Огляд сучасного світового письменництва стосовно щеплення папіломавірусу людини

Яна Гончарова

Клініка репродуктивної медицини НАДІЯ

Вірус папіломи людини (ВПЛ)

- Найбільш поширена ІПСШ
- Людина – єдине джерело інфекції
- Легко передається
- Близько 80% жінок інфікуються одним, або більше, з типів ВПЛ впродовж життя
- Середня частота – 22-35% (FMR 1,4:1)
- Більшість (90%) - минущі, доброякісний перебіг(1-2 роки)

Вірус папіломи людини (ВПЛ)

- **ВПЛ** – ДНК-вірус, що не має оболонки (Papillomaviridae). Геном ВПЛ укладено в білкову оболонку, що складається з великих (L1) і малих (L2) структурних білків

- Більше 130 типів, більше 40 – статеві інфекції

- **Онкогенні типи ВПЛ** (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 69, 73) – CIN низького і високого ступенів, а також аногенітальна карцинома
- В 99% випадків раку шийки матки виявляються онкогенні типи ВПЛ
- ВПЛ 16, 18 - 70% раку шийки матки; 90% раку ануса

- **Неонкогенні типи** (переважно 6 і 11) - 90% генітальних кондилом у жінок і чоловіків, рецидивуючий респіраторний папіломатоз і назофарінгеальні папіломи, а також CIN низького ступеня

Вакцини проти ВПЛ

	Monovalent vaccine	Bivalent vaccine	Quadrivalent vaccine
Manufacturer	Merck, Sharp & Dome (Merck & Co, Whitehouse Station, NJ, USA)	GlaxoSmithKline (GSK, Rixensart, Belgium)	Merck, Sharp & Dome (Merck & Co, Whitehouse Station, NJ, USA)
Antigens	HPV16 (40 μg)	L1 VLPs of HPV16 (20 μg) and HPV18 (20 μg)	L1 VLPs of HPV6 (20 μg), HPV11 (40 μg), HPV16 (40 μg) and HPV18 (20 mg)
Vaccination schedule	3 doses: at day 1, month 2 and month 6	3 doses: at day 1, month 1 and month 6	3 doses: at day 1, month 2 and month 6
Adjuvant	225 μg amorphous aluminium hydroxyl-phosphate sulphate	ASO4: 500 μg Aluminium hydroxide, 50 μg 3-deacylated monophosphoryl lipid A (MPL)	225 μg amorphous aluminium hydroxyl-phosphate sulphate
Trade name	Not commercialised	Cervarix	Gardasil, Silgard
Produced by recombinant technology using	Saccharomyces cerevisae (baker's yeast)	Baculovirus in Trichoplusia in insect cells	Saccharomyces cerevisae (baker's yeast)

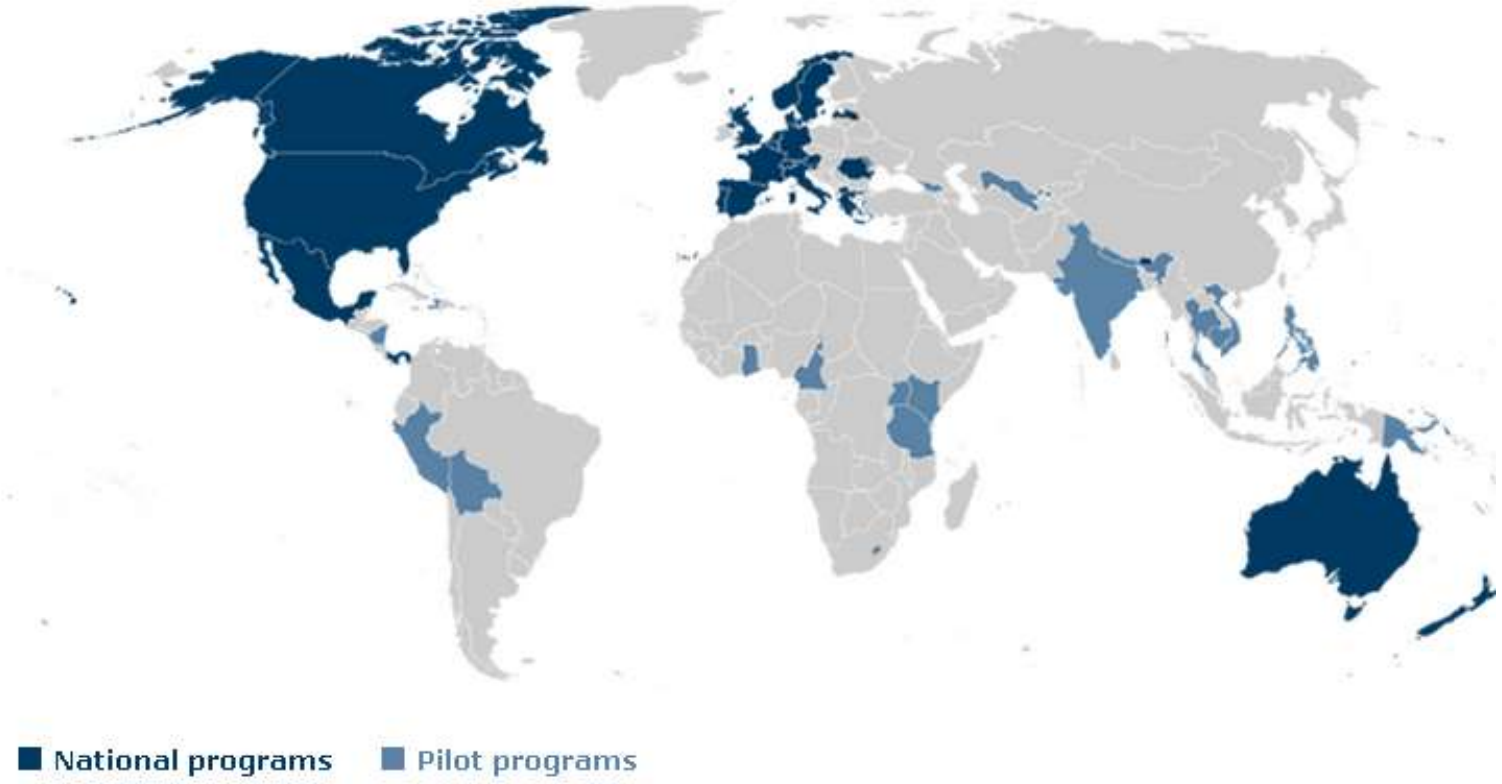
Adapted from WHO 2009.

2007 **2006**

10-14 років (9-26)

Global Progress in HPV vaccine introduction

July 2010



Австралія, Великобританія, США, Канада

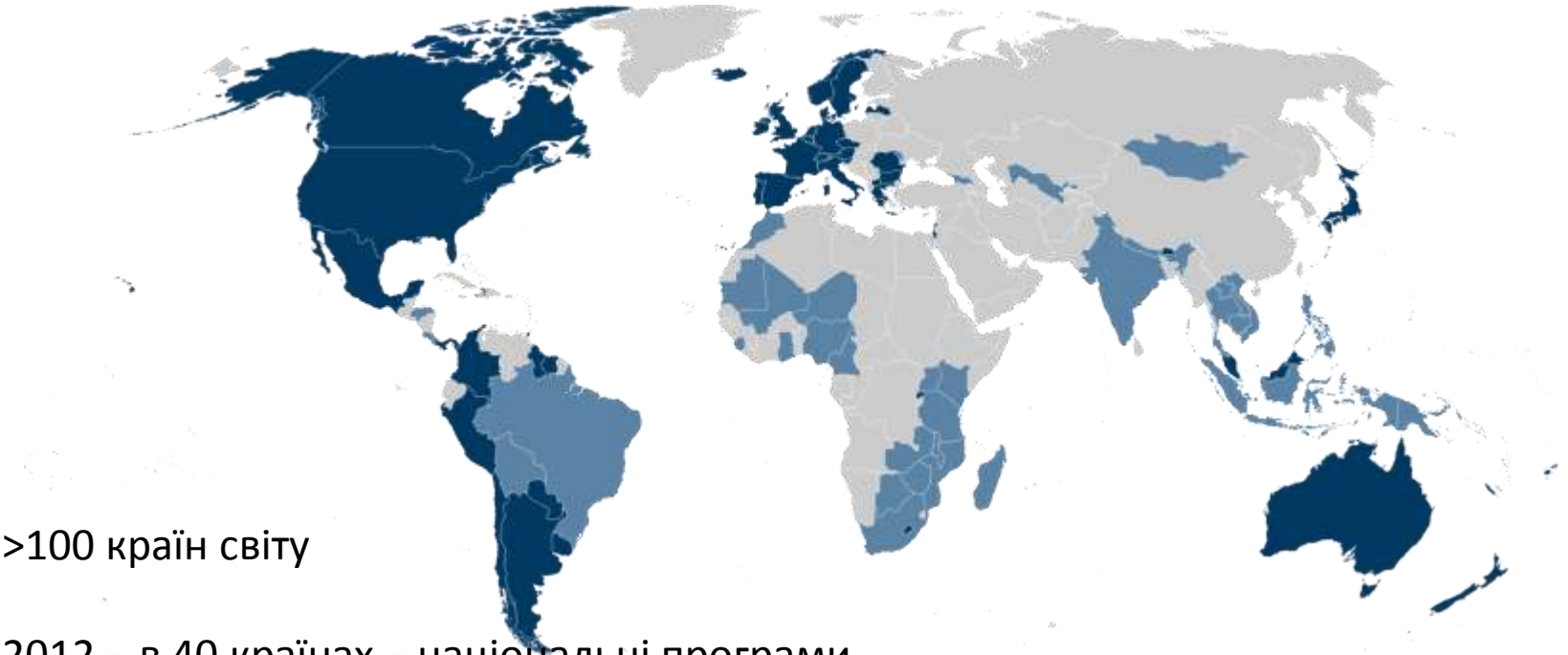
Австралія – перша країна з національною програмою імунізації (59% зниження частоти кондилом за 2 роки)

США (FDA) 2006 – HPV4
2009 – HPV2

Cervical Cancer ACTION
A Global Coalition to STOP Cervical Cancer

Global Progress in HPV vaccine introduction

July 2013



- >100 країн світу
- 2012 – в 40 країнах – національні програми

National programs

American Samoa
Argentina
Australia
Austria
Belgium
Bermuda
Bhutan
Brunei
Bulgaria
Canada
Cayman Islands
Chile
Colombia
Cook Islands
Czech Republic
Denmark
Fiji
France
French Polynesia
Germany
Greece
Guam
Guyana
Iceland
Ireland
Israel
Italy
Japan
Latvia
Lesotho
Luxembourg
Macedonia
Malaysia
Marshall Islands
Mexico
Micronesia
Netherlands
New Caledonia
New Zealand
Niue
Northern Marianas
Norway
Palau
Panama
Paraguay
Peru
Portugal
Romania
Rwanda
San Marino
Singapore
Slovenia
Spain
Sweden
Switzerland
Suriname
Trinidad and Tobago
United Kingdom
United States
Uruguay

Pilot programs

Bolivia
Botswana
Brazil
Cambodia
Cameroon
Costa Rica
Georgia
Ghana
Haiti
Honduras
India
Indonesia
Kenya
Kiribati
Lao PDR
Madagascar
Malawi
Mali
Mauritania
Moldova
Mongolia
Morocco
Mozambique
Nepal
Niger
Nigeria
Papua New Guinea
Philippines
Sierra Leone
South Africa
Tanzania
Thailand
Uganda
Uzbekistan
Vietnam
Zambia
Zimbabwe

Cervical Cancer ACTION
A Global Coalition to STOP Cervical Cancer

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1. Are the Currently Existing Anti-**Human Papillomavirus** Vaccines Appropriate for the Developing World?
van Bogaert L.
Ann Med Health Sci Res. 2013 Jul;3(3):306-312. Review.
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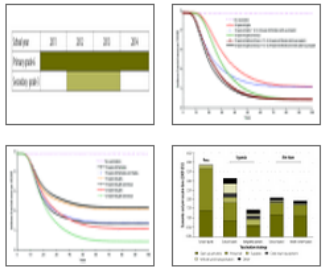


See more (316)...

Імуногенність

- Спостереження 5-6,4 років після вакцинації - **пік рівня титру антитіл спостерігається після третьої дози**, а потім поступово знижується і протягом 24 місяців досягає рівня, що з'являється після введення першої дози*

- **Імуногенність HPV2 проти ВПЛ 16, 18** було продемонстровано до **8,4 років**. Для HPV4 вивчення імуногенності до п'яти років показало, що імунна відповідь проти ВПЛ 18 слабшає після близько чотирьох років

- Ефективність проти інфекції і шийкових уражень, пов'язаних з ВПЛ 16,18, була продемонстрована до **8,4 і 5 років** для **HPV2 і HPV4** відповідно**

* Pedersen C et al. Immunization of early adolescent females with human papillomavirus type 16 and 18 L1 virus-like particle vaccine containing AS04 adjuvant. Journal of Adolescent Health, 2007, 40:564–571.

** Romanowski B. Long-term protection against cervical infection with the human papillomavirus. Review of currently available vaccines. Human Vaccines 2011, 7:2, 161-169

RESEARCH PAPER

Human Vaccines 7:12, 1343-1358; December 2011; © 2011 Landes Bioscience

Comparative immunogenicity and safety of human papillomavirus (HPV)-16/18 vaccine and HPV-6/11/16/18 vaccine

Follow-up from months 12–24 in a Phase III randomized study of healthy women aged 18–45 years

Mark H. Einstein,[1,*] Mira Baron,[2] Myron J. Levin,[3] Archana Chatterjee,[4] Bradley Fox,[5] Sofia Scholar,[6] Jeffrey Rosen,[7] Nahida Chakhtoura,[8] Dorothée Meric,[9] Francis J. Dessy,[9] Sanjoy K. Datta,[9] Dominique Descamps[9] and Gary Dubin[10] on behalf of the HPV-010 Study Group[†]

[1]Department of Obstetrics & Gynecology and Women's Health; Division of Gynecologic Oncology; Montefiore Medical Center; Albert Einstein College of Medicine; Bronx, NY USA; [2]Rapid Medical Research; Cleveland, OH USA; [3]University of Colorado Denver and Health Sciences Center; Aurora, CO USA; [4]Creighton University School of Medicine; Omaha, NE USA; [5]Liberty Family Practice; Erie, PA USA; [6]Walla Walla Clinic; Walla Walla, WA USA; [7]Clinical Research of South Florida; Coral Gables, FL USA; [8]University of Miami; Miami, FL USA; [9]GlaxoSmithKline Biologicals; Belgium; [10]GlaxoSmithKline Biologicals; USA

In this observer-blind study (NCT00423046), women (N = 1,106), stratified by age (18–26, 27–35, 36–45 y), were randomized (1:1) to receive the HPV-16/18 vaccine (*Cervarix*®, GlaxoSmithKline Biologicals, Months 0, 1, 6) or the HPV-6/11/16/18 vaccine (*Gardasil*® Merck and Co., Inc., Months 0, 2, 6). Month 7 results were previously reported; we now report Month 24 results. In the according-to-protocol cohort for immunogenicity (seronegative and DNA-negative at baseline for HPV type analyzed), seropositivity rates of neutralizing antibodies (nAbs) [pseudovirion-based neutralization assay] were, across all age strata, 100% (HPV-16/18 vaccine) and 97.5–100% (HPV-6/11/16/18 vaccine) for HPV-16, and 99.0–100% (HPV-16/18 vaccine) and 72.3–84.4% (HPV-6/11/16/18 vaccine) for HPV-18. Corresponding geometric mean titers (GMTs) were 2.4–5.8-fold higher for HPV-16 and 7.7–9.4-fold higher for HPV-18 with the HPV-16/18 vaccine vs. the HPV-6/11/16/18 vaccine; HPV-16 and HPV-18 GMTs were significantly higher with the HPV-16/18 vaccine than the HPV-6/11/16/18 vaccine ($p < 0.0001$) in the total vaccinated cohort (received ≥1 vaccine dose, irrespective of baseline sero/DNA-status). Similar results were obtained using enzyme-linked immunosorbent assay (ELISA). Positivity rates and GMTs of antigen-specific IgG antibodies in cervicovaginal secretions (ELISA) were not significantly different between vaccines. At Month 24, $CD4^+$ T-cell responses for HPV-16 and HPV-18 were higher with the HPV-16/18 vaccine; memory B-cell response was higher for HPV-18 with the HPV-16/18 vaccine and similar between vaccines for HPV-16. Both vaccines were generally well tolerated. Although an immunological correlate of protection has not been defined, differences in the magnitude of immune response between vaccines may represent determinants of duration of protection.

Двовалентна вакцина викликає більш виразну і більш стійку імунну відповідь, ніж чотиривалентна (?..)

RESEARCH PAPER

Human Vaccines 7:12, 1359-1373; December 2011; © 2011 Landes Bioscience

Comparison of the immunogenicity of the human papillomavirus (HPV)-16/18 vaccine and the HPV-6/11/16/18 vaccine for oncogenic non-vaccine types HPV-31 and HPV-45 in healthy women aged 18–45 years

Mark H. Einstein,[1,*] Mira Baron,[2] Myron J. Levin,[3] Archana Chatterjee,[4] Bradley Fox,[5] Sofia Scholar,[6] Jeffrey Rosen,[7] Nahida Chakhtoura,[8] Marie Lebacq,[9] Robbert van der Most,[9] Philippe Moris,[9] Sandra L. Giannini,[9] Anne Schuind,[10] Sanjoy K. Datta[9] and Dominique Descamps[9] on behalf of the HPV-010 Study Group[†]

[1]Department of Obstetrics & Gynecology and Women's Health; Division of Gynecologic Oncology; Montefiore Medical Center; Albert Einstein College of Medicine; Bronx, NY USA; [2]Rapid Medical Research; Cleveland, OH USA; [3]University of Colorado Denver and Health Sciences Center; Aurora, CO USA; [4]Creighton University School of Medicine; Omaha, NE USA; [5]Liberty Family Practice; Erie, PA USA; [6]Walla Walla Clinic; Walla Walla, WA USA; [7]Clinical Research of South Florida; Coral Gables, FL USA; [8]University of Miami; Miami, FL USA; [9]GlaxoSmithKline Biologicals; Belgium; [10] GlaxoSmithKline Biologicals; USA

Protection against oncogenic non-vaccine types (cross-protection) offered by human papillomavirus (HPV) vaccines may provide a significant medical benefit. Available clinical efficacy data suggest the two licensed vaccines [HPV-16/18 vaccine, GlaxoSmithKline Biologicals (GSK), and HPV-6/11/16/18 vaccine, Merck and Co., Inc.,] differ in terms of protection against oncogenic non-vaccine HPV types -31/45. The immune responses induced by the two vaccines against these two non-vaccine HPV types (cross-reactivity) was compared in an observer-blind study up to Month 24 (18 mo post-vaccination), in women HPV DNA-negative and seronegative prior to vaccination for the HPV type analyzed [HPV-010 (NCT00423046)]. Geometric mean antibody titers (GMTs) measured by pseudovirion-based neutralization assay (PBNA) and enzyme-linked immunosorbent assay (ELISA) were similar between vaccines for HPV-31/45. Seropositivity rates for HPV-31 were also similar between vaccines; however, there was a trend for higher seropositivity with the HPV-16/18 vaccine (13.0–16.7%) vs. the HPV-6/11/16/18 vaccine (0.0–5.0%) for HPV-45 with PBNA, but not ELISA. HPV-31/45 cross-reactive memory B-cell responses were comparable between vaccines. Circulating antigen-specific CD4+ T-cell frequencies were higher for the HPV-16/18 vaccine than the HPV-6/11/16/18 vaccine {HPV-31 [geometric mean ratio (GMR) = 2.0; p = 0.0002] and HPV-45 [GMR = 2.6; p = 0.0092]}, as were the proportion of T-cell responders (HPV-31, p = 0.0009; HPV-45, p = 0.0793). In conclusion, immune response to oncogenic non-vaccine HPV types -31/45 was generally similar for both vaccines with the exception of T-cell response which was higher with the HPV-16/18 vaccine. Considering the differences in cross-protective efficacy between the two vaccines, the results might provide insights into the underlying mechanism(s) of protection.

Перехресний захист від невакцінальних типів виявляється сильнішим у двовалентної вакцини (?..)

2008

Francoise Barre-Sinoussi and Luc Montagnier

Harald zur Hausen

Nobel Prize Scandals: 10 Winners Whose Prizes are Forever Tarnished

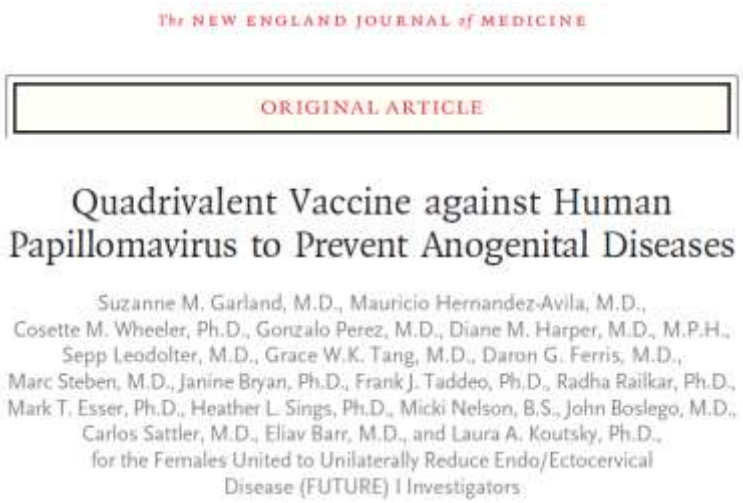
Harald zur Hausen, Physiology or Medicine, 2008:

Doctor Harald zur Hausen was honored with the Nobel Prize in 2008 for his discovery that HPV causes cervical cancer. That this discovery is significant and could potentially save lives is inarguable, but his winning of the Nobel Prize would cause a huge amount of scandal nonetheless. Why? Because of corporate sponsorship. As it turns out, pharmaceutical company AstraZeneca had recently begun sponsoring the Nobel website and had links to two senior figures on the medicine prize's selection committee. More importantly, it held a stake in two HPV vaccines which would be much more publicized, and profitable, with a Nobel Prize linked to them. Unfortunately for Dr. zur Hausen (who was not found to have a role in the scandal), his prize would be tainted by a Swedish police investigation into improper influence, and while charges were never brought against AstraZeneca, the 2008 prize will always be associated with this alleged impropriety.

Клінічна ефективність

- Головний критерій ефективності – CIN II-III, AIS

Клінічна ефективність (HPV4)



- **FUTURE** (Females United to Unilaterally Reduce Endo/Ectocervical Disease):
  - 12 167 жінок (15-26 років)
  - Спостереження 3 роки
  - CIN II+ (16,18) (98%);
  - кондиломи, VINII+, VaINII+ (6,11,16,18) (98-100%)
  - 16, 18+ до включення – ефекту щодо CIN II+ немає
  - Ефективність щодо CIN II+ внаслідок інших онкогенних типів – 44%

Клінічна ефективність (HPV2)

THE LANCET

The Lancet, Volume 374, Issue 9686, Pages 301 - 314, 25 July 2009
doi:10.1016/S0140-6736(09)61248-4 Cite or Link Using DOI
Published Online: 07 July 2009

Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women

Prof J Paavonen MD [a], Prof P Naud MD [b], Prof J Salmerón PhD [c], Prof CM Wheeler PhD [d], Prof S-N Chow MD [e], D Apter MD [f], Prof H Kitchener MD [g], X Castellsague MD [h], JC Teixeira MD [i], SR Skinner PhD [j], J Hedrick MD [k], U Jaisamrarn MD [l], Prof G Limson MD [m], Prof S Garland MD [n], A Szarewski PhD [o], Prof B Romanowski MD [p], Prof FY Aoki MD [q], Prof TF Schwarz MD [r], Prof WAJ Poppe MD [s], FX Bosch MD [h], Prof D Jenkins MD [t], K Hardt PhD [u], T Zahaf PhD [u], D Descamps MD [u], F Struyf MD [u], Prof M Lehtinen MD [v], G Dubin MD [w], for the HPV PATRICIA Study Group

- **PATRICIA** (PApilloma TRial against Cancer In young Adults):
  - 18 644 жінки (15-25 років)
  - Спостереження 34,9 міс (до 6,4 роки)
  - CIN II+ (16,18) (92,9%)
  - 16, 18+ до включення – ефекту щодо CIN II+ немає
  - Ефективність щодо CIN II+ внаслідок інших онкогенних типів – 37,4% (HPV31 – 89,4%)

TABLE 2. Efficacy of bivalent human papillomavirus vaccine (HPV2) and quadrivalent human papillomavirus vaccine (HPV4) in females

Vaccine/Endpoint/HPV type	Vaccine		Control		Vaccine efficacy	
	No.	Cases	No.	Cases	%	(CI*)
Bivalent vaccine (HPV2)†						(96.1% CI)
CIN2/3 or AIS§						
HPV 16 and/or 18	7,344	4	7,312	56	92.9	(79.9–98.3)
HPV 16	6,303	2	6,165	46	95.7	(82.9–99.6)
HPV 18	6,794	2	6,746	15	86.7	(39.7–98.7)
Quadrivalent vaccine (HPV4)¶						(95% CI)
CIN2/3 or AIS**						
HPV 6, 11, 16, and/or 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)
VIN2/3 or VaIN2/3 **						
HPV 6, 11, 16, and/or 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	6,932	2	6,856	189	99.0	(96.2–99.9)

Abbreviations: CIN2/3 = cervical intraepithelial neoplasia grade 2 or 3, AIS = adenocarcinoma in situ, VIN2/3 = vulvar intraepithelial neoplasia grade 2 or 3, VaIN2/3 = vaginal intraepithelial neoplasia grade 2 or 3, HPV = human papillomavirus.

* Confidence interval.

† Phase III trial. According to protocol efficacy analysis included females aged 15 through 25 years who received all 3 vaccine doses, were seronegative at day 1 and HPV DNA negative at day 1 through month 6 for the respective HPV type, and had normal or low grade cytology at day 1, with case counting beginning 1 day after third vaccine dose; mean duration of follow-up post first vaccine dose: 34.9 months.

§ **Source:** Paavonen J, Naud P, Salmeron J, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. Lancet 2009;374:301–14.

¶ Combined analysis of one phase II and two phase III trials. Per protocol efficacy analysis included females aged 16 through 26 years who received all 3 vaccine doses, were seronegative at day 1 and HPV DNA negative at day 1 through month 7 for the respective HPV type, with case counting beginning 1 month after third vaccine dose; mean duration of follow-up post first vaccine dose: 42 months.

** **Source:** Kjaer SK, Sigurdsson K, Iversen OE, et al. A pooled analysis of continued prophylactic efficacy of quadrivalent human papillomavirus (Types 6/11/16/18) vaccine against high-grade cervical and external genital lesions. Cancer Prev Res 2009;2:868–78.

†† **Source:** Food and Drug Administration. Product approval-prescribing information [package insert]. Gardasil [human papillomavirus quadrivalent (types 6, 11, 16, and 18) vaccine, recombinant], Merck & Co, Inc: Food and Drug Administration 2009. Available at http://www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ucm094042.htm. Accessed May 25, 2010.

Клінічна ефективність (HPV4 у хлопчиків)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 3, 2011 VOL. 364 NO. 5

Efficacy of Quadrivalent HPV Vaccine against HPV Infection and Disease in Males

Anna R. Giuliano, Ph.D., Joel M. Palefsky, M.D., Stephen Goldstone, M.D., Edson D. Moreira, Jr., M.D., Mary E. Penny, M.D., Carlos Aranda, M.D., Eftyhia Vardas, M.D., Harald Moi, M.D., Heiko Jessen, M.D., Richard Hillman, M.D., Yen-Hwa Chang, M.D., Daron Ferris, M.D., Danielle Rouleau, M.D., Janine Bryan, Ph.D., J. Brooke Marshall, Ph.D., Scott Vuocolo, Ph.D., Eliav Barr, M.D., David Radley, M.S., Richard M. Haupt, M.D., and Dalya Guris, M.D.

- 4065 хлопчиків (16-26 років)
- Спостереження 3 роки
- Аногенітальні ураження (6,11,16,18) – 90,4% ефективність

June 2013 | Volume 8 | Issue 6 | e67072

OPEN ACCESS Freely available online

PLOS ONE

Vaccinating Girls and Boys with Different Human Papillomavirus Vaccines: Can It Optimise Population-Level Effectiveness?

Mélanie Drolet[1,2], Marie-Claude Boily[3], Nicolas Van de Velde[1,2], Eduardo L. Franco[4], Marc Brisson[1,2,3]*

1 Centre de recherche du CHU de Québec, Hôpital Saint-Sacrement, Québec, Canada, 2 Département de médecine sociale et préventive, Université Laval, Québec, Canada, 3 Department of Infectious Disease Epidemiology, Imperial College, London, United Kindom, 4 Division of Cancer Epidemiology, McGill University, Montreal, Canada

- Вакцинація дівчат HPV2 і хлопчиків HPV4 допоможе покращити запобігання раку шийки матки, оскільки HPV2 має більший перехресний захист, але може підвищити частоту генітальних кондилом, якщо охоплення вакцинацією хлопчиків буде недостатнім

Vaccine
Volume 25, Issue 11, 1 March 2007, Pages 1945–1952

Parental attitudes to pre-pubertal HPV vaccination

Laura A.V. Marlow, Jo Waller, Jane Wardle
Cancer Research UK Health Behaviour Unit, Department of Epidemiology and Public Health, UCL, Gower Street, 2-16 Torrington Place, London WC1E 6BT, United Kingdom

25%

Parental attitudes towards vaccinating sons with human papillomavirus vaccine

Gitte Lee Mortensen

- 76% - "Захистити мого сина від раку“
- 36% - “Захистити мого сина від генітальних кондилом"
- **13%** - "запобігання інфекціям, що передаються статевим шляхом, є спільною відповідальністю”

Контроль ефективності

- Результати, що цікавлять:
  - короткостроковий вплив на конкретний тип ВПЛ інфекції та гострих кондилом **(місяці)**
  - середньострокові результати (ураження шийки матки, рецидивуючий респіраторного папіломатозу **(роки)**
  - довгострокові результати (захворюваність і смертність від раку шийки матки, раку ануса, іншого аногенітального раку і раку ротоглотки **(десятиліття)**

    (різна інфраструктура спостереження, яка включає різні часовий проміжок, вибірку, методологію)

- Кожна країна має різні програми вакцинації проти ВПЛ (у тому числі тип вакцини, час впровадження, цільові групи населення й досягнуте охоплення)

- **Порівняння результатів в різних країнах - складне завдання**

Ann Med Health Sci Res. 2013 Jul-Sep; 3(3): 306–312.

Annals of Medical and Health Sciences Research
Medknow Publications

Are the Currently Existing Anti-Human Papillomavirus Vaccines Appropriate for the Developing World?

LJ van Bogaert

Abstract

Cervical cancer prevention is expected to be achieved by vaccination of girls 2-3 years before sexual debut, and cervical smear cytology follow-up. The existing human papillomavirus (HPV) vaccines target the low-risk 6 and 11, and the high-risk 16 and 18 subtypes, the most common agents of ano-genital pre-invasive and invasive lesions. We conducted the review by searching PubMed using the terms "HPV," "HPV subtypes," "developing world," and "HPV-vaccine" to retrieve articles published between 2000 and 2011. We focused on studies that were relevant to the developing world. The proposed vaccination policy is currently unachievable in the developing world because of the cost of the vaccine, the lack of adequate cytology and follow-up infrastructures. Moreover, the subtypes of HPV involved in cervical pathology, their associations, and natural history (clearance and persistence rates) differ from the industrialized world. Therefore, the current bivalent and quadrivalent anti-HPV vaccines are unlikely to achieve their target in the developing world. It follows from published data that there is an obligation of the pharmaceutical industry and of the public-health policy makers not to embark on mass vaccination campaigns without thorough information and investigation of the local relevance.

Current Pharmaceutical Design

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Human Papillomavirus (HPV) Vaccines as an Option for Preventing Cervical Malignancies: (How) Effective and Safe?

Author(s): Lucija Tomljenovic, Jean Pierre Spinosa and Christopher A. Shaw
Pages 1466-1487 (22)

Abstract:

We carried out a systematic review of HPV vaccine pre- and post-licensure trials to assess the evidence of their effectiveness and safety. We find that HPV vaccine clinical trials design, and data interpretation of both efficacy and safety outcomes, were largely inadequate. Additionally, we note evidence of selective reporting of results from clinical trials (i.e., exclusion of vaccine efficacy figures related to study subgroups in which efficacy might be lower or even negative from peer-reviewed publications). Given this, the widespread optimism regarding HPV vaccines long-term benefits appears to rest on a number of unproven assumptions (or such which are at odd with factual evidence) and significant misinterpretation of available data. For example, the claim that HPV vaccination will result in approximately 70% reduction of cervical cancers is made despite the fact that the clinical trials data have not demonstrated to date that the vaccines have actually prevented a single case of cervical cancer (let alone cervical cancer death), nor that the current overly optimistic surrogate marker-based extrapolations are justified. Likewise, the notion that HPV vaccines have an impressive safety profile is only supported by highly flawed design of safety trials and is contrary to accumulating evidence from vaccine safety surveillance databases and case reports which continue to link HPV vaccination to serious adverse outcomes (including death and permanent disabilities). We thus conclude that further reduction of cervical cancers might be best achieved by optimizing cervical screening (which carries no such risks) and targeting other factors of the disease rather than by the reliance on vaccines with questionable efficacy and safety profiles.

Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors (Protocol)

Arbyn M, Bryant A, Beutels P, Martin-Hirsch PPL, Paraskevaidis E, Van Hoof E, Steben M, Qiao Y, Zhao FH, Schneider A, Kaufmann A, Dillner J, Markowitz L, Hildesheim A

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane protocol, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2011, Issue 4

http://www.thecochranelibrary.com

Безпека

- Найчастіші побічні дії:
  - Запалення в місті введення (HPV2 > HPV4 *)
  - Втома, міалгія
  - Запамороченння **
- Вагітність, лактація – не рекомендується
  - HPV4 – можна вводити при лактації (WHO, 2009)

* Einstein MH, Baron M, Levin MJ et al. Comparison of the immunogenicity and safety of Cervarix and Gardasil human papillomavirus (HPV) cervical cancer vaccines in healthy women aged 18–45 years. Hum. Vaccin. 5(10), 705–719 (2009).

** Crawford NW, Clothier HJ, Elia S, Lazzaro T, Royle J, Buttery JP. Syncope and seizures following human papillomavirus vaccination: a retrospective case series. Med.J. Aust. 194 (1), 16–18 (2011).

VAERS

Vaccine Adverse Event Reporting System

Search web site: Search

The **Vaccine Adverse Event Reporting System (VAERS)** is a national vaccine safety surveillance program co-sponsored by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA). VAERS is a post-marketing safety surveillance program, collecting information about adverse events (possible side effects) that occur after the administration of vaccines licensed for use in the United States.

VAERS provides a nationwide mechanism by which adverse events following immunization may be reported, analyzed, and made available to the public. VAERS also provides a vehicle for disseminating vaccine safety-related information to parents and guardians, health care providers, vaccine manufacturers, state vaccine programs, and other constituencies. more...

Have you or your child had a reaction following vaccination?

1. **Contact your health care provider**
2. **Report the reaction**
3. **Submit Follow-Up Information**
4. **Visit the National Vaccine Injury Compensation** (if appropriate)

Important note: CDC and FDA do not provide individual medical treatment, advice, or diagnosis. If you need individual medical or health care advice, consult a qualified health care provider.

¿Ha tenido usted o su hijo una reacción adversa después de recibir una vacuna?

1. **Contacte a su proveedor de salud**
2. **Reporte una reacción adversa**
3. **Visite el Programa Nacional de Compensación por Daños Derivados de Vacunas** (si es necesario)

Search VAERS Data

VAERS Data last updated: **09/12/2013**

Featured Resources

Seasonal Flu Update

- **Summary of 2013-2014 Influenza Vaccine Information**

Government Agencies

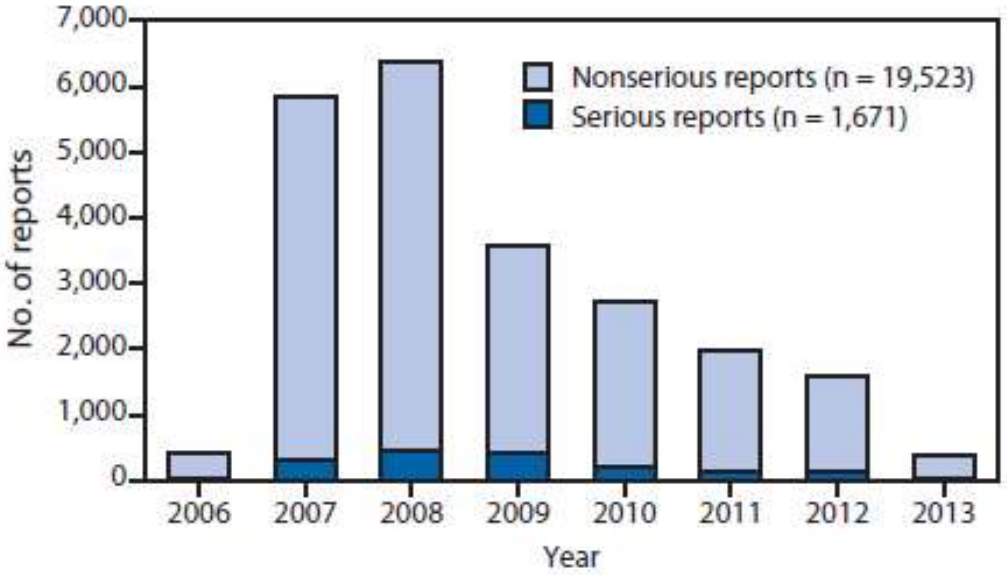
- **Immunization Safety Office**
- **National Center for**

Human Papillomavirus Vaccination Coverage Among Adolescent Girls, 2007–2012, and Postlicensure Vaccine Safety Monitoring, 2006–2013 — United States

> 70 млн. доз в світі

- **56 млн. доз HPV4** (червень 2006 – березень 2013)
- **611 тис. доз HPV2** (жовтень 2009 – травень 2013)
- **21 194 випадків побічної дії** (92,1% - незначні)

FIGURE. Number of serious and nonserious reports of adverse events after administration of quadrivalent human papillomavirus (HPV4) vaccine in females, by year — Vaccine Adverse Event Reporting System, United States, June 2006–March 2013*



* Total number of reports (serious and nonserious) = 21,194. In the Vaccine Adverse Event Reporting System, reports are classified as serious if the submitter reports one or more of the following: hospitalization, prolongation of an existing hospitalization, permanent disability, life-threatening illness, or death.

BMJ Case Reports

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BMJ Case Reports 2012; doi:10.1136/bcr-2012-006879

Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

Premature ovarian failure 3 years after menarche in a 16-year-old girl following human papillomavirus vaccination

Deirdre Therese Little[1], **Harvey Rodrick Grenville Ward**[2]

Summary

Premature ovarian failure in a well adolescent is a rare event. Its occurrence raises important questions about causation, which may signal other systemic concerns. This patient presented with amenorrhoea after identifying a change from her regular cycle to irregular and scant periods following vaccinations against human papillomavirus. She declined the oral contraceptives initially prescribed for amenorrhoea. The diagnostic tasks were to determine the reason for her secondary amenorrhoea and then to investigate for possible causes of the premature ovarian failure identified. Although the cause is unknown in 90% of cases, the remaining chief identifiable causes of this condition were excluded. Premature ovarian failure was then notified as a possible adverse event following this vaccination. The young woman was counselled regarding preservation of bone density, reproductive implications and relevant follow-up. This event could hold potential implications for population health and prompts further inquiry.

"post hoc, ergo propter hoc" (?)

AJRI
American Journal of Reproductive Immunology

American Journal of Reproductive Immunology **70** (2013) 309–316

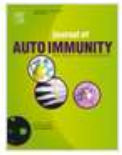
ORIGINAL ARTICLE

Human Papilloma Virus Vaccine and Primary Ovarian Failure: Another Facet of the Autoimmune/Inflammatory Syndrome Induced by Adjuvants

Serena Colafrancesco[1,2], Carlo Perricone[1,2], Lucija Tomljenovic[1,3], Yehuda Shoenfeld[1,4]

[1]Zabludowicz Center for Autoimmune Diseases Sheba Medical Center, Tel-Hashomer, Israel;
[2]Rheumatology Unit, Department of Internal Medicine and Medical Specialities, Sapienza University of Rome, Rome, Italy;
[3]Neural Dynamics Research Group, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada;
[4]Incumbent of the Laura Schwarz-Kipp Chair for Research of Autoimmune Diseases, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Journal of Autoimmunity
Volume 36, Issue 1, February 2011, Pages 4–8



Review

'ASIA' – Autoimmune/inflammatory syndrome induced by adjuvants

Yehuda Shoenfeld[a, b], Nancy Agmon-Levin[a]
[a] The Zabludowicz Center for Autoimmune Diseases, Department of Medicine B' Sheba Medical Center, Tel-Hashomer, Israel
[b] Incumbent of the Laura Schwarz-kipp Chair for Research of Autoimmune Diseases, Sackler Faculty of Medicine, Tel-Aviv University, Israel

- Siliconosis
- Gulf war syndrome (GWS)
- macrophagic myofasciitis syndrome (MMF)
- **post-vaccination phenomena**

were linked with previous exposure to an adjuvant

Suggested criteria for the diagnosis of 'ASIA'

Major Criteria:
- Exposure to an external stimuli (infection, vaccine, silicone, adjuvant) prior to clinical manifestations.
- The appearance of 'typical' clinical manifestations:
  - Myalgia, myositis or muscle weakness
  - Arthralgia and/or arthritis
  - Chronic fatigue, un-refreshing sleep or sleep disturbances
  - Neurological manifestations (especially associated with demyelination)
  - Cognitive impairment, memory loss
  - Pyrexia, dry mouth
- Removal of inciting agent induces improvement
- Typical biopsy of involved organs

Minor Criteria:
- The appearance of autoantibodies or antibodies directed at the suspected adjuvant
- Other clinical manifestations (i.e. irritable bowel syndrome)
- Specific HLA (i.e. HLA DRB1, HLA DQB1)
- Evolvement of an autoimmune disease (i.e. multiple sclerosis, systemic sclerosis)

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Table I The Suggested Criteria of Autoimmune/Inflammatory Syndrome Induced by Adjuvants (ASIA)[7] in the Current Three Cases of Post-Human Papilloma Virus Vaccine Manifested Primary Ovarian Failure (POF). Note That for Positive Diagnosis of ASIA, Fulfilment of Either Two Major or One Major and Two Minor Criteria is Required

	Case 1	Case 2	Case 3
Major criteria			
1. Exposure to an external stimuli (infection, vaccine and/or immune adjuvants) prior to clinical manifestations	+	+	+
2. The appearance of 'typical' clinical manifestations;			
Myalgia, muscle weakness	–	–	Not reported
Arthralgia and/joint pain	+	–	–
Chronic fatigue, un-refreshing sleep or sleep disturbances	+	+	Not reported
Neurological manifestations	+	+	Not reported
Cognitive disturbances	–	+	Not reported
Pyrexia	–	–	–
3. Removal of inciting agent induces improvement	NA	NA	NA
4. Typical biopsy of involved organs	Not assessed	Not assessed	Not assessed
Minor criteria			
1. The appearance of autoantibodies (antiovarian, anti-TPO)	–	+	+
2. Other clinical manifestations (e.g. amenorrhoea)	+	+	+
3. Specific HLA (e.g. HLA DRB1, HLA DQB1)	Not assessed	Not assessed	Not assessed
4. Evolvement of an autoimmune disease (POF)	+	+	+

???

- Дві дози?
- Стимулююча доза?
- Вакцинація проти ВПЛ – частина програми імунізації дітей?
- Антигени інших білків вірусу?
- Чи спостерігатиметься заміна типів та мутації ВПЛ?
- Полівалентна вакцина?...

"Отсебятіна ☺":

(враховуючи дані про безпеку (ASIA):

- Як бути з хлопчиками, вакцинація яких відбувається до моменту, коли їх цікавить репродукція, і у яких немає менструації?

- Якими можуть бути додаткові критерії відбору для вакцинації? (імунологія?..)