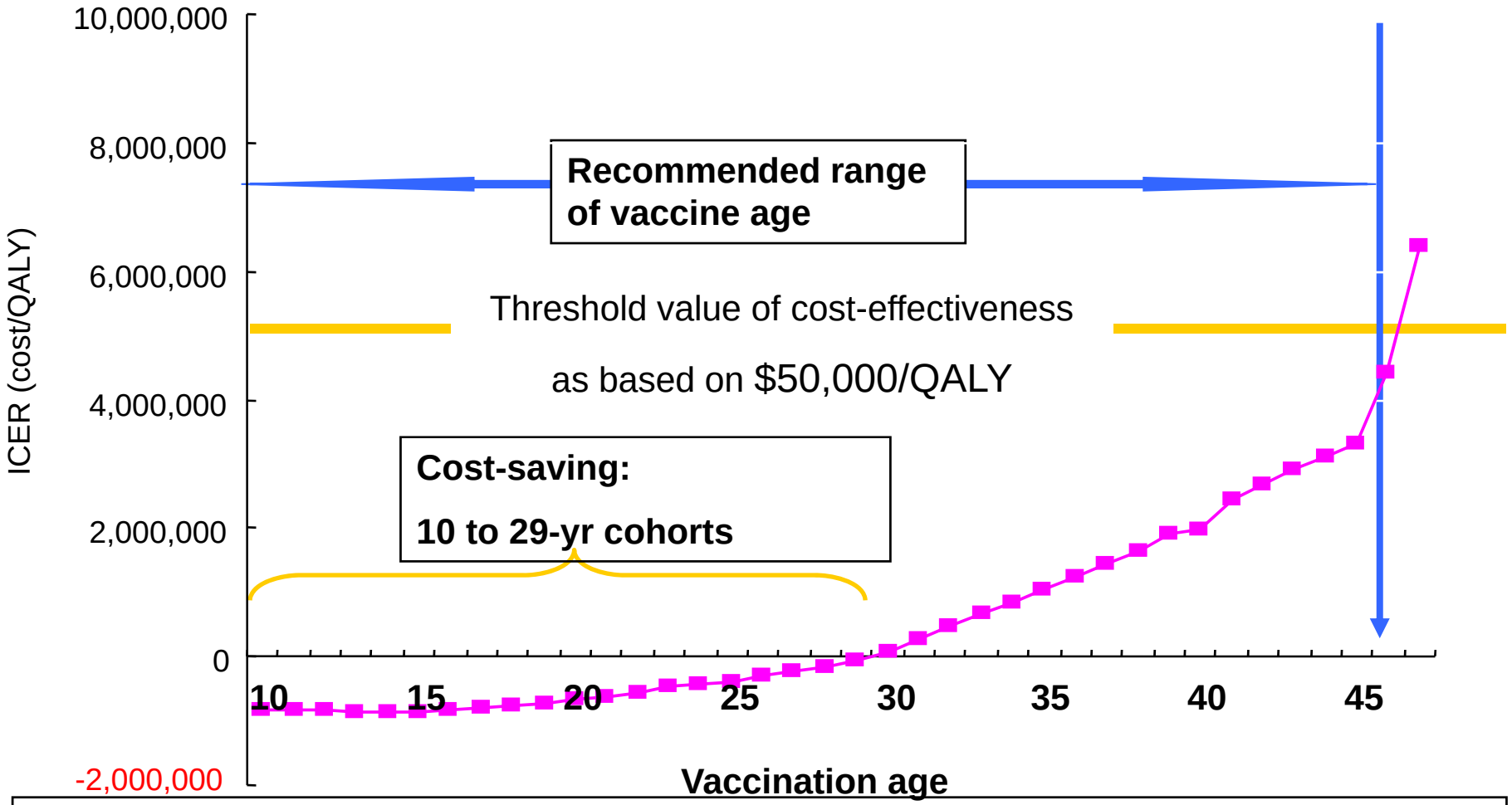
According to a guideline on cost-benefit analysis for assessment of public infrastructures issued by Ministry of Land, Infrastructure, Transportation and Tourism (6th Feb 2004), NPV (net benefit value) and CBR are measure of investment efficiency. Threshold value of CRB is one or more.

Cost-benefit ratio (CBR) = \ 40 billion / \21 billion

= 1.9

>1.0 (threshold CBR for efficiency)

HPV vaccination to all 12-yr females has about 2-fold higher cost-performance than threshold value (CBR: 1.0) for efficiency.



Consists of health care cost, indirect cost, and 100% of vaccine cost (i.e. \ 36,000 per course) at base **1.0% discounting rate**

Simulation of the cost-effectiveness when vaccinating single cohorts from 10 to 45-yr-old was performed. Vaccination up to 29-yr-olds generates savings to the Japan society. Vaccinating as of 30-yr-old will generate costs while still preventing cervical cancer cases and generating QALY over screening programme only. In addition, the ICERs for 30 to 45-yr-old single cohorts were below the generally accepted threshold value of $50,000/QALY gained in the US

- **HPV vaccine reduces disease burden due to reducing incidence and mortality of cervical cancer.**
- **HPV vaccination to all 12-yr females saved about \ 19 billion to Japan society.**
- **HPV vaccination to all 10 to 45-yr females was accepted on the threshold value of cost-effectiveness as based on $50,000/QALY to Japan society.**

Public funding should primarily cover

HPV vaccination to aged 12 years females

Cervical cancer is preventive disease that is different from other cancers

- ✔ Clear causes or risk factors →HPV
- ✔ Precancerous lesion
  →Early detection is possible.
- ✔ Established effective diagnostic tools
  →(Pap test, HPV DNA tests)
  *Treatment without surgery for hysterectomy (conization)
- ✔ Introduction of HPV Vaccine in clinical practice

Q：Who would be likely suffer from cervical cancer?

Any women can have cervical cancer.
It is necessary for all women to have regular screening and vaccine.

HPV Vaccine Recommendation by JSOG, JAOG, JSGO, JSP and Japan Cervical Cancer Eradication Project

The Primary Target	11-14 YO Girls
The Second target	Women aged 15-45
Schedule	3-dose schedule, 0, 1 or 2 and 6 months
Simultaneous administration with other vaccines	measles, rubella, diphtheria and tetanus
Importance of PAP test	Regular screening is necessary even after taking HPV vaccine

Abnormal PAP test	vaccination is valuable[1-3]
HPV positive	vaccination is valuable[4]
Explanation of therapeutic effect	There is no indication that vaccination will have any effect on existing Pap test abnormalities or after treatment of already established dysplasia[5]
Immunocompromised Persons	can be vaccinated, but efficacy might be less than healthy person
During Pregnancy	not recommend[5]
Lactating Women	can be vaccinated[5]

1. Franco EL et al.: J Infect Dis 1999;180:1415–23
2. Molano M et al.: Am J Epidemiol 2003;158:486–94
3. Moscicki AB et al.: J Pediatr 1998;132:277–84.
4. European Research Organization on Genital Infection and Neoplasia, Paris, France.April 23–26, 2006.
5. FDA. Product approval information: Gardasil (quadrivalent human papillomavirus types 6,11,16,18). Merck & Co., Available at http://www.fda.gov/cber/label/HPVmer060806LB.pdf.

The Primary Target Population of HPV Vaccination

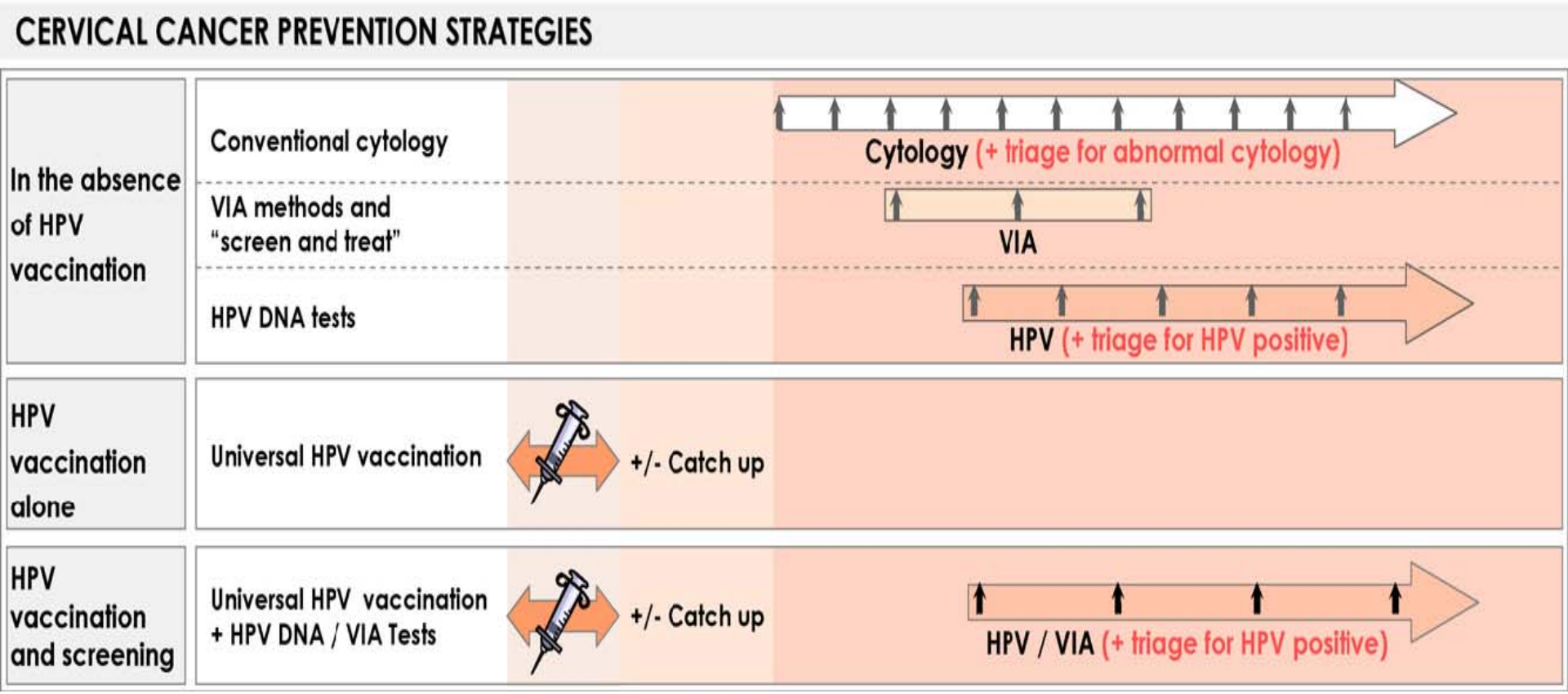
- The HPV vaccine is primarily recommended for 11-14 year-old girls (for Japan) as it is most effective among women who have not been exposed to HPV.
- Public funding is critical to achieve high coverage of HPV vaccination among young adolescent girls who are the primary target of HPV vaccination

The 2nd Target Population of HPV Vaccination

- HPV vaccination for older aged women (age 15~45) who are the 2nd target (or catch-up) is also recommended as it is highly cost-effective, and should be publicly funded.
- 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.

Necessity of education at regional level

- It is necessary to implement special programs to educate school teachers, opinion leaders, healthcare professionals and policy makers about cervical cancer and HPV at regional level in order to strengthen acceptability of vaccination.



1. **Cervical Cancer screening test**
2. **Introduction of HPV typing test**
3. **Introduction of HPV Vaccination**
4. **Implementation of Health Administration for protecting public health**
5. **Long term vision with acceptance of logical scientific evidences**

Garland S, Konno R, Bocsh FX et al. Vaccine 26. Suppl 12, 2008

Cervical cancer prevention: Era of HPV vaccination

- **Persistent infection with one of 15 high-risk HPV types is considered a necessary cause of cervical cancer.**
- **Worldwide, meta-analyses have estimated that HPV-16 and HPV-18 account for 70% of all cervical cancer.**
- **These proportions are broadly similar for all global regions, and highlight the increasing importance of HPV-16/18 with increasing lesion severity.**
- **HPV type-specific DNA prevalence data are useful for estimating the theoretical proportion of cervical cancer and pre-invasive lesions preventable by current HPV-16/18 vaccines.**
- **Any cross-protection of HPV-16/18 vaccines against disease related to other HPV types would increase these theoretically preventable proportions.**
- **Cervical cancer screening should continue in the future (with effective modification).**

Conclusion and recommendation

Cervical cancer prevention in Asia-Pacific region

in Tsukuba, 12-14, November, 2009

Cervical cancer working group
Chair Prof. Ryo Konno

Dept. Obstetrics and Gynecology,
Jichi Medical University
Saitama Medical Center

Prevention of Cervical Cancer

Public health awareness

(healthy and safe sexual behavior)

Early Detection- Screening

Advanced Treatment

Improved Survival

Better Quality of life

Nov 13 2009, Tsukuba

Cervical cancer working group

Chair Prof. Ryo Konno