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子宮頸ガンの第一次予防と第二次予防に関する国際比較―健診とHPVワクチン導入の現況

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子宮頸ガンの第一次予防と第二次予防に関する国際比較－検診とHPVワクチン導入の現況

An International Comparison of Primary and Secondary Cervical Cancer Prevention: Screening and HPV Vaccination

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Abstract

Cervical cancer caused by persistent infection with high risk humanpapilloma viruses (HPV) is one of the most preventable and curable of all cancers. However, it is the second most common cancer in women world-wide. Attempts to eradicate cervical cancer began over 50 years ago with secondary prevention in the form of cervical screening with the Pap smear and have progressed to primary prevention with the recent development of prophylactic HPV vaccines. These vaccines are now licensed in over 85 countries world-wide, but not in Japan. This paper will examine attitudes and policies towards cervical cancer screening and HPV vaccination implementation in 4 countries: Australia, the United Kingdom, the United States and Japan.

A literature review of screening methods, uptake rates, vaccine implementation and attitudes to both of these preventative methods was undertaken for each country. Participation rates in cervical screening programs in Australia, the United Kingdom, the United States and Japan are about 61%, 84%, 82% and 20%, respectively. HPV vaccines have been licensed in the former 3 countries for women aged 9-26 years since 2006 but are not scheduled to be licensed in Japan until 2011. Both Australia and the United Kingdom have free school-based vaccination programs. In the United States the vaccine is covered by the Vaccine for Children Program.

Onset of sexual activity is becoming younger in all 4 countries and the number of sexual partners teenage girls have is increasing. Sexually transmitted infections are also rising in each country. HPV is the most common sexually transmitted infection in the world. With delayed implemtation of the HPV vaccines and poor cervical cancer screening rates, young women in Japan will have a higher risk of developing cervical cancer and at a younger age compared with their counterparts in Australia, the United Kingdom and the United States.

Key Words：HPV, Cervical Cancer, Screening , Vaccine, International Comparison
キーワード：HPV　子宮頸ガン　検診　ワクチン　国際比較

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Introduction

Cervical cancer is one of the most preventable and curable of all cancers. However, it is the second most common cancer in women globally. The World Health Organization recently estimated that there are about 510,000 newly diagnosed cervical cancer cases each year and 288,000 deaths.[1] More than other cancers, cervical cancer reflects global health inequalities. Over 80% of all cases occur in developing countries, where it is often the leading cause of all cancer related deaths and the largest single cause of years of life lost (YLL).[2,3] This is because cervical cancer affects relatively young women and even in industrialized countries it is the second largest cause of death in women under 45 years.[4]

Attempts to eradicate cervical cancer began over 50 years ago with secondary prevention in the form of the "Pap Test" or "Pap smear", and it is estimated that systematic cytology-based screening can reduce deaths from cervical cancer by around 70%.[5] In the 1980s, the next major breakthrough in cervical cancer prevention was made by zur Hausen, who discovered a link between cervical cancer and the humanapilloma Virus (HPV).[6] During the following 20 years many epidemiological studies were undertaken and at the beginning of the 1990s, results clearly demonstrated that specific "high-risk" types of HPV were carcinogenic and persistent infection with these "high risk" types was necessary for the development of cervical cancer.[7] These findings led to the development of sensitive molecular methods such as HPV-PCR to help identify woman with the HPV types responsible for cervical cancer and its precursor lesions.[8]

Identification of a virus such as HPV also implies that successful prophylactic or therapeutic intervention should prevent the disease(s) that it causes. Identification of "high risk" types of HPV led the way for the development of vaccines against primary high risk HPV infections and consequently against specific cancers, and in particular cervical cancer. Large scale clinical trials by two major pharmaceutical companies have proven the prophylactic potential of two HPV vaccines, *Gardasil* (Merck) and *Cervarix* (GlaxoSmithKline) and led to their being licensed in over 85 countries worldwide.[9,10,11]

In most industrialized countries there are three elements to the introduction of a new vaccine: licensing, recommendations for use and funding. This paper will examine how four countries: Australia, the United Kingdom, the United States and Japan have reacted to the development of these vaccines, and what implementation measures, if any, they have taken. It will also examine existing screening programs and women's attitudes to them.

1. HPV

1.1 HPV and Disease

It is estimated that 15% of the 10 million cases of cancer than develop annually are caused by infectious agents. Of these, approximately 30% (～5% of all cancers) are attributable to HPV.[12] Papillomaviruses (PV) are small, double stranded viruses that infect the squamous epithelia (skin and internal mucosae) of both humans and animal. In humans (HPV) over 100 types have been characterized molecularly and about 40 types are able to infect the anogenital tract, where they cause benign lesions. Some of these benign lesions, however, have the potential to progress to invasive cancer, depending of the type of HPV causing the infection。 Anogenital HPV types can be divided into three groups: "high-risk or carcinogenic", "low-risk" and, "probably carcinogenic" since there is limited data available on them.

Table 1
Classification of anogenital human papillomaviruses[13,14]

Classification	HPV types
High-risk or carcinogenic	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82
Probably carcinogenic	26, 53, 66,
Low-risk	6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, 89

The benign lesions induced by low risk HPV types (lrHPV) include non-genital and anogenital skin warts, oral and laryngeal papillomas and anogenital mucosal condylomata.[11] While these conditions are benign, the burden caused by lrHPV is not something to be taken lightly. Genital warts are highly infectious and result in significant morbidity. One in 100 sexually active Americans has been reported to have clinically apparent genital warts[15] and in 2004, almost 80,000 new cases of genital warts were reported in the UK.[16] They are estimated to cost the UK health care system £25-30 million annually. Furthermore, the risk of a rare but potentially devastating disease caused by the growth of benign wart-like neoplasm in the aerodigestive tract, recurrent respiratory papillomatosis (RRP), is increased 231 fold with a maternal history of genital warts.[17] About 90% of anogenital warts are caused by lrHPV 6 and 11.[13]

High-risk HPV types (hrHPV) are associated with cancers and their precursor lesions. Cancers of the cervix, anus, penis, vulva, vagina, as well as a proportion of mouth and oro-pharyngeal cancers, are attributable to persistent hrHPV infection.[2] However, cervical cancer has received the most attention as it is responsible for about 10% of all cancers in women world wide. From Table 2, it can be seen that anogenital tract HPV-associated malignant disease is dominated by persistent infection with hrHPV 16 and 18, which are said to be responsible for 70% of all cases of cervical cancer.[18]

Table 2
Cancers attributable to hrHPV in 2002 and HPV type[2]

Site	Attributable to hrHPV (%)	Of which HPV 16 and /or 18 (%)
Cervix	100	70
Penis	40	63
Vulva, Vagina	40	80
Anus	90	92
Mouth	3	95
Oro-pharynx	12	89

1.2 HPV and Sex

HPV infections are almost always transmitted sexually and are considered to be the most common sexually transmitted viral infection worldwide. They are often acquired shortly after the onset of sexual activity, with the highest incidence of HPV infection found in sexually active women under the age of 25.[14] The incidence rate drops dramatically between the ages of 25 and 35 after which cervical cancer rates begin to peak. Unlike many other STIs, the HPV virus is transmitted through skin-to-skin contact and not by semen or other bodily fluids, so condoms, while offering some protection, may not be able to prevent spread of the infection completely.

Furthermore, since the prevalence rate of HPV infection among women who have sex with women has been reported to be between 13% and 30%[19,20] and HPV-DNA has been reported in about 20% of women who have never had vaginal intercourse,[21] it can be said that the majority of women are at risk for acquiring an HPV infection. The lifetime risk of sexually active males and females acquiring an HPV infection is said to be between 50 and 75%.[14,22]

1.3 From HPV Infection to Invasive Cervical Cancer

While HPV infections are extremely common, most (75%-90% of all infections) will clear spontaneously through normal immune responses within 1-2 yr of exposure.[23] This means that the majority of women, who are infected, even with a hrHPV, will **not** develop cervical cancer. However, because the rate of HPV infection is so high in adults worldwide, along with the fact that many developing countries do not have the means to organize or carry out large-scale screening programs, cervical cancer still remains the second most common cancer in women. Out of the 300,000,000 HPV infections contracted every year, 30,000,000 will develop to low grade squamous intraepithelial lesions (low-SIL), of these 10,000,000 will develop into high grade squamous intraepithelial lesions (high-SIL) and eventually, about 500,000 will develop into cervical cancer.[24] Furthermore, for unscreened women, the risk of invasive cancer occurs earlier (35-55 yr) than for most other adult cancers due to the fact that most infections are transmitted in late adolescence or early adulthood.[25] The interval between hrHPV infection and malignant progression usually takes at least 10 years or longer[23,26]

The most important factor for progression to high grade dysplasia and ultimately the development of invasive cancer is a persistent productive cervical infection with a hrHPV. Apart from lack of screening, other less influential external risk factors are: smoking, early onset of sexual activity (exposure to an immature

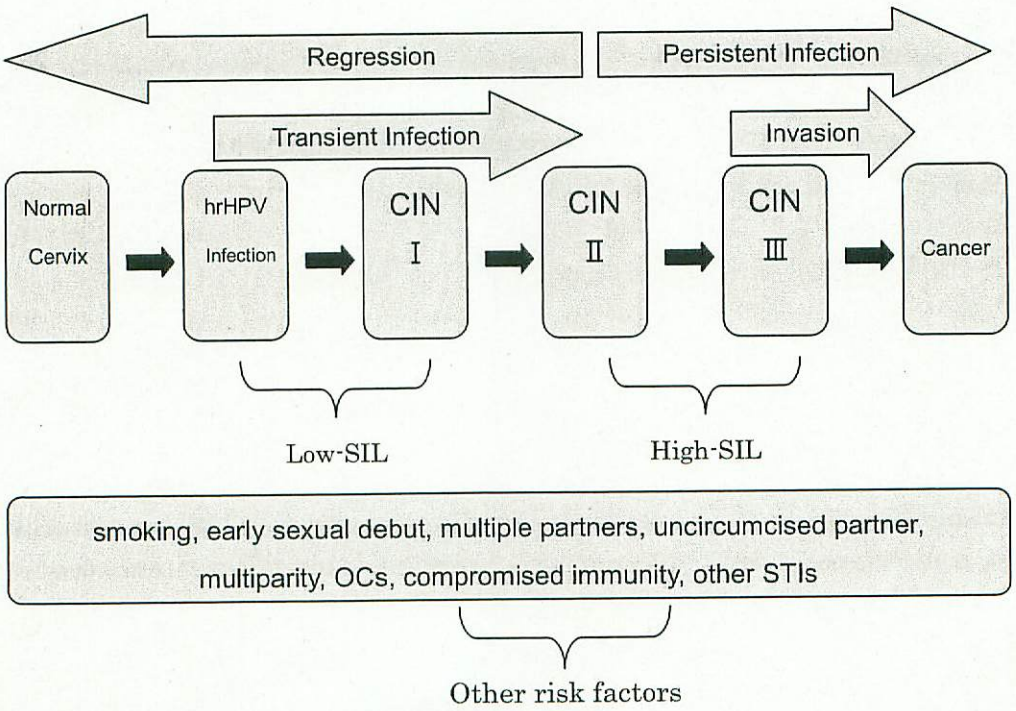

Figure 1: Stages in the development of cervical cancer

cervix), many sexual partners, uncircumcised male partner, multiparity, long-term use (more than 10 years) of oral contraceptives, compromised immunity and infection with other STIs such a *Chlamydia trachomatis* and type 2 Herpes Simplex Virus.[27,28,29] In some countries low socio-economical status is also considered to be a risk factor.

2. HPV Vaccines

HPV vaccines have the potential to prevent or control HPV related infections. As a result, this would decrease the financial burden of their treatment and ultimately reduce or eradicate the incidence of cervical cancer. There are three potential types of vaccines for HPV: prophylactic vaccines that induce viral neutralizing antibodies to prevent HPV infection; therapeutic vaccines that would stimulate regression of HPV induced lesions and chimeric vaccines, which would be a combination of both.

Since 2006, two prophylactic vaccines containing noninfectious, subunit virus-like particle (VLP) have been approved and licensed for use. They were developed using recombinant DNA technology and contain the single viral protein, L1. This protein is the major structural protein of the virus and contains its immunodominant neutralization epitopes. The first vaccine, *Gardasil* (Merck), was approved by the U. S. Food and Drug Administration (FDA) in June 2006. It is a quadrivalent vaccine and available in over 85 countries, including Europe and Australia, but not Japan. The second, a bivalent vaccine, *Cevarix* (GSK), has been approved in both Australia and Europe and is waiting for approval in the US. Licensing permission for both

Table 3
Vaccine characteristics and trial populations

	Gardasil	*Cervarix*
Manufacturer	Merck	GlaxoSmithKline (GSK)
L1-VLP Genotype	6, 11, 16, 18	16, 18
Substrate	Yeast	Baculovirus expression system
Adjuvant	Merck Aluminum adjuvant Proprietary Aluminum Hydroxyphosphate Sulphate	GSK AS04 adjuvant $Al(OH)_3$ Monophosphoryl lipid A
Vaccine Regimen	0.5ml intramuscular injection 0, 2, 6 months	0.5ml intramuscular injection 0, 1, 6 months
Main Efficacy Trials	Females aged 16-26 yr	Females aged 15-25 yr
Lifetime no of partners	0-4	0-6
Adolescent safety and immunogenicity bridging trials	Females and males 9-15 yr	Females 10-14 yr Males 10-18 yr Women 26-55 yr
Ongoing or planned trials	Efficacy study in males Efficacy study in women over 26 yr Safety and immunogenicity in HIV-infected and other immunocompromised groups	Efficacy, immunogenicity, bridging and safety studies in women over 26 yr Safety and immunogenicity in African populations, including HIV infected women

vaccines was filed in Japan in 2007. Both vaccines target hrHPV 16 and 18, which are responsible for over 70% of all cervical cancers. *Gardasil* also targets lrHPV 6 and 11 which are responsible for 90% of genital warts. The HPV vaccine is significant in that it is the first vaccine designed specifically to prevent cancer induced by a virus, since the hepatitis B vaccine was not primary designed for this purpose. Characteristics of the two vaccines and clinical trials are summarized in Tables 3 and 4.

The main histological types of cervical cancer are adenocarcinoma, adenosquamous carcinoma and squamous cell carcinoma. These are preceded by high grade (grades 2 and 3) cervical intraepithelial neoplasms (CIN) and adenocarcinoma in situ (AIS), respectively. While Pap smears have reduced the incidence of squamous cell cervical cancer, rates of cervical adenocarcinoma and its precursor, the incidence of AIS is said to have increased, especially in young women, due to difficulty in detecting these lesions by cytology or coloscopy.[30] Although hrHPV 16 is responsible for over 50% of cervical cancers, hrHPV 18 is closely associated with cervical adenocarcinoma,[31,32] so its inclusion in the vaccines is significant. In terms of the histopathology of pre-cancer, a morphological diagnosis of AIS or CIN-3 is said to be a reliable diagnosis. CIN-2 is heterogeneous and a mixture of CIN-1 and early CIN-3 lesions. While CIN-2 has a sizable regression potential, some lesions also have high malignancy potential, so its cancer potential is equivocal (Fig.1). In most populations the treatment of CIN-2 lesions for cancer prevention is generally recommended.[33] CIN-1 on the other hand is an insensitive histopathological sign of HPV infection and is not precancerous.

Both vaccines were developed with the primary hypothesis that they would reduce the incidence of CIN-2-3 and AIS caused by hrHPV 16 and 18 compared to women who were not vaccinated. Since screening can identify, treat and prevent the majority of cervical cancers, an endpoint of cervical cancer could not be considered ethical. Primary composite endpoints were therefore, a reduction in vaccine type-specific persistent infections, associated CIN-2-3, AIS, and consequently invasive carcinoma of the cervix. A co-primary composite endpoint of *Gardasil* was also a reduction in the incidence of genital warts as well as vulvar/vaginal intraepithelial neoplasma or cancer.

The above mentioned endpoints were carried out in adolescents and young women aged between 15 and 26. In children, however, endpoints of CIN2-3 or AIS are not practical or ethical, since cervical specimens would be required and the endpoint is rare. Bridging studies were therefore conducted using immunogenicity endpoints, where the antibody responses of children were compared with those of women from whom data on the clinical endpoints was available.

2.1 Clinical Trials and Outcomes

Both vaccines underwent randomized, double-blind, placebo controlled phase Ⅲ trials in North America, Latin America, Europe and the Asia-Pacific region. Since the vaccine is supposed to be prophylactic, **the primary efficacy evaluations were done in women who had no evidence of past or present exposure to the vaccine target type** and who received three doses according to the study protocol. This group of women is know as the *per protocol* (PP) group. However, to evaluate the efficacy and safety of vaccines in a general population that includes women already infected with HPV, the trials also enrolled participants irrespective of baseline HPV status or Pap test results. This group is known as the *intention-to-treat* (ITT) group. In the PP group almost near perfect efficacy against the cytological and histological endpoints for up to 5 years was shown.[9,10,11,34,35,36] If all women enrolled in the trials are included, including those who were HPV-positive and

those with precancerous lesions at baseline, **vaccine efficacy was significantly less.** Efficacy results are shown in Table 4.

Table 4
Clinical trial characteristics and outcomes

	Gardasil	*Cervarix*
Clinical Trial	Villa et al[33] (Stage Ⅱ)	Harper et al[35] (Stage Ⅱ)
Age range (yr)	16-23	15-25
Mean follow up (yr)	5	4
No of participants (PP)	552	393
No of sex partners	≦4	≦6
PP efficacy against persistent infection	**96%**	**95%**
Clinical Trial	Joura et al[11] (Stages Ⅱ, Ⅲ)	NR
Age range (yr)	16-26	
Mean follow up (yr)	3	
No of participants (PP)	7785	
PP efficacy against high grade (VIN-2-3) vulva/vaginal lesions	**100%**	
ITT efficacy	**† 71%, ‡ 49%**	
Clinical Trial	Garland et al[34] (Stage Ⅲ)	NP
Age range (yr)	16-24	NR
Mean follow up (yr)	3	
No of participants (PP)	2216	
PP efficacy against genital warts	**100%**	
ITT efficacy	**† 73%, ‡ 34%**	
Clinical Trial	Future Ⅱ[10] (Stage Ⅲ)	Paavonen et al[9] (Stage Ⅲ) §,
Age range (yr)	15-26	15-25
Mean follow up (mt)	36	15
No of participants	5305	7788
PP efficacy against CIN-2-3, AIS	**98%**	
ITT efficacy	**† 44%, ‡ 17%**	
Modified ITT efficacy against CIN-2-3		**90%**

PP = per protocol, ITT = intention to treat, NR = not reported

† vaccine type specific HPV infection at baseline, ‡ infection of any HPV type at baseline, § interim results

From these results it can be seen that the efficacy of the vaccine is modest in the ITT group. Only in those women who had no signs of present or past HPV infection at baseline, was the efficacy high, proving that the vaccine is indeed prophylactic and not therapeutic. Consequently, many important questions and challenges regarding these first generation vaccines still remain. For example the value of vaccinating women in the upper age limit of 19-26 years, since women who have had several sexual partners and have already been exposed to the vaccine targets types may already have developed partial immunity and cannot be distinguished from

unexposed women with present HPV-DNA testing. Furthermore, since the vaccines do not treat preexisting lesions or infection, they would be most effective in (young) girls to confer immunity at an age before sexual activity has begun. The cost of the vaccine is also a significant issue. It has been estimated that the vaccine would have to be sold at $1 per dose to be affordable in developing countries where is burden of cervical cancer is greatest, however, at a cost of about $120 per dose, this is far from achievable. The main unresolved issues regarding the vaccines are summarized in Table 5.

Table 5
Questions and challenges regarding HPV vaccines

Questions
1. Duration of protection and booster necessity
2. Efficacy and safety of boosters
3. Efficacy and duration of cross-protection against other related types
4. Efficacy of fewer than the recommended 3 doses
5. Efficacy / benefits in boys and men
6. Changes in the natural history of other carcinogenic types
7. Protection against other HPV-related cancers
8. Optimum age to vaccinate
Challenges
1. Vaccinating young girls before the onset of sexual activity
2. Continued compliance with screening programs
3. High cost
4. Introduction of vaccines into developing countries

3. International Comparison of Cervical Screening and Vaccine Implementation

3.1 Australia

3.1.1 Cervical Screening and Cancer

In 2006, Australia had the second-lowest incidence of cervical cancer and the lowest mortality rate from cervical cancer in the word. Between 1985 and 2005, the number of cases of cervical cancer halved and the number of deaths dropped by about 60%. This is mainly due to the government investment of more than $90 million in the National Cervical Screening Program which was established in 1991.[37] The program aims to reduce both morbidity and mortality from cervical cancer in a cost-effective manner. Since the introduction of the Program, cervical cancer had dropped from the eighth most common cancer in Australian women to the sixteenth. Women aged 20 to 69 are invited to have a pap smear every 2 years. Since women are recommended to have a pap smear 2 years after the onset of sexual activity, those younger than 20 can also take part in the screening program. The incidence of cervical cancer in the target age group dropped from 17.2 per 100,000 women in 1991 to 9.1 in 2003, while mortality rates dropped from 4.0 in 1991 to 1.8 in 2004.[38]

All women are kept on a confidential registry which recommends and reminds women who have not had a recent pap smear to go and have one. Screening services are primarily provided by GPs, but are also available at community or women's health centers, family planning clinics or sexual health clinics. In 2004-2005, the

screening program participation rate of women in the target age group of 20-69 was 61.0%.[36]

3.1.2 HPV Vaccine Approval

In Australia, all medicines and vaccines considered for funding by the Australian Government must first be approved by the Therapeutic Good Administration (TGA). The TGA guarantees safety and clinical efficacy, but does not access cost effectiveness. *Gardasil* was approved by the TGA on 16 June 2006 for females aged 9-26 and males ages 9-15. However, before a vaccine can be made part of the Australian National Immunization Program, or put on the Pharmaceutical Benefits Scheme, it also has to be evaluated by the Pharmaceutical Benefits Advisory Committee (PBAC). The PBAC is comprised of both male and female health professionals, health economists and consumer advocates who assess whether a vaccine is both clinically and cost-effective. Furthermore, whenever the PBAC considers a vaccine it seeks advice from the Australian Technical Advisory Group on Immunization (ATAGI). One of the members of the PBAC is also a member of ATAGI. Before making any recommendation on *Gardasil*, the PBAC also consulted experts in the field of immunology and sexual health for additional advice. *Gardasil* was initially rejected by the PBAC as not being cost-effective. However, after negotiations with the suppliers, who reduced the price and offered more favorable conditions for supply, the PBAC considered the vaccine to be cost-effective at the new conditions offered. After being recommended by the PBAC, the Australian government agreed that *Gardasil* should be funded for girls aged 12 to 26 by their National Immunization Program starting in the 2007 school year.[39]

3.1.3 Vaccine Implementation

The Australian government agreed to fund *Gardasil* for the following three cohorts:

1. An ongoing school-based vaccination program for the target group of 12 and 13 year old girls; generally administered in the first year of secondary school.
2. A predominantly school-based 2 year catch up program for 13-18 year old girls peviod.
3. A community-based program 2 year catch up program for women up to and including the age of 26; generally administered through General Practitioners (GP).

While *Cervarix* has also been approved for use in Australia for woman up to the age of 45, the government is not funding the vaccine in women older than 26. Similarly, it is not, at the moment, funding a vaccine program of *Gardasil* for boys.

As with the National Cervical Screening Program, a confidential National HPV Vaccine Program Register is being developed to collect data about the program. Those women, who are sexually active and present for the vaccination program without being up-to-date with their Pap smears, will also be offered a Pap smear at the same time.

3.1.4 Vaccine Cost

The estimated cost of the vaccine is $436 million dollars over the first 4 years, including the cost for the 2 year catch-up program for girls and women aged 13 to 26. Once the catch-ups are complete, the ongoing cost of the vaccination program for girls in the first year of secondary school is estimated to be under $50 million dollars a year.[39] When the vaccine is administered by the GP, the vaccine itself is free, but a charge for GP consultation is sometimes occurred.

Since the present prophylactic vaccines are said to cover 70% of all cervical cancers caused by HPV, a meta-analysis was done to estimate the proportion of cervical cancer in Australia attributable to the hrHPV 16 and 18.[40] The results showed that 77.7% of cervical cancers could have been prevented by the present prophylactic vaccines, which implies that Australia may gain even higher benefits from their HPV vaccination program than some other countries.

3.2 UK

3.2.1 Cervical Screening and Cancer

While screening for cervical cancer began in the 1960's in the UK, the National Cervical Screening Programme was not set up until 1988. The program aims to reduce the number of women who develop invasive cancer as well as the number of women who die from it. Cervical cancer has now been reduced to the twelfth most common cancer in the UK and one analysis of mortality trends before and after the introduction of screening estimated that about 5000 deaths have been prevented per year.[41] The incidence of cervical cancer in the UK decreased from 15.4 per 100,000 in 1986 to 3.4 in 2004. Furthermore, mortality rates in 2004 were 2.8 per 100,000 females, a decrease of more than 60% compared to 1975 when they were 7.5 per 100,000 females.[42] The cost of cervical screening, as well as the treatment of pre-cancerous lesions is said to be around £157 million a year, or £37.50 per woman.[43] Since all medical care in the UK is free, cost-effectiveness is an important issue.

In Scotland, Wales and Northern Ireland, women aged 20 to 69 are invited to go for a pap smear every 3 years. From 2003, based on findings published in the Cancer Research UK audit[44], the screening frequency and age was changed for women in England. They are now invited every 3 years to go for screening between the ages of 25 and every 5 years from the ages of 50 and 64. The reason given for this change was that invasive cancer is rare in women under 25, but cervical changes (that could be treated later if they did not regress) are not and many young women were having unnecessary investigations and treatment that could be detrimental to them both mentally and physically. In women over 50, it was felt that abnormal cells develop more slowly and screening every 3 years did not give an extra protection. Women aged 65 who have had three consecutive negative Pap smears in the preceding ten years are taken out of the recall system. Women aged 65 and over who have never had a Pap smear are entitled to one. In all 4 countries, women with abnormal results are followed-up as appropriate. From 2003, liquid based cytology was also introduced throughout the UK, which has resulted in less inadequate samples and quicker results. Pilot testing of HPV triage for borderline or mild dyskaryosis has been introduced at 6 cytology laboratories throughout the country, but cost effectiveness of HPV triaging has not yet been proven.[45]

Screening rates in the UK are high. In 2003, 84% of women aged 20-64 had gone for a Pap smear in the last 5 years.[46] Screening normally takes place at the woman's general practitioner's clinic, where the computerized Pap smear call-recall registry is kept, and can be done by the GP or a nurse at the clinic. Women are given the choice of having a female doctor do the test if their GP is male. It can also be done at community clinics, such as well-women clinics, ante-natal clinics or family planning clinics. Patient education is also high, with many booklets, pamphlets and posters explaining about the test and why it is necessary. Special attention has recently been given to women from different ethnic backgrounds and women with learning disabilities whose rate of attendance is low, and various measures such as easy to understand booklets in 17 languages and Braille, pre-

testing visits to the clinic by the women or home visits by nurses, have been undertaken so that these women can also make an informed decision about having a Pap smear.[47] The rate of attendance in women under 35 years has also fallen recently and surveys are taking place to find out why and how to resolve the situation.[44]

3.2.2 HPV Vaccine Approval

Gardasil was first approved by the European Union in September 2006 and was licensed in the UK for children and adolescents, 9 to 15 years, and adult females 16 to 26 years of age one month later. *Cervarix* was licensed from October 2007. After recommendations from the Joint Committee on Vaccines and Immunisation (JCVI), which provides the Department of Health (DoH) with independent expert advice on all vaccines issues, the DoH decided that a HPV vaccination program would be available on the National Health Service (NHS) from September 2008.[48] It estimated that 400 lives could be saved each year, but also admitted that the effects would not be seen for decades. The JCVI committee did not make any recommendations about which vaccine should be offered. Since cost-effectiveness plays a large part in the NHS, it is likely that the company that offers the best price will be chosen. The DoH has been criticized by many patient groups for delaying the implementation of the HPV vaccine. It has been suggested that it did this to wait for *Cervarix* being licensed in the UK so that a "cost-war" could be invoked among the two companies making the vaccines to get a better price.

3.2.3 Vaccine Implementation

The DoH agreed to fund the vaccine for the following two cohorts:

1. An ongoing school-based vaccination program for the target group of 12 and 13 year old girls; generally administered in the first year of secondary school.
2. A predominantly school-based 2 year catch up program for 13-18 year old girls

In Scotland the catch up program will be for 2 to 3 years and begin in 2008,[49] while in other parts of the UK it will be a 2 year catch up program beginning in 2009. Unlike Australia, a catch up program for women up to the age of 26 was not found to be cost-effective, but the DoH had admitted it may be beneficial to some women and the issue is under review.

3.2.4 Vaccine Cost

The estimated cost of the vaccine is £100 million per year for the school-based program and another £400 million for the 2 year catch-up program for girls aged 13-18 years.[46] It will be the most expensive vaccination program undertaken by the NHS. Since all NHS medical consultations in the UK are free, vaccines given to girls who have left school but are 18 or under will be administered free by their GP. At the moment the vaccine can be given for a fee of about £450 for a three-dose course in private clinics. Since the EU marketing authorization for *Gardasil* did not exclude males, a trend had been seen among men who have sex with men wanting the vaccine to protect them from genital warts as well as anal and penile cancer, since the incidence of anogenital cancers is higher in this group and the incidence of hrHPV 16 and 18 in anal cancer, in particular, is high.[50] (Table 1)

About 81.2% of invasive cervical cancers in the UK are attributable to hrHPV 16 and 18.[46] Furthermore, the total reported number of cases of genital warts increased 8-fold in men and 11-fold in women between 1971

and 2004 in England and Wales.[51] Consequently, the UK may also gain higher benefits from their HPV vaccination program than some other countries.

3.3 USA

3.3.1 Cervical Screening and Cancer

While there is no national screening program for cervical cancer in the USA, in 2002, more than 82% of women aged 25 years or above had a Pap smear in the last 3 years.[52] Pap smears are normally done as part of a woman's routine health-check by her physician, a nurse midwife or nurse practitioner in primary care practices. The Centers for Disease Control (CDC) provide low-income, uninsured, and underserved women access to cervical cancer screening through the National Breast and Cervical Cancer Early Detection Program (NBCCEDP). An estimated 8-11% of U.S. women of screening age (18-64) are eligible to receive NBCCEDP services.[53] Current guidelines recommend that a woman have a Pap smear at least once very 3 years, beginning 3 years after the start of intercourse, but no later than age 21. Women aged 65 to 70 years with at least three normal pap smears and no abnormal Pap smear in the last 10 years may chose to stop having one.[54] The American Cancer Society (ACS) also recommends HPV testing from the age of 30 years.

3.3.2 HPV Vaccine Approval

In June 2006, the FDA approved *Gardasil* for use in females aged 9-26 years. *Cervarix* is currently being evaluated. The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control (CDC) is the federal agency charged with grading the level of recommendation for all vaccines. It recommended routine vaccination of 11-12 year old girls and catch-up vaccination for females 13-26 years of age.[55] However, guidelines issued by the ACS[56] recommend that:

1. Females aged 11 to 12 years are vaccinated
2. Females aged 13 to 18 years undergo catch-up immunization

It stated insufficient data to recommend for or against vaccination in females aged 19 to 26 years and believes this decision should be made between a woman and her physician regarding her past sexual history and risk of HPV exposure. Finally, it does not recommend vaccinating women over 26 years or males of any age. Both the ACIP and ACS note that vaccination could be started in girls as young as 9 years of age.

3.3.3 Vaccine Implementation

There are no federal laws requiring immunization of children with HPV vaccine. Laws concerning immunization for entry into childcare or schools are state laws and vary from state to state. Several jurisdictions have been considering mandatory vaccination of 11-12 year old girls before they enter middle school, but this is very controversial. In 2007, at least 24 states and the District court of Columbia introduced mandate legislation for the HPV vaccine.[57] Most of these include "opt-out" options for medical, religious or philosophical beliefs. The only state with a mandate in place is Virginia because a Texas executive order mandating HPV vaccination was overridden by the Texas legislature. Many pro-family and anti-vaccination groups strongly oppose mandatory HPV vaccination.

3.3.4 Vaccine Cost

As is the case in both the UK and Australia, the HPV vaccine is the most expensive childhood vaccine in the USA. It will cost $120.50 for each of the three doses in the private sector (not including practitioner fees) and $96.75 per dose under the federal vaccine contract. In the USA, private insurer vaccination coverage has generally followed recommendations by the ACIP. The Vaccine for Children Program (VCP) provides free vaccines to children and adolescents under 19 years of age, who are either uninsured, Medicaid-eligible, American Indian or Alaska Native.[58] However, while the (VCP) has added HPV to its vaccine plan for 9-18 year old females,[59] not all private insurers have approved coverage, so the uninsured or underinsured may only have limited access, especially women aged 19-26 years. The prevalence of hrHPV 16 or 18 in women with cervical cancer in the US is estimated to be 77.1%.[52]

3.4 Japan

3.4.1 Cervical Screening and Cancer

Cytological screening for cervical cancer began in selected areas of Japan in 1961. Most of the early programs were voluntary and jointly organized by gynaecologists and local government officials. In 1967, screening began at a national level after government funding was introduced. In 1983 the Health and Medical Service Law for the Aged was passed and cervical screening was established as one aspect of the government's cancer screening program to be implemented throughout the country at each town, city or prefecture. In 1998, national government funding for cancer screening was stopped and the Health and Medical Service Law for the Aged almost ceased to function. Implementation of the law was left to regional governments. However, the continuation of screening programs has been strongly recommended by the national government and medical organizations. Today the screening programs for cervical cancer are funded by regional governments that arrange mass screening for which women have to pay 10-30% of the total cost. In addition to screening organized by regional governments, many women have the chance to undergo cervical cancer screening as part of the health insurance or benefits package of their place of employment. Screening is always done by gynaecologists and most of the time the women have to go to a local health center or cancer center where they have no choice or knowledge about the doctor doing the Pap smear.

After the introduction of the Health and Medical Service Law for the Aged, the target population was all women over 30 years of age and the screening interval was set at 1 year. In 2004, however, this was revised and the target population was set at women 20 years and over with the interval increased to every 2 years. Compared to other industrialized countries with screening programs in places, participation in Japan is extremely low. A participation rate of about 15% has been reported for government sponsored programs and[60] the overall participation rate, including private companies has been estimated to be about 20-24%.[61,62] Furthermore, over half of these women who do undergo screening are over 50 years of age. In one 2004 survey by Jichi Medical University of women aged 20-59 years, the main reasons for not taking part in the screening program were: *too bothersome, don't have the time, have to pay for it and its embarrassing*, in that order.[64] In another conducted in the Hokuriku area reasons given were also time and money for women over 30 years and for women under 30 years it was embarrassment and hesitancy, which is similar to a survey of women in their 20s in the United Kingdom, who quoted embarrassment and fear of pain as main reasons.[65,45]

Cervical cancer is the seventh most common cause of cancer deaths in women in Japan and the fourth most

common cancer in women.[66] By 2020, it is estimated that it will be the second or third most common cancer in women in Japan. This may partly be due to the fact that the incidence of cervical cancer in young women is increasing.[65] Unlike in other industrialized countries where breast cancer is the most common cancer among young women, in Japanese women aged 20-39 years, it is cervical cancer that comes first.[65] In 1960 the mortality rate for cervical cancer was 21.3. This decreased to 5.3 in 1993.[67] However, according to data from the National Cancer Center of Japan, compared to 1985, the mortality rate for cervical cancer in women aged 25-29 years had increased 5-fold in 2005. In 1975, 1985 and 2000, the incidence rate of cervical cancer, including carcinoma in situ, for women aged 20-29 was 2.0, 3.1 and 8.0, respectively. In women aged 30-39, the incidence rate was 16.0, 25.0 and 40.0, respectively.[64] Furthermore, in one study carried out in Niigata prefecture, the incidence rate of cervical carcinoma in situ among women 20-29 years increased 13 fold between 1982 and 1996.[68] This increase in carcinoma in situ in young Japanese women, along with the low cervical screening rates, suggests that a cervical cancer time-bomb in Japan may be waiting to explode.

3.4.1.2 HPV Vaccine Approval and Implementation.

At present no vaccine against HPV has been approved for use in Japan. Japanese bridging trials started in 2006 where women aged 18-26 years were enrolled for *Gardasil* and women aged 20-25 years for *Cervarix*. Both GSK and Merck filed for licensing permission in September and November of 2007, respectively. The vaccines are expected to be approved for use in 2011. While there are no guidelines yet for HPV vaccination in Japan, at present it is likely to be only given to females.[69] Unlike in Australia, the UK and the US, hrHPV 18 is not so common in Japan and the present vaccines are said to only cover between 50- 60% of all cervical cancers there.[31,70] While *Cervarix* is said to also offer cross-protection with hrHPv 31 and 45, many Japanese researchers have expressed the need to develop a vaccine specific to Japan that would include hrHPV 16, 33, 52 and 58, which are more common there.[65,69] However, a study by Nakagawa et al did show that hrHPV 18 occurred most in cancers of women in their 20s and 30s when progression of the disease is rapid.[31]

4. Conclusion

Cervical cancer is the second most common cancer in women worldwide. However, it can be prevented, detected, and treated successfully when caught early enough. Since the latter half of the 20th century, the most successful strategy for cervical cancer prevention has been secondary prevention in the form of population-based organized screening, where slow progressing cytological abnormalities are identified and treated before invasive disease appears. However, imperfect cytology is said to be responsible for 30% of all cervical cancers and it is estimated that even with optimal screening procedures, an incidence rate of 2.2 per 100,000 women can be expected.[71]

Identification of the humanpapilloma virus by zur Hausen in the 1980s led to the development of primary prevention at the beginning of the 21st century in the form of prophylactic vaccines. Two of these vaccines *Gardasil* (Merck) and *Cervarix* (GSK) developed using recombinant DNA technology and containing noninfectious, subunit virus-like particle (VLP) have been approved and licensed for use in over 85 countries worldwide, but not yet in Japan. Many important questions and challenges still remain regarding these vaccines. **Most importantly, it must be remembered that HPV vaccines do not prevent cervical cancer, they prevents infection of the virus (HPV) that causes it.** Since HPV is a sexually transmitted infection, the

vaccine has to be administered before the establishment of persistent HPV infection to be most effective. Given that a high incidence of HPV infection occurs within a few years of the onset of sexual activity, the vaccine should then be administered before sexual activity begins. The average age of the onset of sexual activity varies from country to country, but most countries that have adopted the vaccine have set the target ages as 11-12 years. Other unresolved issues are whether to vaccinate adolescent girls and women who are already sexually active, the duration of vaccine efficacy, whether to vaccinate boys, changes in the natural history of other carcinogenic types, cost, and how to have widespread availability in developing countries where 80% of cervical cancers occur.

In countries such as Australia, the UK and the USA, with high participation in population-based screening programs, HPV vaccines will have a larger effect on reducing the cost of treating HPV related morbidity such as precancerous lesions or genital warts rather than HPV related mortalities. In Japan with low screening rates, a significant increase in sexually transmitted infections, including HPV,[72] as well as an increase in the incidence of precancerous lesions in young women, HPV vaccines have the potential to save many lives. However, at present with delayed implementation of the HPV vaccines and poor screening rates, it must be said that young women in Japan will have a higher risk of developing cervical cancer and at a younger age compared to their counterparts in Australia, the United Kingdom and the United States.

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