성인예방접종

유 병 욱

순천향대학교 서울병원 가정의학과

COI (Conflict of Interest) Declaration

본 강좌의 내용에 대해서

본 강의의 강사는

한국MSD(유)의 부스 및 광고

후원을 받았음을 밝힙니다

2016년 대한임상건강증진학회 춘계학술대회

왜 성인백신 접종이 필요한가?
Why do we need Adult vaccination?

20세기 가장 위대한 의학적 성과

순 위	성 과	득표율(%)
1	깨끗한 물과 하수도 (개인위생)	15.8
2	항생제	14.5
3	마취	13.9
4	백신	11.8
5	DNA 구조 발견	8.8
6	세균 이론	7.4
	경구 피임약	
8	근거중심의학	5.6
9	의학영상 (X-ray 등)	4.2
10	컴퓨터	3.6

1. Annabel Ferriman et al. Sanitation is greatest medical milestone since 1840 *BMJ* 2007;334(7585):111.

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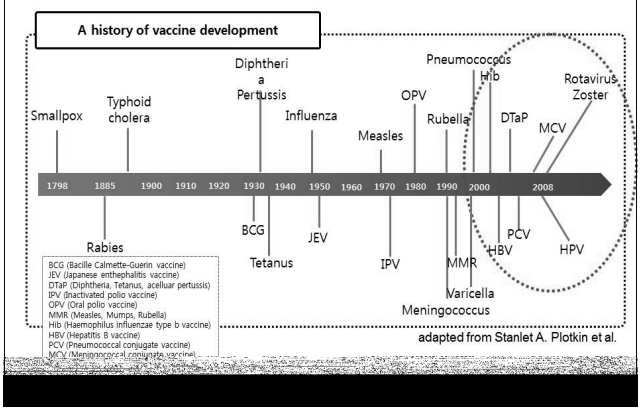
백신 개발의 연혁



대상포진의 질병부담

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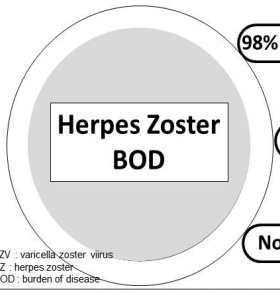
대상포진 질병부담



- 98% have had VZV infection in US[1]
- 1 in 3 will have HZ in lifetime[1]
- No screening test to prevent HZ[2]

VZV : varicella-zoster virus
HZ : herpes zoster
BOD : burden of disease

This 'Cause' need to be taken up by multiple stake holders.

Of the estimated 1 million cases per year,[1] approximately 70% occur in adults ≥50 years of age[4]

1. Harpaz R et al. Prevention of Herpes Zoster. *MMWR.* 2008;57(RR-5):1–30.
2. Weaver BA. Herpes Zoster Overview: Natural History and Incidence. *J Am Osteopath Assoc.* 2009;109(suppl 2):S2–S6.
3. Oxman MN. Herpes Zoster Pathogenesis and Cell-Mediated Immunity and Immunosenescence. *J Am Osteopath Assoc.* 2009;109(suppl 2):S13–S17.
4. Pappagallo M et al. Pharmacological Management of Postherpetic Neuralgia. *CNS Drugs.* 2003;17:771–780

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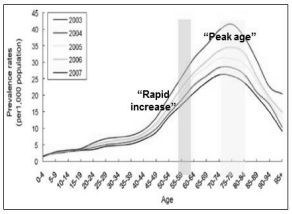
대상포진 질병부담(한국,2003-2007)

- Prevalence rates increased sharply after 50 years and reached a peak at 70 years
- The prevalence of zoster was about 1.4 times higher in women than in men Total socioeconomic cost of herpes zoster was $75.9–143.8 million per year, increasing every year by14–20%

Patients diagnosed with HZ during 2003-2007 [HIRA]



Rates of clinic visits	• 7.93–12.54 / 1000 population
Rates of hospitalizations	• 0.22–0.32 / 1000 population
Increase in socioeconomic cost per year	• 14–20%

HIRA: Health Insurance Review & Assessment Service

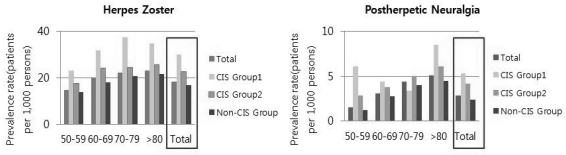
*Study design: We used the database of the Health Insurance Review & Assessment Service of Korea and analyzed the data of patients who had herpes zoster as a principal diagnosis during the period from 2003 to 2007. We investigated the annual prevalence, rate of clinical visits, rate of hospitalization, and the pattern of medical services use. The socioeconomic burden of herpes zoster was calculated by a conversion into cost.

1. Won Suk Choi et al. Disease burden of herpes zoster in Korea. *Journal of Clinical Virology* 2010;47:325-329

VACC-1118664-0031 09/2017

한국의 대상포진, 대상포진후신경통 발병률2009 [HIRA]

- Prevalence aged ≥50 years: HZ:18.54 per 1000 PY, PHN:2.88 per 1,000 PY
- Highest prevalence rate observed in severe immunodeficiency



- CIS: compromised immune status
  - CIS group 1 : Includes patients primarily diagnosed with severe CIS such as transplantation, hematological malignancies, or autoimmune deficiency disease.
  - CIS group 2 : Included those who were diagnosed with mild or moderate CIS such as rheumatoid arthritis, a solid tumor, or diabetes and excluded those who were in CIS group 1
- HIRA K-NPS: Health Insurance Review and Assessment Service National Patients Sample
- HZ: Herpes Zoster. PHN: Postherpetic Neuralgia, PY: Person Year

*Study Design: This is retrospective, population-based study using 2009 database from HIRA K-NPS to calculate the prevalence and rate of healthcare utilization related to HZ and PHN among Korean patients stratified by immune status. HZ and PHN patients aged ≥ 50 years were categorized into three groups by immune status; severely immunocompromised group, moderately compromised group, and non-compromised group. The prevalence, disease-related healthcare utilization, and medical costs were compared across the three groups.

*Reference : CL Cheong et al. Prevalence and healthcare utilization of herpes zoster and postherpetic neuralgia in Korea: Disparity among patients with different immune status. *Epidemiol Health* 2014;36:e2014012.

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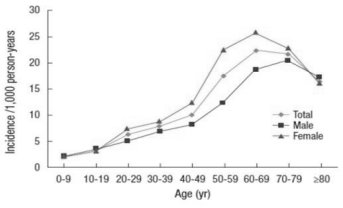
한국인의 나이에 따른 HZ Incidence 2011[HIRA]

Age adjusted incidence of HZ according to sex



Overall Incidence:10.4 per 1,000 PY
Incidence in women:12.6 per 1,000 PY
Incidence in men:8.3 per 1,000PY
1.5 fold higher incidence in women

HZ: Herpes Zoster, PY: Person Year
HIRA: Health Insurance Review & Assessment Service

- Incidence of HZ is 10.4 per 1,000 PY strongly correlated with age.
- HZ Incidence is higher than previous studies (median 4-4.5 per 1,000 PY).

*Study Design: The purpose of this study was to evaluate the incidence and other epidemiological features of HZ in the general Korean population. We used population-based medical records from the Health Insurance Review & Assessment Service, which includes 50,908,646 medical insurance subscribers, to calculate the incidence of HZ. Also, we analyzed an age-stratified random sample of 1,375,842 individuals to study descriptive epidemiologic characteristics of HZ in Korea in 2011.

*Reference : YJ Kim et al. Population-Based Study of the Epidemiology of Herpes Zoster in Korea. *JKMS* 2014;29:1706-1710.

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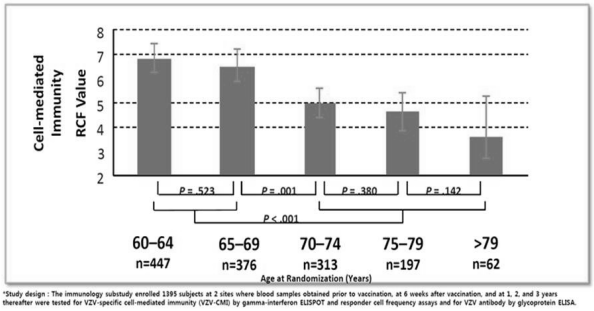
연령에 따른 CMI 감소

CMI : Cell mediated immunity



*Study design : The immunology substudy enrolled 1395 subjects at 2 sites where blood samples obtained prior to vaccination, at 6 weeks after vaccination, and at 1, 2, and 3 years thereafter were tested for VZV-specific cell-mediated immunity (VZV-CMI) by gamma-interferon ELISPOT and responder cell frequency assays and for VZV antibody by glycoprotein ELISA.

RCF=Responder cell frequency value (the number of responding CD4+ memory T cells per 10^6 peripheral blood mononuclear cells).

1. Levin MJ et al. Varicella-zoster virus-specific immune responses in elderly recipients of a herpes zoster vaccine. *J Infect Dis.* 2008;197(6): 825-835

VACC-1118664-0031 09/2017

대상포진 위험인자

(Age, DM, COPD, CKD, Family History)

DM : Diabetes mellitus
COPD : Chronic obstructive pulmonary disease
CKD : Chronic kidney disease

VACC-1118664-0031 09/2017

대상포진 위험인자

- Age[1]
- Diabetes Mellitus[2]
- COPD[3]
- Chronic Kidney Disease[4]
- Family History[5]

1. Won Suk Choi et al. Disease burden of herpes zoster in Korea. *Journal of Clinical Virology* .47 (2010) 325–329;
2. Jose et al. Incidence of Herpes Zoster and Persistent Post-Zoster Pain in Adults with or without diabetes in the United States *OFID*. 2014 DOI: 10.1093/ofid/ofu049
3. Ya-Wen Yang MD MS et al. Risk of herpes zoster among patients with chronic obstructive pulmonary disease: a population-based study. *CMAJ* 2011. DOI:10.1503 /cmaj.101137
4. Mei-Yi Wu et al. Risk of Herpes Zoster in CKD: A Matched-Cohort Study Based on Administrative Data. *Am J Kidney Dis.* 2012;60(4):548-552
5. Hernandez PO, Family history and herpes zoster risk in the era of shingles vaccination. *J Clin Virol.* 2011 Dec;52(4):344-8

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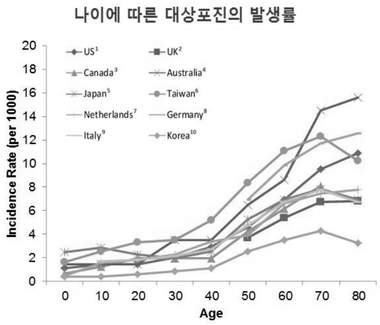
연령이 증가함에 따라 대상포진 발병이 증가(Worldwide)



References: **1**. Insinga RP et al. *J Gen Intern Med.* 2005;20(8):748-753; **2**. Gauthier, A et al. *Epidemiol Infect.* 2008, 137:38-47; **3**. Brisson M et al. *Epidemiol Infect.* 2001, 127:305-314; **4**. Stein AN et al. *Vaccine.* 2009, 27:520-529; **5**. Toyama N et al. *Journal of Medical Virology.* 2009, 81:2053-2058; **6**. Lin YH et al. *Vaccine.* 2010, 28:1217-1220; **7**. de Melker et al. *Vaccine.* 2006 24:3946-3952 ; **8**. Ultsch B et al. *BMC Infectious Diseases.* 2011, 4; **9**. Gialloreti et al. *BMC Infectious Diseases.* 2010, 10:230; **10**. Won Suk Choi et al. *Journal of Clinical Virology* .47 (2010) 325–329;

VACC-1118664-0031 09/2017

당뇨 환자에서의 대상포진 위험

자료	국가	출처	연구 설계	연구 대상	기간	결과 (당뇨 환자에서의 대상포진 위험)
1)	미국	**Medical and pharmacy claims**	Retrospective observational study	전체 5,100만명 중 대상포진 (n= 420,515)	2005-2009	당뇨 환자에서 **대상포진 HR = 1.45** 대상포진 후 **지속적 통증 HR = 1.18**
2)	미국	**보험청구** 자료	matched cohort study	**1형 당뇨** (n=20,397) 대조군 (n=81,588) **2형 당뇨** (n=380,401) 대조군 (n=1,521,604)	1997-2006	1형 당뇨 : No evidence **2형 당뇨** - 65세 이상 **HR 3.12** - 40~ 64세 사이 **HR 1.51**
3)	영국	**C**linical **P**ractice **R**esearch **D**atalink	Case-control study	대상포진 (n= 144,959) 대조군 (n=549,336)	2001-2011	**1형 당뇨** : 보정된 OR **1.27** 2형 당뇨 : No evidence
4)	미국	MarketScan	Case-control study	대상포진 (n= 59,173) 대조군 (n=616,177)	2007 1-12월	**20-64세** 사이 보정된 OR : **1.06** (1.03-1.09)
5)	일본	**Kitano** Hospital Research Database	Retrospective hospital-based cohort study	기저질환을 가진 55,492 명의 환자	2001-2007	보정된 HR : **2.44** (2.10-2.85)
6)	이스라엘	Maccabi **Healthcare Services**	Nested Case Control study	대상포진 (n=22,294) 대조군 (n = 88,895)	2002 - 2006	OR = **1.53** (1.44–1.62)

1) Jose et al. Incidence of Herpes Zoster and Persistent Post-Zoster Pain in Adults with or without diabetes in the United States *OFID.* 2014 DOI: 10.1093/ofid/ofu049
2) A.P. GUignard et al. Risk of herpes zoster among diabetes: a matched cohort study in a US insurance claim database before introduction of vaccination, 1997-2006. *Infection* (2014) 42:729-735
3) Harriet J et al. Quantification of risk factors for herpes zoster:population based case-control study *BMJ* 2014;348:g2911 doi: 10.1136/bmj.g2911
4) Riduan M. Joesoef et al. Chronic Medical Conditions as Risk Factors for Herpes Zoster. *Mayo Clin Proc.* 2012;87(10):961-967.

당뇨 환자에서의 대상포진 위험: 미국 보험청구 database (2)

- **연구 방법**
  - ➢**1997-2006년** 자료, Retrospective cohort study
  - ➢미국 **IHCIS** (Integrated Health Care information services database) 활용
  - ➢연구 집단
    - ○ **1형 당뇨 : 20세 이전 당뇨 증세가 있고 인슐린을 투여받는 사람**
    - ○ **2형 당뇨 : 모든 경구용 항당뇨제를 복용하는 환자**
    - ○ 1형 당뇨 환자 (n=20,397) + matched control (n=81,588)
    - ○ 2형 당뇨 환자 (n=380,401) + matched control (n=1,521,604)
  - ➢**면역억제 상태 or 치료 환자는 제외됨**
    - ○ 암, 신질환, 간질환, 대사성 질환, 대상포진 병력 환자 등
    - ○ COPD, cardiac disease 환자는 포함
  - ➢**Cox**-proportional hazard regression analysis using a **stepwise method**

Reference) A.P. Guignard et al. Risk of herpes zoster among diabetes: a matched cohort study in a US insurance claim database before introduction of vaccination, 1997-2006. *Infection* (2014) 42:729–735

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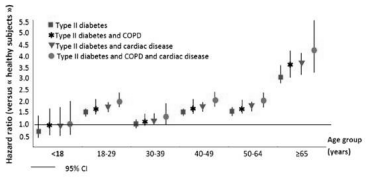
당뇨 환자에서의 대상포진 위험: 미국 보험청구 database (2)

- **2형 당뇨병** 환자가 대상포진의 증가된 위험과 관계가 있었음
  - ➢ **≥ 65 years : HR 3.12** [2.77-3.52], adjusted for gender
  - ➢ **40 ~ 64 years** : **HR 1.51** [1.42-1.61]
- 1형 당뇨병의 대상포진의 impact에 대해서는 evidence 가 없었음
- 심장 질환 (HR 1.92) 및 만성 폐질환 (HR 1.52) 역시 위험 인자였음

연령별, 2형 당뇨 및 동반질환과 관련된 대상포진의 Hazard Ratio (reference - 당뇨와 동반질환이 없었던 "건강한" 피험자)



*Study Design: The study conducted a retrospective cohort study using the Integrated Health Care Information Services database, during the period 1997–2006. A type I diabetes cohort, a type II diabetes cohort and two non-diabetic cohorts matched for date of enrolment and duration of follow-up were defined. HZ and diabetes were defined using a combination of ICD-9 and prescription drug codes. Individuals with immunosuppressive conditions or treatments were excluded. Cox Proportional Hazards regression analysis using a stepwise method with backward elimination was applied to estimate the hazard ratios (HR) of HZ, including age, gender and co-morbidities as covariates.

Reference) A.P. Guignard et al. Risk of herpes zoster among diabetes: a matched cohort study in a US insurance claim database before introduction of vaccination, 1997-2006. *Infection* (2014) 42:729–735

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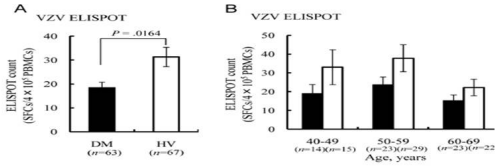
당뇨환자의 세포매개면역

Comparison of Varicella-Zoster Virus-Specific Immunity of Patients with Diabetes mellitus and Healthy Individuals

- Blood samples for the IFN-γ ELISPOT assay and gpELISA were collected during a single phlebotomy session (63 DM, 67 healthy pts)
- VZV-specific CMI, but not the humoral immunity, was statistically significantly lower among patients with diabetes mellitus than it was among healthy volunteers



CMI = Cell-Mediated Immunity, VZV=Varicella-Zoster Virus, DM = Diabetes Mellitus, HV = Healthy volunteers, HbA1c = hemoglobin A1c , SFC = spot-forming cell

*Study design : Blood samples for the IFN-γ ELISPOT assay and gpELISA were collected during a single phlebotomy session (63 DM, 57..3years, 67 healthy pts.M.2years). IFN-g ELISPOT counts and gpELISA antibody titers were compared between patients with diabetes mellitus and healthy individuals with use of the Mann–Whitney U test. Spearman's correlation coefficient by rank test was used to analyze the correlation between IFN-g ELISPOT counts and the percentage of hemoglobin A1c (HbA1c)

Shigefumi Okamoto et al. Comparison of Varicella-Zoster Virus-Specific Immunity of Patients with Diabetes mellitus and Healthy Individuals. *JID* 2009;200:1606–10.

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COPD환자, 대상포진 발병위험이 증가

Reference	Country	Data Source	Study Design	Study Population	Period	Results (Risk for HZ in COPD patients)
1)	Taiwan	Taiwan Longitudinal Health Insurance Database	Cohort Study	COPD patients (n= 8,486) matched control patients (n=33,944)	2004-2006	Crude HR: **1.98** (95% CI 1.73-2.26) Adjusted HR: **1.68** (95% CI 1.45–1.95)
2)	UK	Clinical Practice Research Datalink	Case-control study	HZ case(n= 144,959) Control(n=549,336)	2001-2011	Chronic obstructive pulmonary disease were associated with increased risk of zoster 6815(4.7%) v 20 201 (3.7%); **1.32**, 1.27 to 1.37
3)	US	MarketScan data	Case-control study	HZ case(n= 59,173) Control(n=616,177)	Jan 1, 2007 - Dec 1,2007	**Adjusted OR**(95% CI) with COPD among cases and controls aged 20 to 64 is **1.35**(1.23-1.47)

- COPD:Chronic obstructive pulmonary disease –HZ: Herpes Zoster

1) Ya-Wen Yang MD MS et al. Risk of herpes zoster among patients with chronic obstructive pulmonary disease: a population-based study. *CMAJ* 2011. DOI:10.1503 /cmaj.101137.
2) Harriet J et al. Quantification of risk factors for herpes zoster: population based case-control study *BMJ* 2014;348:g2911 doi: 10.1136/bmj.g2911
3) Riduan M. Joesoef et al. Chronic Medical Conditions as Risk Factors for Herpes Zoster. *Mayo Clin Proc.* 2012;87(10):961-967

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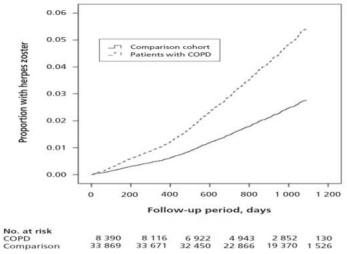
COPD환자,대상포진 위험증가 Taiwan 연구결과



Crude HR of HZ: **1.98** (95% CI 1.73-2.26) Adjusted* HR of HZ: **1.68** (95% CI 1.45–1.95)

* Adjusted for potential confounding factors in the multivariate analysis; including diabetes, cancer, rheumatic diseases, use of inhaled or oral corticosteroids, Charlson comorbidity index, monthly income and urbanization level of the community in which the patient resided.

• COPD: chronic obstructive pulmonary disease
• CI: confidence interval

Herpes zoster event rates for patients with COPD and comparison patients from 2004 to 2006. Log-rank test: $p < 0.001$

- **Patients with COPD were at increased risk of herpes zoster relative to the general population.**

*Study Design: To investigate the risk of HZ among patients with COPD, we conducted a cohort study using data from the Taiwan Longitudinal Health Insurance Database. We performed Cox regressions to compare the hazard ratio (HR) of herpes zoster in the COPD cohort and in an age- and sex-matched comparison cohort. We divided the patients with COPD into three groups according to use of steroid medications and performed a further analysis to examine the risk of herpes zoster

•Reference: Ya-Wen Yang MD MS et al. Risk of herpes zoster among patients with chronic obstructive pulmonary disease: a population-based study. CMAJ 2011. DOI:10.1503/cmaj.101137

VACC-1118664-0031 09/2017

CKD 환자, 대상포진 위험 증가

Reference	Country	Data Source	Study Design	Study Population	Period	Results (Risk for HZ in CKD patients)
1)	Taiwan	Taiwan Longitudinal Health Insurance Database	Matched-Cohort Study	CKD patient (n=13,321), comparison cohort (n=66,605)	2004-2006	Crude HR for HZ: **1.64**(1.46-1.85) Adjusted* HR for HZ: **1.60**(1.41-1.81)
2)	UK	Clinical Practice Research Datalink	Case-control study	HZ case (n= 144,959) Control (n=549,336)	2001-2011	**CKD** is associated with a greater than 10% increased risk of zoster(8724 (6.0%)v 29 437 (5.4%); **1.14**, 1.09 to 1.18)
3)	Taiwan	Longitudinal Health Insurance Database in Taiwan	Retrospective cohort study	13,321 patients with CKD diagnosis	Jan 1, 1996 up to Dec 31, 2008	• **Renal transplantation (HR, 8.46**; 95% CI 5.85–12.2) • **Peritoneal dialysis (HR 3.61; 95%** CI 2.49–4.83) • **Hemodialysis (HR 1.35**; 95%CI 1.18–1.55) compared with the comparison group (p <0.0001)
4)	Japan	Kitano Hospital Research Database	Retrospective hospital-based cohort study	55,492 patients with underlying disease	2001-2007	Adjusted HR (95% CI) for HZ in patients with **renal failure** is **2.14**(1.65-2.79)

- CKD: Chronic Kidney Disease –HZ: Herpes Zoster

1) Mei-Yi Wu et al. Risk of Herpes Zoster in CKD: A Matched-Cohort Study Based on Administrative Data. Am J Kidney Dis. 2012;60(4):548-552
2) Harriet J et al. Quantification of risk factors for herpes zoster:population based case-control study *BMJ* 2014;348:g2911 doi: 10.1136/bmj.g2911
3) Shih-Yi Lin et al. A Comparison of Herpes Zoster Incidence across the Spectrum of Chronic Kideny Disease, Dialysis and Transplantation. Am J Nephrol. 2012;36:27-33
4) A. Hata et al. Risk of Herpes zoster in patients with underlying diseases: a retrospective hospital-based cohort study. *Infection.* 2011;39(6):537-44.

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가족력과 대상포진

자료	국가	연구 설계	결과
1)	미국	Case control study, - 1103 acute herpes zoster patients and 523 controls - 2006.07-2010.07	대상포진 환자 중 가족력 있음 (43.5%) vs. 대조군 환자 중 가족력 있음 (10.5%) 1촌 가족력 있는 경우, Odds Ratio = 4.44
2)	프랑스	National, matched case-control study - 250 cases of HZ and 500 controls, - 2009.04-2010.09	가족력과 대상포진은 유의한 연관성을 보임 Odds Ratio = 3.69
3)	이란	Case-control study - 217 case and 200 control groups . - 2009.02-2011.12	대상포진 환자 중 1촌 가족력이 있음 (30%) vs. 대조군 중 가족력 있음 (8%) Odds Ratio = 4.91

1. Hernandez PO, Family history and herpes zoster risk in the era of shingles vaccination. *J Clin Virol.* 2011 Dec;52(4):344-8.
2. Lasserre A, Herpes zoster: Family history and psychological stress—Case–control study. *J Clin Virol.* 2012 Oct;55(2):153-7.
3. Ansar A, Association between Family History and Herpes Zoster: A Case-Control Study. *J Res Health Sci.* 2014;14(2):111-4.

VACC-1118664-0031 09/2017

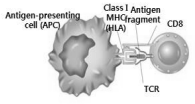
대상포진과 유전 인자

HLA 유전형과 PHN risk에 대한 메타분석[1]

- 이전에 실시되었던 HLA 유전형 관련 연구들을 메타분석한 결과, HLA-A*33 및 HLA-B*44 형질이 PHN환자에서 유의하게 많이 발현되었으나, HLA-A*02 및 HLA-B*40 의 경우 유의하게 발현되지 않음
- VZV peptide와 affinity 분석을 한 결과, HLA-A*02 이 B*44번에 비해 ~7배 더 높은 affinity를 보임
- PHN의 가능한 underlying cause 가 약한 HLA binding peptide affinity로 인한 이상적이지 않은 anti-VZV immune response 로 인한 것이라고 시사

대상포진 환자에서 Genome-wide association analysis[2]

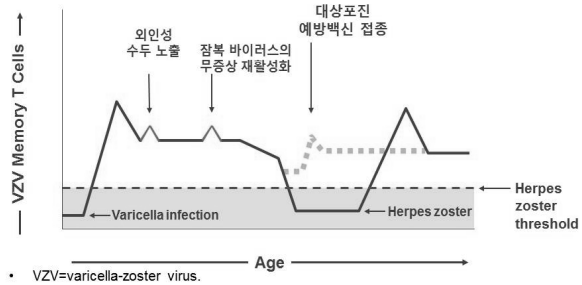
- 22,981명의 환자 (2,280명의 대상포진 환자 포함)를 대상으로 실시한 genome-wide association analyses 에서, MHC complex 내 non-coding gene HCP5 (HLA complex P5)가 대상포진 발병 연령과 관계되어 있다고 밝혀짐



1. Meysman P et al. Varicella-zoster virus-derived MHC class I-restricted peptide affinity is a determining factor in the HLA risk profile for the development of PHN. *J Virol.* 2015 Jan 15;89(2):962-9.
2. Crosslin DR et al. Genetic variation in the HLA region is associated with susceptibility to herpes zoster. *Genes Immun.* 2015 Jan;16(1):1-7.

VACC-1118664-0031 09/2017

세포매개 면역의 약화와 잠복한 VZV의 재활성화와의 관련성[1]



- VZV=varicella-zoster virus.
- **1.** From *N Engl J Med*, Arvin A, Aging, immunity, and the varicella-zoster virus, Vol 352, p 2266-2267, © 2005 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

VACC-1118664-0031 09/2017

About ZOSTAVAX™ [Zoster Vaccine Live (Oka/Merck)]

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ZOSTAVAX™ [Zoster Vaccine Live (Oka/Merck)] 제품 프로파일[2]

- 약독 VZV 생바이러스 백신
- Dose당 19,400 PFU 이상[1]
  - VARIVAX™ [Varicella Virus Vaccine Live (Oka/Merck)] 14배 이상의 효력
- 보존제 없음
- 동결건조 제품
- 1회 피하주사

PFU=plaque-forming unit; VZV=varicella-zoster virus.
1. Oxman MN et al. *N Engl J Med.* 2005;352:2271–2284.
2. 조스타박스 제품설명서, MSD Korea.

VACC-1118664-0031 09/2017

ZOSTAVAX™ [Zoster Vaccine Live (Oka/Merck)] 적응증과 금기사항

적응증

- ZOSTAVAX는 50세 이상 성인의 백신 접종에 사용됩니다.
- 대상포진의 예방

금기

- 젤라틴, 네오마이신 등 이 백신의 구성 성분에 대해 과민반응이 있는 자
- 원발성 및 후천적 면역결핍 환자
- 고용량 코르코스테로이드 포함, 면역억제요법을 받고 있는 환자
- 치료받고 있지 않는 활동성 결핵 환자
- 임부 또는 임신 가능성이 있는 여성

1. 조스타박스™ 제품설명서

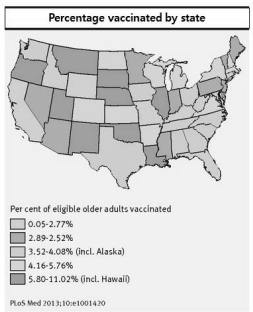
VACC-1118664-0031 09/2017

조스타박스™의 Real world effectiveness[1]

- 조스타박스는 **303,044명**(조스타박스 접종자 **75,761명**)을 대상으로한 대규모 **Real World Study**에서도 입증된 유효성을 보였습니다.
- 목적 : **general practice setting** 에서 백신 접종자의 대상포진 발생 위험을 평가하고자 함.[1]
- 방법 : 후향적 관찰 코호트 연구 (**2007/1/1 – 2009/12/31**)로 **Kaiser Permanente Southern**

미국 : 대상포진 국가접종 후 효과측정[a]

- 2007-2009
- Medicare



- 766,330명의 가능한 피험자 중 29,785명이 연구 기간 중 대상포진 백신 접종, ≥ 65세

대상포진 발병 감소효과 : 48%

[a]Study design:
A cohort study of 766,330 fully eligible individuals aged $65 years was undertaken in a 5% random sample of Medicare who received and did not receive zoster vaccination between 1st January 2007 and 31st December 2009. Incidence rates and hazard ratios for zoster and PHN were determined in vaccinated and unvaccinated individuals. Analyses were adjusted for age, gender, race, low income, immunosuppression, and important comorbidities associated with zoster, and then stratified by immunosuppression status.

1. Langan SM et al. Herpes zoster vaccine effectiveness against incident herpes zoster and post-herpetic neuralgia in an older US population: a cohort study. *PLOS Med*. 2013;10(4):e1001420

VACC-1118664-0031 09/2017

대상포진의 비용대비 백신효과에 대한 연구[a]

*"영국, 캐나다, 미국에서 백신 대비 대상포진질환으로 인한 질병 부담 및 직간접적 발생비용에 대한 연구를 한 결과, 비용대비 삶의 질 개선 측면에서 유리하였다는 결론"**

Table II. Summary of cost-utility analyses of varicella zoster virus vaccine based on vaccine efficacy data from the Shingles Prevention Study.[161] Costs and benefits were modelled over a lifetime horizon and discounted at 3%,[160,161] 3.5%[159] and 5%[160,161] annually

Study (country, year of costing, perspective, design)	Incremental cost per QALY gained (zoster vaccine vs no vaccination)	Study methods
Van Hoek et al.[21] (England and Wales, 2006, healthcare provider, decision analysis model)	£20 412 at a vaccine cost of £55 per dose (costs and QALYs were discounted while cases and hospitalizations were not discounted)	The models were for a cohort vaccinated at age 65 y and with 73.5% vaccination coverage. Costs included community and hospital care, deaths, pain, opthalmic zoster, incidence of PHN and QALY loss. The vaccine waning rate was estimated from 4 y HZ incidence rates after vaccination
Hornberger and Robertus[160] (US, 2006, societal, decision theoretical model)	<$US100 000 at a vaccine cost of <$US100, regardless of the duration of vaccine efficacy beyond 3 y, and <$US100 000 at a vaccine cost of $US200 for all models with vaccine efficacy duration of <30 y	Assumptions included base case aged 69 y; vaccine effects on HZ and PHN were modelled. Models were constructed for vaccine effect durations in the range of 3–30 y
Pellissier et al.[159] (US, 2006, healthcare payer and societal, decision analytic model)	Ranged from $US16 229 (societal perspective for age-specific population estimates of HZ for all cases) to $US27 609 (payer perspective restricted to cases in immunocompetent persons)	Assumed vaccination at age >60 y and that duration of protection against PHN was the same as for HZ. Included vaccine effects on HZ, PHN, and other HZ complications in the total population and in an immunocompetent subpopulation. Models were based on a duration of vaccine efficacy of >12 y
Rothberg et al.[154] (US, 2006, societal, decision analytic model)	$US12 375, overall, but varied according to age and sex from $US43 650 in women aged 70 y to $US123 484 in women aged 80 y	The model was for healthy immunocompetent adults aged >60 y, vaccinated at age 60 y, with vaccine effects on HZ incidence, complications and burden of illness, PHN and death. The model did not account for PHN-associated costs/benefits for the period beyond 3 y post-vaccination
Brisson et al.[155] (Canada, 2005, healthcare payer, cohort model)	$Can33 000 at a unit vaccination cost of $Can150 and no waning of vaccine efficacy, and <$Can40 000 in >76% of simulations with waning vaccine efficacy of >4.5% per y	The model was for incidence and complications of HZ and PHN, assuming vaccination at age 65 y
Najafzadeh et al.[156] (Canada, 2008, healthcare payer, discrete event simulation model)	$Can41 709 with a vaccine waning rate of 4.5% per y ($Can26 357 if vaccination programme restricted to adults aged 60–74 y)	Vaccination of a cohort aged >60 y (mean age 71 y). The model accounted for incidence, duration and treatment of HZ and PHN, and death

HZ=herpes zoster; **PHN**=postherpetic neuralgia; **QALY**=quality-adjusted life-year.

[a]Study design:
MEDLINE, EMBASE and AdisBase search terms were 'varicella zoster virus vaccine live' or 'zoster vaccine live'. Searches were last updated 4 December 2009.
* 영국의 경우 65세 이상, 미국의 경우 70-80세, 캐나다의 경우 60-74세 이상에 해당

1. Sanford M., Keating G.M. Zoster Vaccine (Zostavax) A Review of its Use in Preventing Herpes Zoster and Postherpetic Neuralgia in Older Adults. *Drugs Aging* 2010; 27 (2): 159-176

VACC-1118664-0031 09/2017

ZOSTAVAX™의 접종으로 대상포진과 관련된 의료비 부담을 감소

의료 이용의 감소에 대한 예측

- 미국에서 60세 이상의 1,000,000명에게 접종을 하면 대상포진관련 **의료이용의 중요한 감소** 가 나타날 것으로 예상된다
  - 11,685명의 입원
  - 11,251명의 응급실 방문
  - 359,581건의 외래 방문

*study design: An age-specific decision analytic model was designed to estimate the lifetime costs and outcomes associated with HZ, PHN and other HZ-related complications for vaccinated and non-vaccinated cohorts aged ≥60 years. Clinical trial data, published literature and other primary studies were used to inform the model. Robustness of results to key model parameters was explored through a series of one-way, multivariate and probabilistic sensitivity analyses. Both societal and payer perspectives were considered.

PHN=post-herpetic neuralgia
HZ=herpes zoster

1. Pellissier JM et al. Evaluation of the cost-effectiveness in the United States of a vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *Vaccine*. 2007;25:8326-37.

VACC-1118664-0031 09/2017

조스타박스™의 NNV (Number-needed to vaccinate)

- 조스타박스로 HZ-관련 결과변수를 예방하기 위한 NNV[1]
  - HZ의 증례: 9 - 55
  - HZ의 상담: 4 – 25
  - PHN의 증례: 41 - 67
  - 입원일: 32 - 33
  - QALY 손실: 154 - 289
  - 입원: 374 - 428
- 다른 성인 백신으로 1 증례를 예방하기 위한 NNV*
  - 백일해: 20 - 60[2]
  - 인플루엔자: 43[3]

조스타박스는 대상포진을 예방하는 효과적인 접근법이다

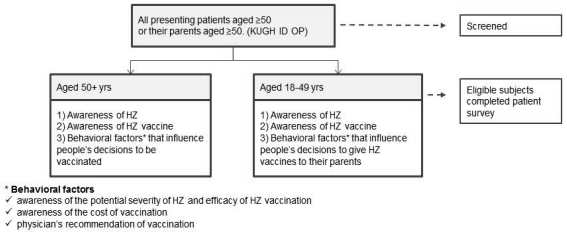
HZ = Herpes Zoster, PHN = Post-Herpetic Neuralgia, QALY = Quality Adjusted Life Year

1. Brisson M. Estimating the Number Needed to Vaccinate to Prevent Herpes Zoster-related Disease, Health Care Resource Use and Mortality. *Can J Public Health.* 2008; 99:383-6;
2. VanRie A et al. Adolescent and adult pertussis vaccination: computer simulations of five new strategies. *Vaccine.* 2004:22, 3154-3165;
3. Kelly H et al. The number needed to vaccinate (NNV) and population extensions of the NNV: comparison of influenza and pneumococcal vaccine programmes for people aged 65 years and over. *Vaccine.* 2004; 22:2192-8.

Patients' Attitudes toward the Herpes Zoster Vaccination in South Korea

Patients' Attitudes toward the Herpes Zoster Vaccination in South Korea

- **Study Overview**



* **Behavioral factors**
- ✓ awareness of the potential severity of HZ and efficacy of HZ vaccination
- ✓ awareness of the cost of vaccination
- ✓ physician's recommendation of vaccination

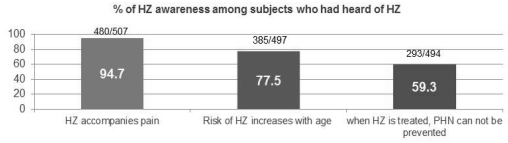
- **Study Design**: Cross-sectional, Single Center Study [23Aug,2013 -15Sep,2013]

KUGH: Korea University Guro Hospital, ID: Infectious disease, OP: Outpatient, HZ: Herpes Zoster

Tae Un Yang et. al. Survey on public awareness, attitudes, and barriers for herpes zoster vaccination in South Korea. *Hum Vaccin Immunother.* 2015;11(3):719-26.

Awareness of HZ and HZ vaccination

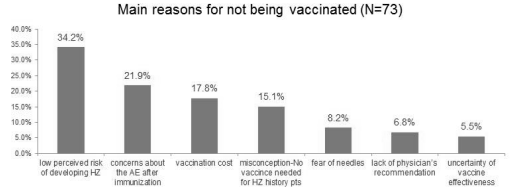
- 85.7% (517/603) reported they had heard of HZ and 43.6% (225/516) were aware of HZ vaccination
- Subjects aware of HZ were more likely to be women and younger, except for the group aged 20–29 y
- Subjects who reached higher education levels were more likely to be aware of HZ (p <0.001, linear by linear test)
- Higher monthly income were generally more likely to be aware of HZ



Tae Un Yang et. al. Survey on public awareness, attitudes, and barriers for herpes zoster vaccination in South Korea. *Hum Vaccin Immunother.* 2015;11(3):719-26.

Attitude toward being vaccinated or vaccinating parents against HZ

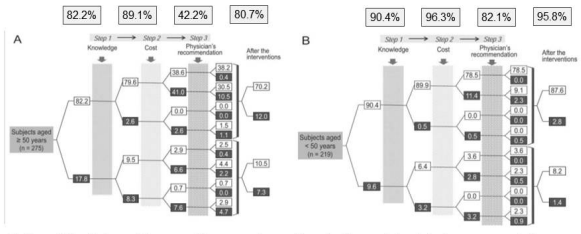
- 85.6% (507/592) subjects aware of HZ were willing to be vaccinated or vaccinate their parents against HZ
- Main concern for subjects aged **≥50 y** was the cost of vaccine (58.8%, 20/34) and that for subjects aged **<50 y** was lack of physician's recommendation (36.4%, 4/11) and adverse events following immunization (36.4%, 4/11)



Tae Un Yang et. al. Survey on public awareness, attitudes, and barriers for herpes zoster vaccination in South Korea. *Hum Vaccin Immunother.* 2015;11(3):719-26.

Willingness to be vaccinated and barriers for vaccination

Impact of knowledge, cost, and physician's recommendation on the intention to be vaccinated(A), or allowing parents to be vaccinated (B) against HZ among subjects who had heard of HZ

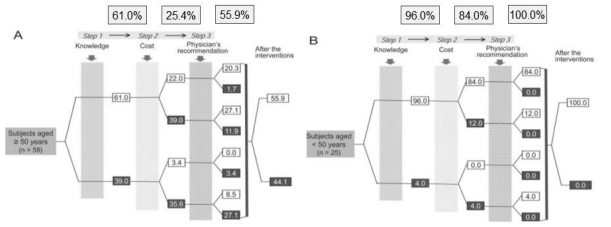


- ✓ Overall the high cost decreased the acceptance of vaccination and physician's recommendation restored this acceptance.
- ✓ Among <50 y, with knowledge of the HZ and its vaccine, cost, and physician's recommendation, the acceptance proportion increased from 90.4% to 95.8% while aged ≥ 50 y decrease from 82.2% to 80.7%.

Tae Un Yang et. al. Survey on public awareness, attitudes, and barriers for herpes zoster vaccination in South Korea. *Hum Vaccin Immunother.* 2015;11(3):719-26.

Willingness to be vaccinated and barriers for vaccination

Impact of knowledge, cost, and physician's recommendation on the intention to be vaccinated(A), or allowing parents to be vaccinated (B) against HZ among subjects who had never heard of HZ



✓ Among subjects aged ≥50y and <50y who had never heard of HZ, 55.9% and 100% decided to be vaccinated after physician's recommendation

Tae Un Yang et. al. Survey on public awareness, attitudes, and barriers for herpes zoster vaccination in South Korea. *Human Vaccines & Immunotherapeutics* 2015

VACC-1118664-0031 09/2017

Conclusion

- Among 603 subjects who completed the survey, 85.7% and 43.6% subjects were aware of HZ and HZ vaccination, respectively
- Women, younger age group, those with higher income or higher education levels were more likely to be aware of HZ
- 85.8% of subjects aware of HZ were willing to be vaccinated or vaccinate their parents
- The main obstacles for the increased acceptance toward vaccination were the high cost and low perceived risk, which decreased acceptance to 60.2%
- However, physician's recommendation reversed 69.5% of the refusal to accept HZ vaccine

Tae Un Yang et. al. Survey on public awareness, attitudes, and barriers for herpes zoster vaccination in South Korea. *Human Vaccines & Immunotherapeutics* 2015

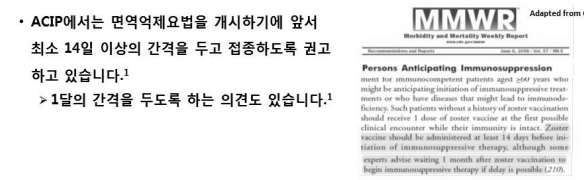
VACC-1118664-0031 09/2017

FAQ

VACC-1118664-0031 09/2017

Q. 면역억제 요법을 앞둔 환자에게 조스타박스™를 접종해도 되나요?

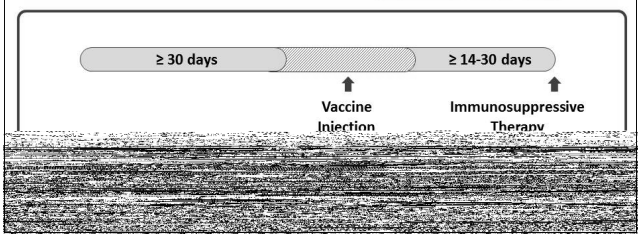
- **ACIP에서는 면역억제요법을 개시하기에 앞서 최소 14일 이상의 간격을 두고 접종하도록 권고하고 있습니다.[1]**
  - **➢ 1달의 간격을 두도록 하는 의견도 있습니다.[1]**


MMWR Morbidity and Mortality Weekly Report

Adapted from CDC.

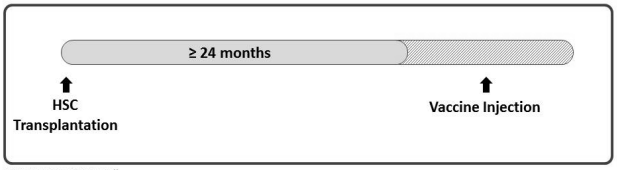
Persons Anticipating Immunosuppression

ment for immunocompetent patients aged ≥60 years who might be anticipating initiation of immunosuppressive treatments or who have diseases that might lead to immunodeficiency. Such patients without a history of zoster vaccination should receive 1 dose of zoster vaccine at the first possible clinical encounter while their immunity is intact. Zoster vaccine should be administered at least 14 days before initiation of immunosuppressive therapy; although some experts advise waiting 1 month after zoster vaccination to begin immunosuppressive therapy if delay is possible (*210*).



Q. 조혈모세포 이식 받은 환자에게 조스타박스™ 를 접종해도 되나요?

- According to ACIP guideline, HCPs should Assess the immune status of the recipient on a case-by-case basis to determine the relevant risks. If a decision is made to vaccinate with zoster vaccine, the vaccine should be administered at least 24 months after transplantation.



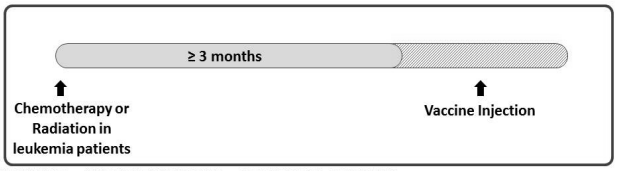
HSC = Hematopoietic Stem Cell

*위 내용은 미국ACIP가이드라인에 근거한 것이며, 한국MSD 에서 가이드하고 있는 사항이 아닙니다.

1. Harpaz R et al. Prevention of Herpes Zoster recommendations of the Advisory Committee on Immunization Practices(ACIP). *Morbidity and Mortality Weekly Report(MMWR)* 2008;57(RR-5): 1-30.

Q. 항암제를 투여 받고 있는 환자에게 조스타박스™ 를 접종해도 되나요?

- **ACIP Guideline:**
  - Zoster vaccine should not be administered to persons with leukemia, lymphomas, or other malignant neoplasm affecting the bone marrow or lymphatic system
  - However, patients whose **leukemia** is in remission and who have not received chemotherapy (e.g., alkylating drugs or antimetabolites) or radiation for at least 3 months can receive zoster vaccine.

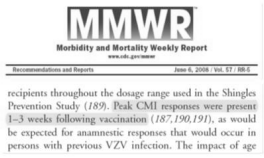


*위 내용은 미국ACIP가이드라인에 근거한 것이며, 한국MSD 에서 가이드하고 있는 사항이 아닙니다.

1. Harpaz R et al. Prevention of Herpes Zoster recommendations of the Advisory Committee on Immunization Practices(ACIP). *Morbidity and Mortality Weekly Report(MMWR)* 2008;57(RR-5): 1-30.

Q. 접종 후 언제 효능이 생기나요?

- 조스타박스는 수두-대상포진 바이러스에 대한 면역을 증강(boosting)시켜 작용을 나타냅니다.[1]
  - 대상포진 예방 시험(SPS)의 substudy에서는 조스타박스 투여 6주 후 수두-대상포진 바이러스에 대한 면역원성을 확인하였습니다.[2]
  - 수두-대상포진 바이러스에 대한 세포매개 면역반응(cell-mediated immunity, CMI)은 수두-대상포진 바이러스 감염이 있었던 사람에게 나타날 수 있는 기왕성 반응으로 예상되며 백신 접종 후 1~3주에 최대로 나타납니다.[2,3,4]


MMWR
Morbidity and Mortality Weekly Report
Recommendations and Reports June 6, 2008 / Vol. 57 / RR-5

recipients throughout the dosage range used in the Shingles Prevention Study (*189*). Peak CMI responses were present 1–3 weeks following vaccination (*187*,*190*,*191*), as would be expected for anamnestic responses that would occur in persons with previous VZV infection. The impact of age

Adapted from CDC

*SPS: Shingles Prevention Study

1. ZOSTAVAX. US prescribing information. Merck & Co., Inc.
2. Harpaz R et al. Prevention of HerpesZoster recommendations of the Advisory Committee on Immunization Practices(ACIP). *Morbidity and Mortality Weekly Report(MMWR)* 2008;57(RR-5): 1-30.
3. Food and Drug Administration. Biological Products Advisory Committee, 2005. Available at < http://www.fda.gov/ohrms/dockets/ac/05/slides/5-4198S2_1.pdf > Accessed on Sep 21. 2015
4. Schlienger K, Lange J, Tyring SK, et al. Immunogenicity, kinetics of VZV-Specific CD4+ T-cell g-IFN production and safety of a live attenuated Oka/Merck zoster vaccine in healthy adults ≥60 years of age [Abstract 857]. *44th Annual Meeting of IDSA*, Oct. 12–15, 2006, Toronto.
5. Sperber SJ, Smith BV, Hayden FG.Serologic response and reactogenicity to booster immunization of healthy seropositive adults with live or inactivated varicella vaccine. *Antiviral Res* 1992;17:213–22.

Q. 타백신과 동시 접종할 수 있나요?

- 조스타박스와 모든 다른 백신과의 동시 접종에 관한 데이터는 없으나 ACIP 권고사항에 따르면 생백신과 사백신은 동시접종 할 수 있습니다.[1]

*ACIP 권고사항[2]

백신 조합	최소 접종간격 권고사항
두가지 이상의 사백신	병용투여 가능
생백신과 사백신	병용투여 가능
두가지 이상의 생백신	병용투여하지 않는다면, 최소 28일의 간격을 두고 접종

*사백신 예시: A형 간염 백신, B형 간염 백신, 디프테리아/파상풍/백일해 백신, 인플루엔자 사백신 등[3]

※ 조스타박스 제품설명서 - 상호작용 :조스타박스와 폐렴구균폴리사카라이드백신의 병용투여는 조스타박스의 면역원성을 감소시키므로, 조스타박스와 폐렴구균폴리사카라이드백신은 병용투여하지 않습니다.[4]

1. Harpaz R et al. Prevention of Herpes Zoster recommendations of the Advisory Committee on Immunization Practices(ACIP). *Morbidity and Mortality Weekly Report(MMWR)* 2008;57(RR-5): 1-30.
2. Kroger AT et al. General recommendations on Immunization recommendations of the Advisory Committee on Immunization Practices(ACIP). *Morbidity and Mortality Weekly Report(MMWR)* 2011;60(2): 1-61
3. 이덕철. 예방접종 대상 감염병의 역학과 관리 제 4판 수정판. 질병관리본부. 2011
4. 조스타박스 국내 제품설명서, MSD Korea.

성인예방접종 –노후를 위한 준비

1. HPV and related disease

HPV : Human papillomavirus (인유두종바이러스)

인유두종 바이러스 (HPV : Human papillomavirus)

- >190 types identified[2]
- ≥30–40 anogenital[2,3]
- ~15–20 oncogenic*[,2,3]

HPV 16 and HPV 18 types account for the majority of all cervical cancers.[4,5]

- Non-oncogenic** types

HPV 6 and 11 are responsible for >90% of genital warts.[5]

*High risk; ** Low risk.

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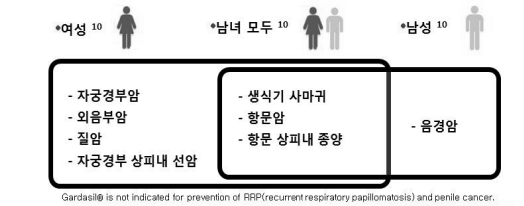
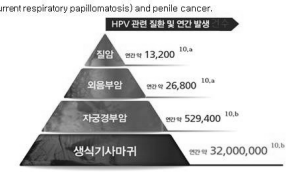
1. Howley PM, Lowy DR. In: Knipe DM, Howley PM, eds. *Fields Virology*. 4th Edition. Philadelphia, Pa: Lippincott-Raven; 2001:2197–2229. 2. Schuster, M. Human papillomavirus vaccines WHO position paper. WHO. 2014 ;43:465–492. 3. Wiley DJ, Douglas J, Beutner K, et al. External Genital Warts: Diagnosis, Treatment, and Prevention. *Clin Infect Dis*. 2002;35(suppl 2):S210–S224. 4. Muñoz N, Bosch FX, Castellsagué X, et al. AGAINST WHICH HUMAN PAPILLOMAVIRUS TYPES SHALL WE VACCINATE AND SCREEN? THE INTERNATIONAL PERSPECTIVE. *Int J Cancer*. 2004;111:278–285. 5. Jansen KU, Shaw AR. HUMAN PAPILLOMAVIRUS VACCINES AND PREVENTION OF CERVICAL CANCER *Annu Rev Med*. 2004;55:319–331.

HPV 는 다양한 생식기 질환을 일으킬 수 있습니다.[10]



Gardasil® is not indicated for prevention of RRP(recurrent respiratory papillomatosis) and penile cancer.

- HPV 16, 18형 [10, 11]
자궁경부암, 외음부암, 질암 발병원인의 ~70%
- HPV 6, 11형 [11]
전체 생식기 사마귀 발생원인의 ~90%



HPV : Human papillomavirus

a. 2002년WHO/ICO HPV Information Centre data
b. 2008년WHO/ICO HPV Information Centre data

10. WHO/ICO HPV information centre. Human Papillomavirus and Related Cancers in World. Summary report 2010. Available at<http://www.who.int/hpvcentre>. Published 15 Nov 2010. Accessed on 23 Apr. 2015 11. Data on file, MSD.
STD and TB Prevention 2010. 1-2.

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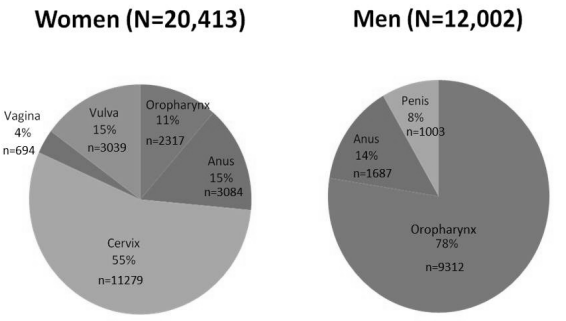
성별에 따른 HPV 관련 암 발생건수

United States, 2005-2009



Gardasil is not approved for prevention of RRP, Head and neck cancer, and penile cancer.

HPV : Human papillomavirus

1. Jemal A et al., Annual Report to the Nation on the Status of Cancer,1975–2009, Featuring the Burden and Trends in Human Papillomavirus (HPV) *J Natl Cancer Inst* 2013;105:175-201

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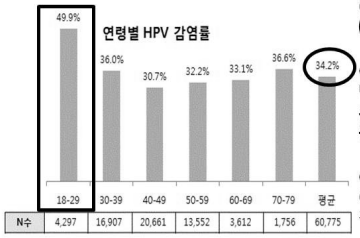
한국 여성 10명 중 3명이 HPV에 감염 [1]


ORIGINAL ARTICLE
Laboratory Medicine
JKMS
Prevalence and Distribution of Human Papillomavirus Infection in Korean Women as Determined by Restriction Fragment Mass Polymorphism Assay



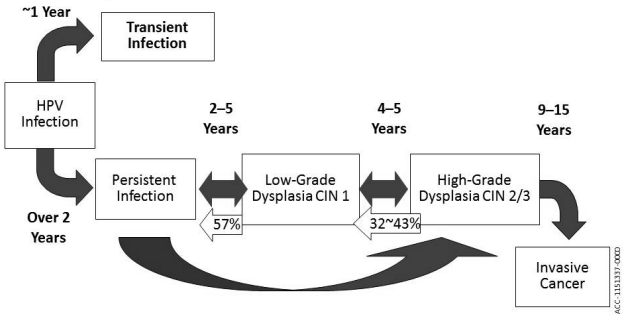
- 18-79세의 한국여성 약 6만명을 조사한 바에 의하면 평균 3명 중 한 명이 HPV에 감염된 것으로 보고[1]
- 연령에 따른 HPV유병률은 젊은 여성층(18~29세)에서 약 2명 중 1명 (49.9%) 으로 가장 높음[1]
- HPV의 감염에 대한 특별한 치료 방법은 없으며 감염으로 인한 특정한 임상적 징후에 따라 치료, 관리[2]
- 성생활을 하는 여성의 80% 이상은 50세까지 HPV 감염을 경험합니다.[2]

HPV : Human papillomavirus
1. Eun Hee Lee, Tae Hyun Umet al., Prevalence and Distribution of Human Papillomavirus Infection in Korean Women as Determined by Restriction Fragment Mass Polymorphism Assay. *J Korean Med Sci* 2012; 27: 1091-1097. 2. Centers for Disease Control and Prevention (CDC). Human papillomavirus. In: Atkinson W, Wolfe C, Hamborsky J. et al., eds. Epidemiology and Prevention of Vaccine-Preventable Diseases. 12th revised. Washington DC: Public Health Foundation; 2011:139-150

VACC-1151337-0000

High risk HPV 감염의 자연사

90% 이상의 HPV 감염은 1년 이내에 자연적으로 사라짐.



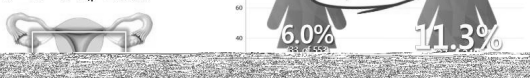
HPV : Human papillomavirus CIN: Cervical Intraepithelial Neoplasia

1. Pagliusi SR, Aguado MT. Efficacy and other milestones for human papillomavirus vaccine introduction *Vaccine*. 2004;23:569–57

VACC-1151337-0000

자궁경부암

- 자궁경부암 유병률& 사망률
  - 전세계 매 1분마다 1명 자궁경부암 진단 / 2분 마다 1명 사망[1]
  - 우리나라 매일 10명 자궁경부암 진단 / 매일 3명이 자궁경부암으로 사망[2]
  - 한국은연평균약 **3,520**명에서 자궁경부암이 발생하며,약 **1,000**명이 이로 인해 사망 [4]
  - 특히, **2008**년도 연구에 따르면 자궁경부암환자에서 **35**세 미만이 차지하는 비율이 증가하고 있음 [5]
- 자궁경부암 발생 연령[3]
  - **20세 – 34세 : 14%**
  - 35 – 44세: 25.9%
  - 45 – 54세: 23.9%



국내 자궁경부암 환자에서 35세 미만이 차지하는 비율 [5]

국내 시판 중인 HPV 백신 허가사항[1,2]

(2014년 9월 제품설명서 기준)

종류	기본 3회 접종	2회 접종	접종 허가 연령	적응증	수유부에 대한 투여
Gardasil®[1] HPV 4가 백신 (HPV 6, 11, 16, 18)	0-2-6개월 3회 접종	9 – 13세 여아,남아 모두 가능	9 – 26세 여성과 남성	-자궁경부암 -외음부암 -질암 -항문암 -생식기 사마귀 -자궁경부 상피내 선암 -자궁경부 상피내 종양 (1기, 2기, 3기) -외음부 상피내 종양(2기, 3기) -질 상피내 종양(2기, 3기) -항문 상피내 종양(1기, 2기, 3기)	1,133명의 수유부 대상 3상 임상실험 결과 수유부에 접종할 수 있다.
HPV 2가 백신[2] (HPV 16, 18)	0-1-6개월 3회 접종	9 – 14세 여아	9 – 25세 여성	-자궁경부암 -(HPV 16, 18형에 의한) 일시적, 지속적 감염 -유의성이 불확실한 비정형 편평세포를 포함하는 세포학적 이상 -자궁경부 상피내 종양(1기, 2기, 3기)	임상 결과 없음. 수유부에는 접종에 의한 가능한 유익성이 위험성을 상회한다고 판단되는 경우에만 투여한다.

제품설명서의 단순 배열이며 직접적인 비교가 아님

HPV : Human papillomavirus

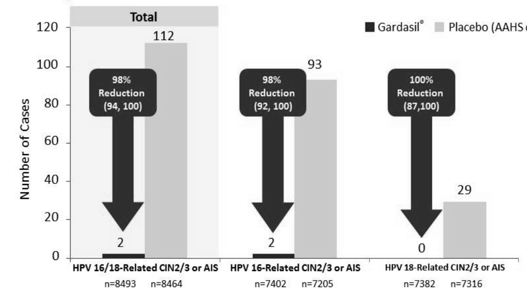
1.Gardasil Product Information. MSD Korea 2. 서바릭스 제품설명서. GSK Korea

VACC-1151337-0000

Gardasil® 의 자궁경부전암성/이형성 병변에 대한 높은 예방효과† : 98%

Analysis of efficacy of **Gardasil®** in the Per-protocol Efficacy* population of 16-through 26-year-old Girls and Women for Vaccine HPV Types

FUTURE I/II trials



* The PPE population consisted of individuals who received all 3 vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, and were naive (PCR negative and seronegative) to the relevant HPV type(s) (Types 6, 11, 16,and 18) prior to dose 1 and through 1 month postdose 3 (Month 7).

CIN = cervical intraepithelial neoplasia; AIS = adenocarcinoma *in situ*.

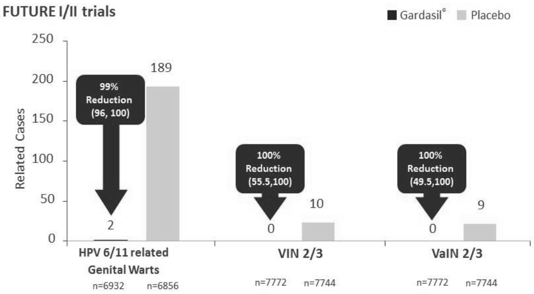
† Analyses of the combined trials were prospectively planned and included the use of similar study entry criteria*Reference: Data on file, MSD

VACC-1151337-0000

Gardasil® 의 다양한 HPV 관련 질환에 대한 높은 예방효과 : 99%

Analysis of efficacy of **Gardasil®** in the Per-protocol Efficacy* population of 16-through 26-year-old Girls and Women for Vaccine HPV Types

FUTURE I/II trials



* The PPE population consisted of individuals who received all 3 vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, and were naive (PCR negative and seronegative) to the relevant HPV type(s) (Types 6, 11, 16 and 18) prior to dose 1 and through 1 month postdose 3 (Month 7).

1. Data on file, MSD.

VACC-1151337-0000

이전에 HPV 감염이 있었던 여성§에 대한 Gardasil® 의 높은 예방효과

과거 HPV에 감염되었다가 현재는 DNA detection이 되지 않는 여성 2,617명을 대상으로 **Gardasil®** 의 효과를 분석한 결과.

Sero-Positive & PCR DNA-Negative (n=2617, mean f/u: 40 mo)

Endpoints (HPV 6/11/16/18-related)	Gardasil® (n=1,243)	Placebo (n=1,283)	Efficacy (95% CI), %
CIN (any grade) or AIS	0	7	100 (29, 100)
*VIN2/3 or VaIN2/3	0	2	100 (<0, 100)

Gardasil® has not been demonstrated to provide protection against disease from vaccine and non-vaccine HPV types to which a person has previously been exposed through sexual activity.

HPV : Human papillomavirus

1. Sven-Eric Olsson. Evaluation of quadrivalent HPV 6/11/16/18 vaccine efficacy against cervical and anogenital disease in subjects with serological evidence of prior vaccine type HPV infection *Human Vaccines* 2009;5: 696-704

VACC-1151337-0000

Gardasil® 의 새로운 질환 발생 감소 효과[1]

< 이전에 HPV 관련질환으로 진단받거나 치료받은경험이 있는 여성에서 >

Impact of quadrivalent HPV vaccine on incidence of subsequent HPV related disease among

	Vaccine (n=587)		Placebo (n=763)		
Women undergone cervical surgery					
	No of women with a lesion†	Rate‡	No of women with a lesion†	Rate‡	% reduction in rate with vaccine (95%CI)
Disease related to vaccine HPV types (6, 11, 16 or 18)					
Cervical intraepithelial neoplasia grade I or worse	2/474	0.3	9/592	1.1	74.2 (-24.8 to 97.3)
Genital Warts	2/474	0.3	21/589	2.5	89.0 (54.9 to 98.7)
Vulvar or vaginal intraepithelial neoplasia grade II or worse	1/474	0.1	3/589	0.4	61.2 (-383.1 to 99.3)
Women diagnosed with a vulvar or vaginal disease					
	Vaccine (n=229)		Placebo (n=475)		
	No of women with a lesion†	Rate‡	No of women with a lesion†	Rate‡	% reduction in rate with vaccine (95%CI)
Disease related to vaccine HPV types (6, 11, 16 or 18)					
Cervical intraepithelial neoplasia grade I or worse	8/210	1.9	44/421	6.6	71.8 (39.5 to 88.5)
Genital Warts	10/209	2.4	39/413	5.9	60.4 (19.2 to 82.3)
Vulvar or vaginal intraepithelial neoplasia grade II or worse	3/209	0.7	13/413	1.9	63.0 (-34.8 to 93.2)

† Number of women with at least one follow-up visit for the respective end point after surgery. A woman is counted only once for each end point (that is, once in each row) but may have developed more than one end point (and so may appear in more than one row).

‡ Cases per 100 person years at risk

가다실은 9-26세 남녀에서 HPV 6,11 형에 의한 생식기 사마귀에 허가 받았습니다.

가다실은 진행중인 외부 생식기 병변, 자궁경부암, 외음부암, 질암, 자궁경부 상피내 종양(CIN), 외음부 상피내 종양(VIN), 질 상피내 종양(VaIN) 의 치료를 대상으로 하지 않습니다.[2]

1. Elmar A Joura et al., Effect of the human papillomavirus (HPV) quadrivalent vaccine in a subgroup of women with cervical and vulvar disease: retrospective pooled analysis of trial data, *BMJ* 2012; 344:e1401 2. GARDASIL® Local Product Circulator, MSD Korea

Gardasil® 의 높은 예방효과는 여러 대규모 임상을 통해 입증되었습니다.

Centers for Disease Control and Prevention

MMWR

August 29, 2014

Vaccine Endpoint related type	Vaccine No.	Vaccine Cases	Control No.	Control Cases	Vaccine efficacy %	Vaccine efficacy (95% CI)
가다실*						
CIN2/3 or AIS†						
HPV 6, 11, 16, 18	7,864	2	7,865	110	98.2	(93.3–99.8)
HPV 16	6,647	2	6,455	81	97.6	(91.1–99.7)
HPV 18	7,382	0	7,316	29	100.0	(86.6–100.0)
VIN/VaIN2/3†						
HPV 6, 11, 16, 18	7,900	0	7,902	23	100.0	(82.6–100.0)
HPV 16	6,654	0	6,467	17	100.0	(76.5–100.0)
HPV 18	7,414	0	7,343	2	100.0	(<0–100.0)
Genital warts§						
HPV 6 and/or 11	6,718	2	6,647	186	98.9	(96.1–99.9)
Bivalent vaccine¶						
CIN2/3 or AIS						
HPV 16, 18	7,338	5	7,305	97	94.9	(87.7–98.4)
HPV 16	6,296	2	6,160	81	97.6	(91.0–99.7)
HPV 18	6,789	3	6,739	23	87.1	(57.2–97.5)

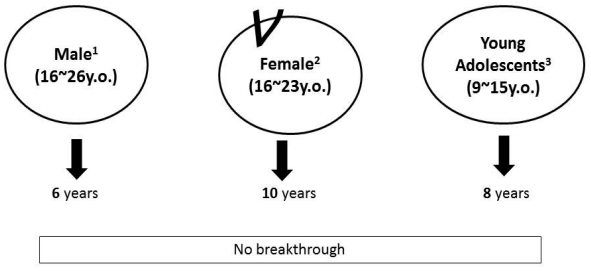
Study design: Quadrivalent human papillomavirus (HPV) vaccine was a 3 years, international, randomized, double-blind, placebo-controlled. A total of 18,174 females ages 16 to 26 years allocated into one of three clinical trials (protocols 007, 013, and 015). Vaccine (N = 9,087) or placebo (N = 9,087) was given at baseline, month 2, and month 6. Pap testing was conducted at regular intervals. vaccine efficacy against HPV 6/11/16/18

‡study design:two international, double blind ,placebo controlled, randomised 42 months' follow-up.17 622 women aged 16-26 years enrolled between December 2001 and May 2003. Vaccine efficacy against cervical, vulvar, and vaginal intraepithelial neoplasia grade I and condyloma

¹study design: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial end-of-study analysis Vaccine efficacy against CIN3+ associated with HPV-16/18

VACC-1151337-0000

Gardasil® 의 장기간 **Effectiveness data**는
여러 국가에서 지속적으로 추적/관찰하고 있습니다



No breakthrough

VACC-1149118-0000

1. Stephen G et al. Poster presented at HPV 2014, 29th International Papillomavirus Conference & clinical workshop, Seattle, USA, Aug 20-25, 2014
2. Kjaer SK et al, Long-term effectiveness and safety of Gardasil(TM) in the Nordic countries, Presented at EUROGIN 2015, Sevilla, Spain, 4-7 Feb 2015
3. Daron Ferris et al. Long-term study of a Quadrivalent Human papillomavirus vaccine, Pediatrics. 2014.

VACC-1151337-0000

Long-Term Effectiveness Data of Gardasil®
(Female 16-23 yrs)

EUROGIN HOMEPAGE FRIDAY, MAY 15, 2015

EUROGIN 2015
International Multidisciplinary Congress

OC 6-1

LONG-TERM EFFECTIVENESS AND SAFETY OF GARDASIL™ IN THE NORDIC COUNTRIES

Kjaer, SK[1,2], Nygård, M.[3], Dillner, J.[4], Munk C.[1], Marshall, B.[5], Hansen, B.T.[3], Sigurdardottir, L.G.[6], Hortlund, M.[4], Tryggvadóttir, L.[6], Saah, A.[5]

1. Unit of Virus, Lifestyle & Genes, Danish Cancer Society Research Center, Copenhagen, Denmark; 2. Gynecologic Clinic, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; 3. Department of Research, Cancer Registry of Norway, Oslo, Norway; 4. Department of Medical Microbiology, Skåne University Hospital, Malmö, Sweden; 5. Merck, Sharp & Dohme, Whitehouse Station, NJ, USA; 6. Icelandic Cancer Registry, Icelandic Cancer Society, Reykjavik, Iceland

FUTURE II – Nordic study: Female (16-23 years old)

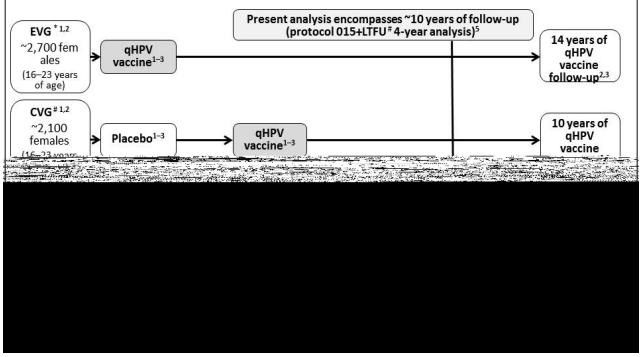
VACC-1149118-0000

1. Kjaer SK et al, Long-term effectiveness and safety of Gardasil(TM) in the Nordic countries, Presented at EUROGIN 2015, Sevilla, Spain, 4-7 Feb 2015.

VACC-1151337-0000

Long-term effectiveness and safety of Gardasil® in the Nordic Countries- Study Design and Methods

Vaccine effectiveness against HPV 16/18–related CIN* 2+ estimated by calculating exp ected incidence in an unvaccinated cohort, using historical registry data[1,2]



Gardasil® 2회 접종 허가 사항

기존 허가사항 [1]
9~26세 여성 및 남성에게, 다음의 접종 일정에 따라 1회 0.5 mL씩 3회 근육주사한다.

- 1차접종: 방문일
- 2차접종: 1차 접종으로부터 2개월 후
- 3차접종: 1차 접종으로부터 6개월 후

2회 접종 여아(9-13세) vs 3회 접종 여성(16-26세) 면역원성 비교 평가 임상시험에 근거 [2,a]

변경된 현재 허가사항 [3]
9~26세 여성 및 남성에게,
다음의 접종 일정에 따라 1회 0.5 mL씩 3회 근육주사한다.

- 1차접종: 방문일
- 2차접종: 1차 접종으로부터 2개월 후
- 3차접종: 1차 접종으로부터 6개월 후

9~13세에 대하여 이 백신을 2회 접종 일정 (0, 6개월)에 따라 접종할 수 있다.

*The study design is present in the bottom of the slide notes.

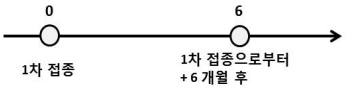
1. 가디실 LPC, July 25 2013., 2. Simon R. M. Dobson, MD, et al. Immunogenicity of 2 Doses of HPV Vaccine in Younger Adolescents vs 3 Doses in Young Women A Randomized Clinical Trial JAMA, May 1, 2013—Vol 309, No. 17, 3. 가디실 LPC, Sep 04 2014

V-ADD-151337-0000

WHO **Recommendation** on 2 dose regimen

- 15세 이전의 소아청소년들에게는 2회 접종 가능 [1, ‡]
- 2회 접종 시, 기본 접종 일정은 0, 6개월 (최소 간격 : 6개월) [1]
  만약 접종 일정이 지연될 경우 12-15개월 안에 2차 접종을 완료 [2]
- 15세 이상‡ 이거나, 면역 저하자(HIV 감염 등)인 경우 0, 1-2, 6개월 일정 ‡ 에 맞추어 3회 접종 권고 [1,2]

만 9-13세 Gardasil® 접종 스케쥴 [3]



‡ Gardasil® 은 **9~13세** 남아/여아에게 2회 접종가능하도록 허가 받았습니다.

1. Weekly epidemiological record Relevé épidémiologique hebdomadaire 23 MAY 2014, 89th year No. 21, 2014, 89, 225-236
2. Schuster, M. Human papillomavirus vaccines WHO position paper, WHO. 2014; 43:465-492
3. 가디실 LPC, Sep 04 2014

VACC-1151337-0000

Gardasil® **2**회 접종의 근거[a]

- 임상 목적: 예방효과가 입증된 **16-26**세 여성 대상 Gardasil® **3**회 투여 시의 면역원성과 **9-13**세의 여아 대상 Gardasil® **2**회 투여 시의 면역원성 비교
- 임상 디자인: 연령, 접종 횟수에 따라 **3** 그룹으로 나누어 면역원성 평가 **(36**개월 추적 조사)

	9 – 13세 여아		16 – 26세 성인 여성
	Group 1	Group 2	Group 3
Dose Regimen	2 dose	3 dose	3 dose
Dosing Schedule	0, 6개월	0, 2, 6개월	0, 2, 6개월
Cohorts	259명	261명	310명

*Study design : Randomized, phase 3, postlicensure, multicenter, age-stratified, noninferiority immunogenicity study of 830 Canadian females from August 2007 through February 2011. Follow-up blood samples were provided by 675 participants (81%).

1. Simon R. M. Dobson, MD, et al. Immunogenicity of 2 Doses of HPV Vaccine in Younger Adolescents vs 3 Doses in Young Women A Randomized Clinical Trial, JAMA, May 1, 2013—Vol 309, No. 17

VACC-1151337-0000

Gardasil® **2**회 접종의 근거[a]

- 임상 결과: 여아 2회 접종시 항체가가 성인 여성 3회 접종 항체가에 비해 열등하지 않았으며 **안전성과 내약성을 입증**하였음 [1,a]

Immunogenicity was assessed at 7 months in ITT(intention-to-treat) population. (1 month after the last dose)

Assay(cLIA)	Group1: 9-13 y.o females (2 dose)		Group2: 9-13 y.o females (3 dose)		Group3: 16-26 y.o females (2 dose)	
	N	GMT(95% CI)	n	GMT(95% CI)	n	GMT(95% CI)
Anti-HPV6	253	2117(1787-2508)	254	1876(1585-2221)	300	943(807-1101)
Anti-HPV11	254	2339(2088-2619)	256	2117(1891-2370)	300	1268(1143-1408)
Anti-HPV16	254	7344(6310-8547)	256	7736(6651-8999)	300	3545(3083-4076)
Anti-HPV18	254	1169(1021-1338)	256	1730(1512-1980)	300	664(586-752)

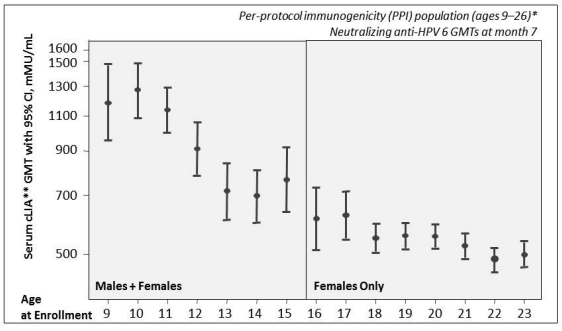
*HPV : Human Papillomavirus(인유두종 바이러스) GMT : geometric mean titer

1.Simon R. M. Dobson, MD, et al. Immunogenicity of 2 Doses of HPV Vaccine in Younger Adolescents vs 3 Doses in Young Women A Randomized Clinical Trial, JAMA, May 1, 2013—Vol 309, No. 17
2. Smolen KK, Gelinas L, Franzen L, et al. Age of recipient and number of doses differentially impact human B and T cell immune memory responses to HPV vaccination. Vaccine. 2012;30(24):3572-3579.
*The study design is present in the bottom of the slide notes

VACC-1151337-0000

어릴 수록 HPV 백신에 대한 높은 면역원성을 보임

- Gardasil® 의 면역원성은 소아청소년군에서 보다 높게 나타났습니다. [1]
- Gardasil® 은 소아청소년은 물론 성인 여성을 대상으로 예방효과를 입증하였습니다. [2]



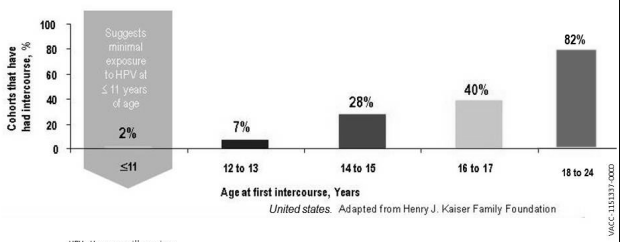
HPV : Human Papillomavirus

*Inclusive of five study protocols (all GMTs measured using cLIA); **cLIA = competitive Luminex Immunoassay
1. Data on file, MSD. 2. Dawn Ferris et al. Long-term Study of a Quadrivalent Human Papillomavirus Vaccine Pediatrics 2014;134;e657

VACC-1151337-0000

소아청소년에게서의 HPV 백신 접종이 중요한 이유

- **HPV**에 노출되기 이전의 연령에 접종하는 것이 중요
- 최근 연구 결과들에 따르면, 어린 연령의 소아청소년에게서도 성 경험이 있는 것으로 나타남



HPV : Human papillomavirus

•Markowitz MMWR 2007; Holl Henry J Kaiser Found 2003; *Mosher Adv Data* 2005

VACC-1151337-0000

4. Gardasil® in NIP - Other countries case

In Korea, Gardasil® vaccination is not included in NIP.

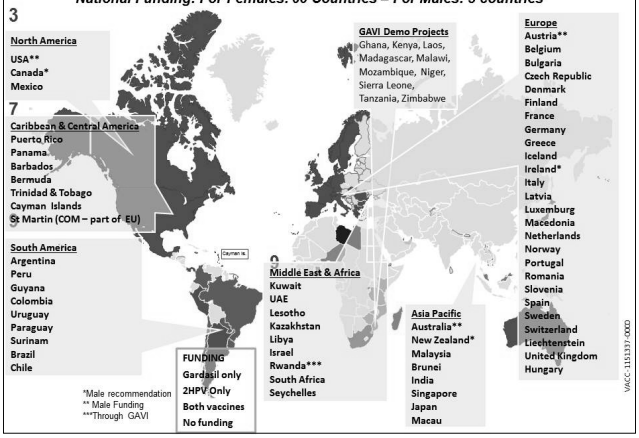
NIP : National immunization program (국가 필수 예방접종 프로그램)

VACC-1151337-OOO

많은 국가들이 NIP에 Gardasil® 을 도입

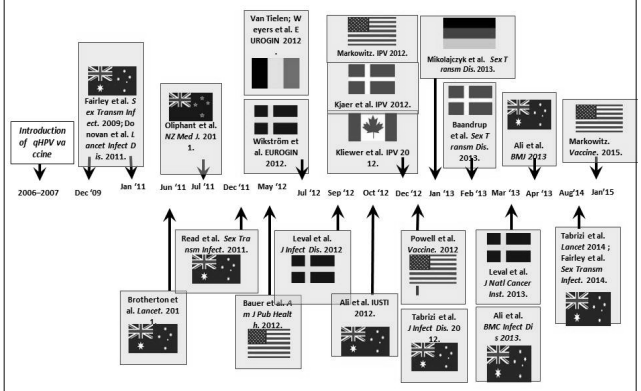
HPV백신 접종을 국가 예방접종 프로그램에 포함한 62개국 중에 56개국이 Gardasil® 을 선택

National Funding: For Females: 60 Countries – For Males: 3 countries



VACC-1151337-OOO

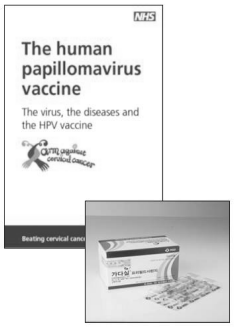
Impact of Gardasil® in Public Vaccination Programs: Select Reports as of Feb 2015[1–24]



qHPV=quadrivalent human papillomavirus.

Please see corresponding slide note for references.

영국 정부, NIP 2가 백신에서 Gardasil® 로 대체



- 영국 정부는 2008년 자국 회사 백신인 2가 백신으로 NIP 시작
- 3년 후 NIP 백신 재계약 시, 생식기사마귀 등 추가적인 질환에 대한 예방 효과 및 비용-효과 측면 고려 하여 Gardasil® 로 변경

The HPV vaccine

Vaccines are available to protect against the two most common HPV types (16 and 18) that cause cervical cancer and the two most common HPV types that cause genital warts (6 and 11). The national immunization program began in 2008 using a bivalent HPV vaccine against HPV 16 and 18. **In 2012, the programme changed to use a quadrivalent vaccine (Gardasil®) against HPV 6, 11, 16, and 18.**

VACC-1151337-OOO

*NHS : National Health Service, HPV : Human papillomavirus(인유두종바이러스)
National centre for immunisation Research & surveillance. HPV vaccines for australians:information for immunisation providers. NCIRS Fact sheet. 2013

영국 조사 결과 Gardasil® 은 2가 백신 대비 QALY & 의료비 절감에 효과적[a]

QALY : Quality-Adjusted Life Year

The Health Protection Agency suggested Gardasil has higher QALY and median cost saved level than Bivalent HPV vaccine.

- In the base case, authors assumed that the bivalent and quadrivalent vaccine had the same duration as protection against vaccine types.
- Use of the quadrivalent vaccine is expected to decrease the incidence of vaccine type (HPV 6, 11) warts by up to 95% , if duration of protection is lifelong.
- Quadrivalent HPV vaccination may prevent 430 (380–490) to 630 (950–670) vulvar, vaginal cancers a year by 2109.

VACC-1151337-OOO

*The study design is present in the bottom of the slide notes

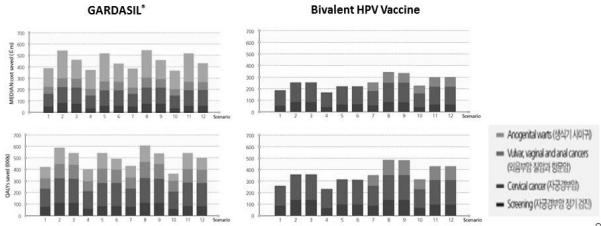
Mark Jit et al, Comparing bivalent and quadrivalent human papillomavirus vaccines:economic evaluation based on transmission model, *BMJ* 2011;343:d5775

영국 조사 결과 Gardasil® 은 2가 백신 대비 QALY & 의료비 절감에 효과적[a]

QALY : Quality-Adjusted Life Year

- 영국의 남성 및 여성을 대상으로 각 백신의 보험 적응증, 장기간의 면역원성 등을 고려하여 QALY 및 Median Cost saved(의료비)를 비교한 결과 Gardasil® 은 다음 질환에 대해 2가 HPV 백신보다 의료비와 QALY 측면에 있어 유리할 수 있음을 입증하였습니다.

GARDASIL® **Bivalent HPV Vaccine**



- The size of the contribution to the vaccine cost difference from warts prevention by the quadrivalent vaccine is much greater than that of additional protection against cancer by the bivalent vaccine in all the scenarios. Hence, **overall reduction of the discount rate favors the quadrivalent vaccine**.

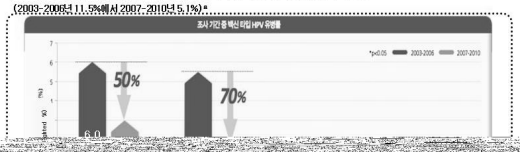
VACC-1151337-OOO

*The study design is present in the bottom of the slide notes

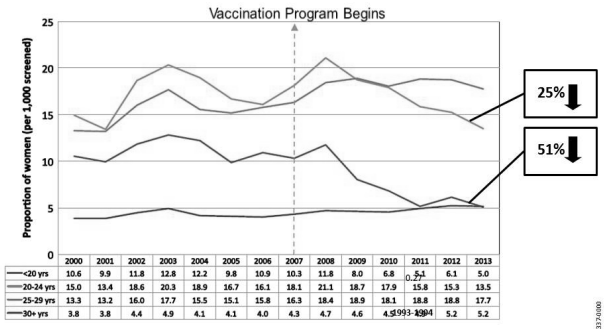
Mark Jit et al, Comparing bivalent and quadrivalent human papillomavirus vaccines:economic evaluation based on transmission model, *BMJ* 2011;343:d5775

[미국 NIP] Gardasil® 의 Real World Impact

CDC 발표에 따르면 Gardasil® 도입 이후
미국 14-19세 여성들의 백신유형 HPV 감염유병률 56% 감소[47]
(2003-2006년 11.5%에서 2007-2010년 5.1%)*



[호주 NIP] Gardasil® 의 Real World Impact :
: Trends in High Grade Cervical Abnormalities



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
<20 yrs	10.6	9.9	11.8	12.8	12.2	9.8	10.9	10.3	11.8	8.0	6.8	5.1	6.1	5.0
20-24 yrs	15.0	13.4	18.6	20.3	18.9	16.7	16.1	18.1	21.1	18.7	17.9	15.8	15.3	13.5
25-29 yrs	13.3	13.2	16.0	17.7	15.5	15.1	15.8	16.3	18.4	18.9	18.1	18.8	18.8	17.7
30+ yrs	3.8	3.8	4.4	4.9	4.1	4.1	4.0	4.3	4.7	4.6	4.5	4.4	5.2	5.2

Trends in high-grade cervical abnormalities (histologically confirmed) by age group, 2000–2013, Victorian Cervical Cytology Registry (Data as held on 20 May 2014. The National HPV Vaccination Program commenced in April 2007)

Julia ML et al., Human papillomavirus vaccination is changing the epidemiology of high-grade cervical lesions in Australia, *Cancer Causes Control* 2015, June 26(6) Volume 26, 953-954

VACC-1151337d000

[덴마크 NIP] Gardasil® 의 Real World Impact
: Cervical Neoplasia

ARTICLE

Early Impact of Human Papillomavirus Vaccination on Cervical Neoplasia—Nationwide Follow-up of Young Danish Women

Birgitte Baldur-Felskov, Christian Dehlendorff, Christian Munk, Susanne K. Kjaer

Manuscript received July 26, 2013; revised November 27, 2013; accepted December 9, 2013.

Table 2. Model 1: Risk for cervical lesions among human papillomavirus vaccinated women compared with nonvaccinated women in Danish birth cohorts 1989–1999, October 2006 to March 2012*

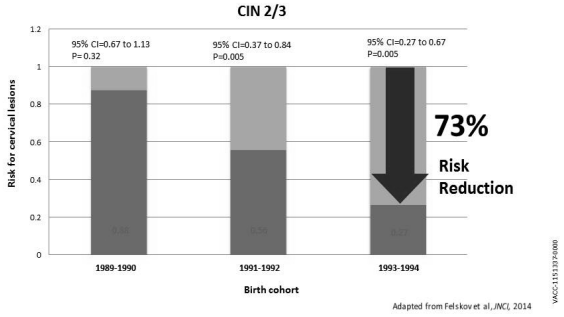
	CIN2/3		CIN3	
Birth cohort	HR (95% CI)	*P*†	HR (95% CI)	*P*†
1989–1990	0.88 (0.67 to 1.13)	.32	0.78 (0.54 to 1.13)	.20
1991–1992	0.56 (0.37 to 0.84)	.005	0.64 (0.36 to 1.14)	.13
1993–1994	0.27 (0.10 to 0.67)	.005	0.20 (0.06 to 0.71)	.01
1995–1996	—	—	—	—
1997–1999	—	—	—	—

Baldur-Felskov B, Dehlendorff C, Munk C, Kjaer SK. Early Impact of Human Papillomavirus Vaccination on Cervical Neoplasia-Nationwide Follow-up of Young Danish Women. *J Natl Cancer Inst.* 2014 Feb 19

VACC-1151337-0000

[덴마크 NIP] Gardasil® 의 Real World Impact
: Cervical Neoplasia

Hazard ratios for cervical lesions among vaccinated women compared with unvaccinated women



Adapted from Felskov et al, *JNCI*, 2014

Baldur-Felskov B, Dehlendorff C, Munk C, Kjaer SK. Early Impact of Human Papillomavirus Vaccination on Cervical Neoplasia-Nationwide Follow-up of Young Danish Women. *J Natl Cancer Inst.* 2014 Feb 19

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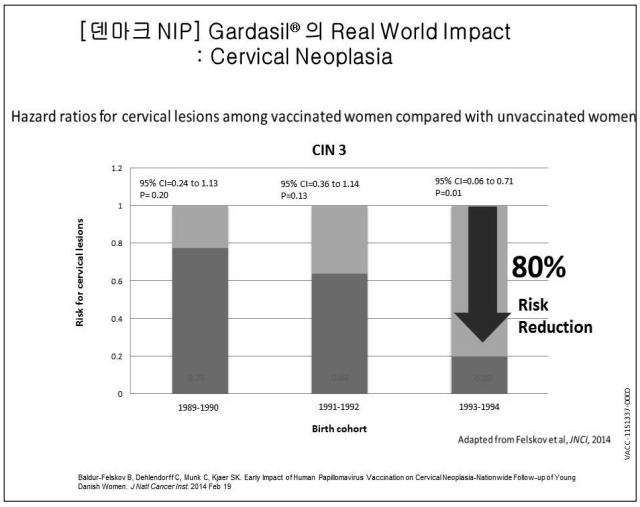
[덴마크 NIP] Gardasil® 의 Real World Impact
: Cervical Neoplasia
Hazard ratios for cervical lesions among vaccinated women compared with unvaccinated women
CIN 3
95% CI=0.24 to 1.13
P= 0.20
95% CI=0.36 to 1.14
P=0.13
95% CI=0.06 to 0.71
P=0.01
80%
Risk
Reduction
Risk for cervical lesions
1.2
1
0.8
0.6
0.4
0.2
0
0.78
0.64
0.29
1989-1990
1991-1992
1993-1994
Birth cohort
Adapted from Felskov et al, JNCI, 2014
VACC-1151337-0000
Baldur-Felskov B, Dehlendorff C, Munk C, Kjaer SK. Early Impact of Human Papillomavirus Vaccination on Cervical Neoplasia-Nationwide Follow-up of Young Danish Women. J Natl Cancer Inst. 2014 Feb 19