

# **HPV Vaccines**

## **Are they really safe?**

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1 October, 2009

## Cancer jab girl 'died of tumour'



**A girl who was vaccinated against cervical cancer died from a malignant tumour of the chest and not from a reaction to the jab, it has emerged.**

Natalie Morton, 14, died after being given the injection at the Blue Coat Church of England School in Coventry.

Deputy coroner for Coventry Louise Hunt said the vaccine was not thought to have been a contributing factor. A pathologist said her undiagnosed condition was "so severe that death could have arisen at any point".


Natalie collapsed less than two hours after being given the *Cervarix* vaccine on Monday and was pronounced dead at Coventry's University Hospital.

The deputy coroner, who opened and adjourned the hearing at Coventry Magistrates' Court, said: "It appears that Natalie died from a tumour in her chest involving her heart and her lungs." The inquest was told that the tumour had "heavily infiltrated" her heart and extended into her left lung.

# Safety issues

- Important to distinguish “temporality” from “causality”
- Take into account the “background rates” of diseases when assessing individual reports of adverse events<sup>1</sup>

# Vaccine Adverse Event Reporting System (VAERS)

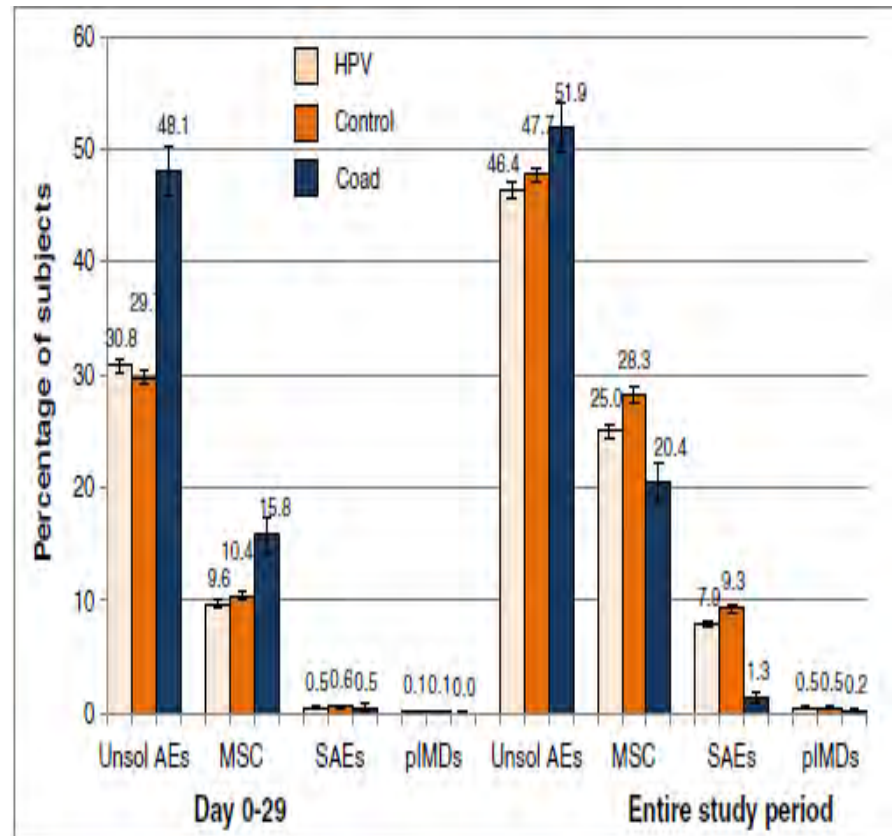
- Post-licensure vaccine safety monitoring in USA
  - Independently conducted by federal agencies and vaccine manufacturers, monitored by CDC & FDA
  - 67 million doses of HPV vaccine June 2006 - March 2014
  - 25,000 adverse events reported, 92% “non-serious”
  - Most common reported symptoms were
    - Injection-site reactions
    - Dizziness
    - Syncope
    - Nausea
    - Headache
- 

# Cervarix™ Vaccine Pooled Safety Analysis

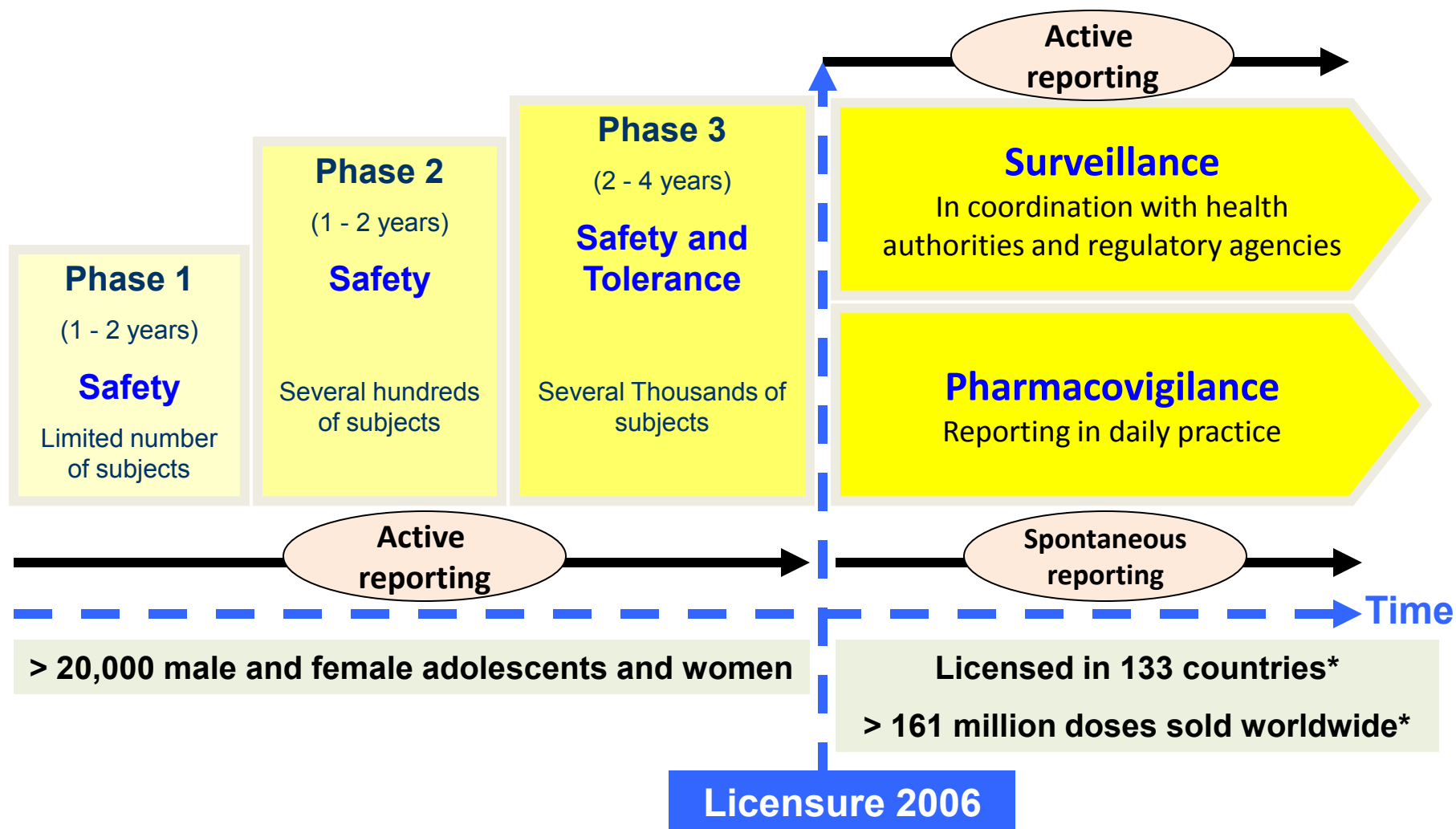
## Pooled clinical trial data analysis

Pooled analysis of data from 42 completed/on-going clinical studies  
(**57,580 subjects**)

- Incidences & distribution of AEs were similar among *Cervarix*™ recipients and controls
- No new safety signals were identified
- No increase in risk in presumed autoimmune disease
- Pregnancy outcomes were similar between *Cervarix*™ vaccinees and controls



# Evaluation of Safety for quadrivalent HPV vaccine: From clinical studies to comprehensive surveillance in real-life populations



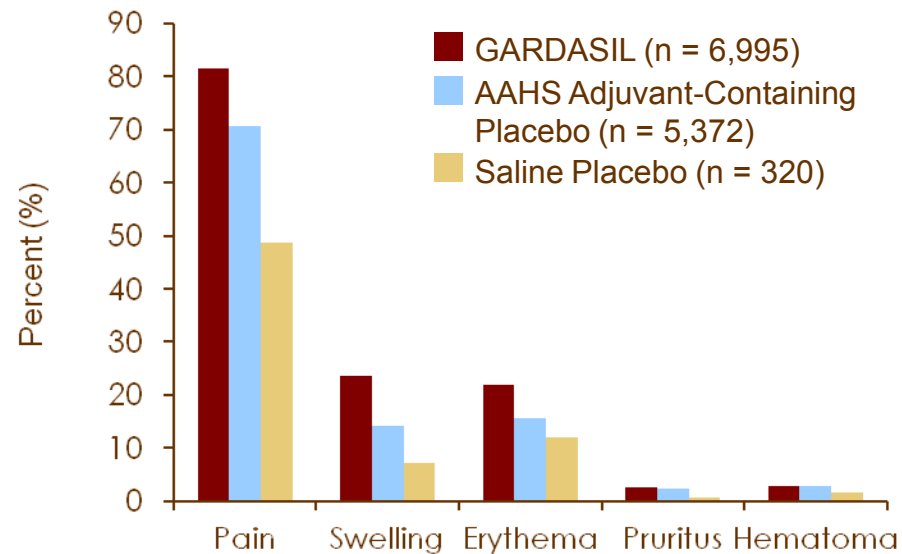
\* Data on file. Data was derived in July 2014.

# Vaccine-Related Injection-Site and Systemic Adverse Experiences: Quadrivalent HPV vaccine clinical studies<sup>1</sup>

Girls and Women 9 Through 45 Years of Age

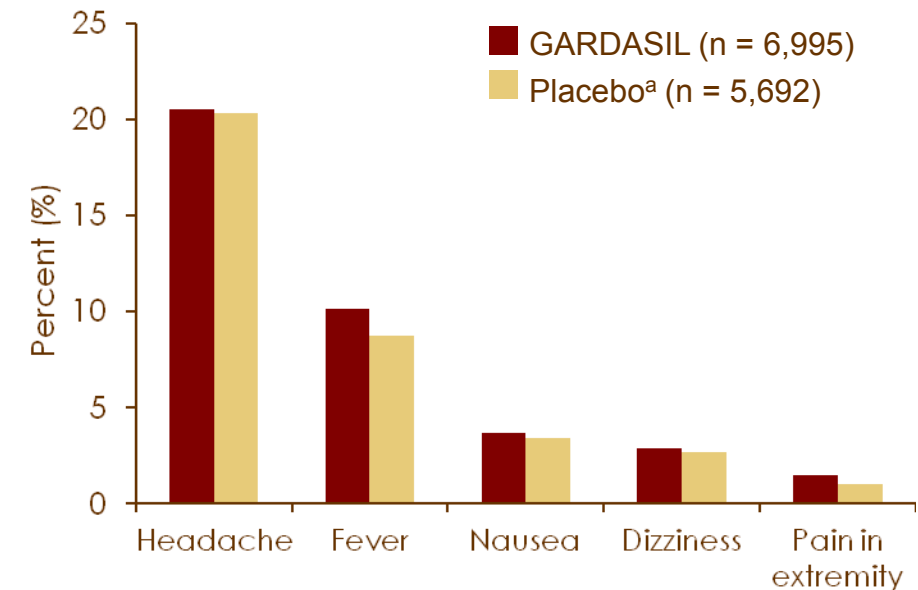
## Injection Site

(1 to 5 days postvaccination)



## Systemic

(1 to 15 days postvaccination)



The vaccine-related adverse experiences that were observed among recipients of GARDASIL at a frequency of at least 1% and also at a greater frequency than that observed among AAHS control or saline placebo recipients.

<sup>a</sup>Data were pooled for AAHS adjuvant-containing placebo and saline placebo.

AAHS = amorphous aluminum hydroxyphosphate sulfate.

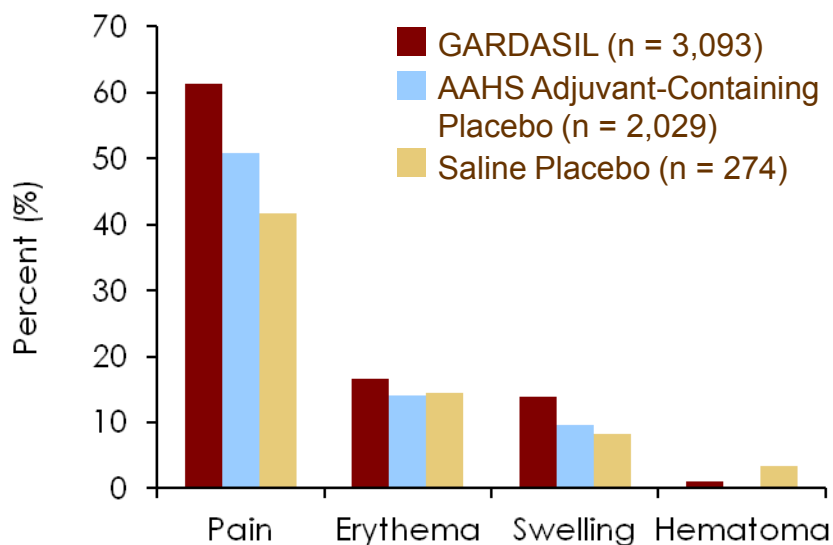
1. Data on file, MSD \_\_\_\_\_.

# Vaccine-Related Injection-Site and Systemic Adverse Experiences: Quadrivalent HPV vaccine clinical studies<sup>1</sup>

Boys and Men 9 Through 26 Years of Age

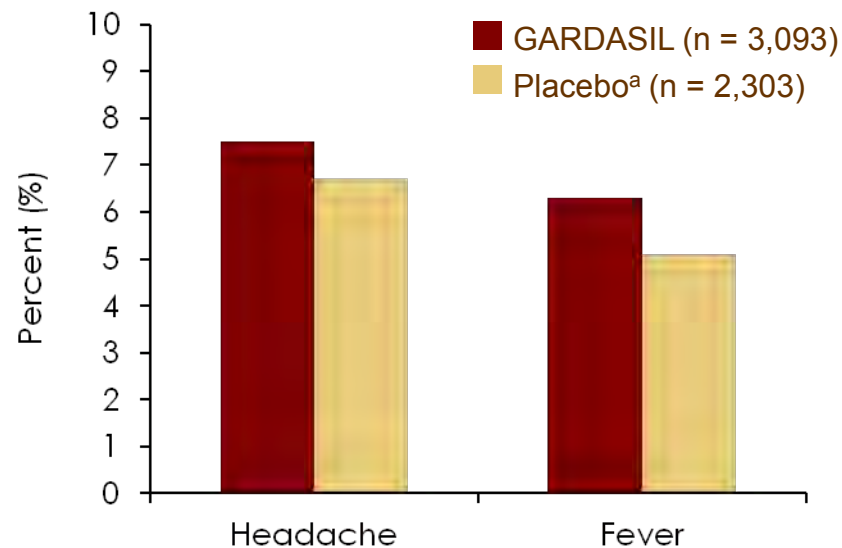
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1. Data on file, MSD \_\_\_\_\_.

# Safety Summary from Nordic Long-Term Follow-Up study of quadrivalent HPV vaccine (7 years after vaccination)<sup>1</sup>

- 22% of all subjects in the LTFU study had at least 1 new medical history condition.
- Most common new medical conditions were related to pregnancy and delivery.
- Number of subjects with cancers, conditions of potential autoimmune etiology, or who died were varied and extremely small.
- Overall, there was no specific pattern of new medical conditions.

LTFU = long-term follow-up.

# Published population-based, postlicensure observational safety studies of quadrivalent HPV vaccine in U.S. females aged 9–26 years

Organization	System or review	No. of doses evaluated	Description	Methods	Findings
CDC	Vaccine Safety Datalink*	600,559	Large database used for active surveillance and research; safety assessment of seven prespecified health outcomes among female HPV4 vaccine recipients at seven managed-care organizations <sup>†</sup>	Cohort design with weekly sequential analyses of electronic medical data <sup>§</sup>	No statistically significant increase in risk for the outcomes monitored
Merck	Postmarketing commitment to FDA <sup>¶</sup>	346,972	General study assessment of HPV4 vaccine after routine administration at two large managed-care organizations	Self-controlled risk interval design, supplemented with medical record review	HPV4 vaccine associated with syncope on the day of vaccination and skin infections** in the 2 weeks after vaccination; no other vaccine safety signals detected
Merck	Postmarketing commitment FDA <sup>††</sup>	346,972	Assessment of 16 prespecified autoimmune conditions after routine use of HPV4 vaccine at two large managed-care organizations	Retrospective cohort using electronic medical data, supplemented with medical record review <sup>§§</sup>	No confirmed safety signals for the outcomes monitored

Although one study found an increased risk for syncope, no serious safety concerns have been identified in these large post-licensure observational studies.

# **HPV Vaccines**

## **Pregnancy-related issues**

# Pregnancy and Infant Outcomes in Quadrivalent HPV vaccine Clinical Trials<sup>1</sup>

- **OBJECTIVE:** To present an updated combined analysis of the pregnancy outcomes for women enrolled in clinical trials of qHPV vaccine<sup>a</sup>
- **METHODS**
  - 20,551 women aged 16 through 45 years received qHPV vaccine or placebo across 5 clinical trials.<sup>b</sup>
  - Urine pregnancy tests were performed immediately before each injection; participants testing positive were not vaccinated.
  - Women who became pregnant after enrollment were discontinued from further vaccination until resolution of pregnancy.
  - All pregnancies were followed for outcomes.

<sup>a</sup>Protocols 013, 015, 016, 018, 019; <sup>b</sup>Sexually naïve adolescents from Protocol 016 and 018 were excluded from analysis.

qHPV = quadrivalent human papillomavirus.

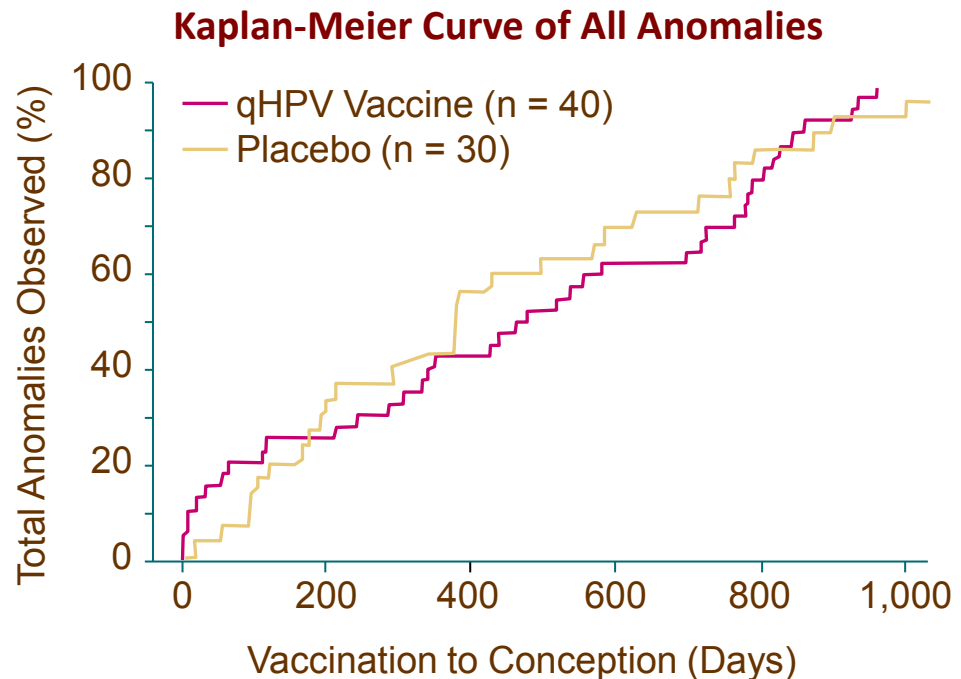
1. Garland SM et al. *Obstet Gynecol.* 2009;114:1179–1188.

# Pregnancy and Infant Outcomes in Quadrivalent HPV vaccine Clinical Trials<sup>1</sup>

## *(continued)*

### RESULTS

- No significant difference between vaccine and placebo groups in terms of live births or adverse outcomes.
- Abnormalities observed were common (prevalence similar to general population).
  - Data similar for spontaneous abortions
- Vaccination not recommended during pregnancy.



qHPV = quadrivalent human papillomavirus.

1. Garland SM et al. *Obstet Gynecol.* 2009;114:1179–1188.

# Cervarix - safety and pregnancy outcomes, PATRICIA (TVC)

Safety outcomes	Vaccine	Control
Number of women assessed	9,319	9,325
<b>Serious adverse event</b>	<b>835 (9.0%)</b>	<b>829 (8.9%)</b>
<b>Vaccine-related serious adverse event</b>	<b>10 (0.1%)</b>	<b>5 (0.1%)</b>
<b>Medically significant condition*</b>	<b>3,298 (35.4%)</b>	<b>3,378 (36.2%)</b>
<b>New onset chronic disease</b>	<b>285 (3.1%)</b>	<b>307 (3.3%)</b>
<b>New onset autoimmune disease</b>	<b>99 (1.1%)</b>	<b>95 (1.0%)</b>
<b>Deaths†</b>	<b>10 (0.1%)</b>	<b>13 (0.1%)</b>
Pregnancy and pregnancy outcomes§		
Number of pregnancies	<b>2,257</b>	<b>2,257</b>
Ongoing pregnancies	12 (0.5%)	11 (0.5%)
<b>Normal infant</b>	<b>1,642 (72.8%)</b>	<b>1,671 (74.0%)</b>
<b>Abnormal infant</b>	<b>26 (1.2%)</b>	<b>22 (1.0%)</b>
Congenital anomaly	18 (0.8%)	13 (0.6%)
Medically significant condition	8 (0.4%)	9 (0.4%)
<b>Spontaneous abortion</b>	<b>205 (9.1%)</b>	<b>195 (8.6%)</b>
Elective termination	212 (9.4%)	228 (10.1%)

\* Medically significant conditions were defined as adverse events prompting either emergency room visits, physician visits that are not routine or related to common diseases, or serious adverse events that are not related to common diseases

† No deaths were considered to be possibly related to vaccination. §Some less frequent pregnancy outcomes are not listed.

# Outcomes From the Pregnancy Registry<sup>1</sup>

- **OBJECTIVE:** To better describe the safety profile of inadvertent pregnancy exposures to qHPV vaccine using postmarketing data
- **METHODS**
  - Subject data from corporate database (Merck & Co., Inc., Pregnancy Registry for GARDASIL)<sup>a</sup>
  - Enrollment criteria:
    - Identifiable patient and health care provider in United States, France, or Canada
    - Exposure to qHPV vaccine  $\leq 1$  month before onset of last menstrual period or during pregnancy
  - Pregnancy outcomes: live births, fetal deaths, elective terminations, spontaneous abortions, and birth defects

<sup>a</sup>For more information on the Pregnancy Registry for GARDASIL<sup>®</sup>, see: <http://www.merckpregnancyregistries.com/gardasil.html>.

qHPV = quadrivalent human papillomavirus.

1. Dana A et al. *Obstet Gynecol.* 2009;114:1170–1178.

# Outcomes From the Pregnancy Registry<sup>1</sup>

## *(continued)*

### Results

- Analysis covers first 2 years postlicensure (June 2006–May 2008).
- No association observed between vaccination and adverse pregnancy or fetal outcomes.
- Vaccination during pregnancy is not recommended.

	Prospective Reports (n = 787) <sup>a</sup>
Number of exposed pregnancies with known outcomes	517
Elective abortion	26
Spontaneous abortion	34
Fetal death <sup>b</sup>	7
Ectopic	0
Live births	451 <sup>b</sup>
Total number of neonates	454 <sup>c</sup>
Normal	440
Major birth defect	10
Minor birth defect	4
Early neonatal death	1

<sup>a</sup>The primary analysis cohort had prospective data received before the outcome of the pregnancy was known.

<sup>b</sup>One twin pregnancy resulted in 2 different outcomes (1 fetal death and 1 live birth).

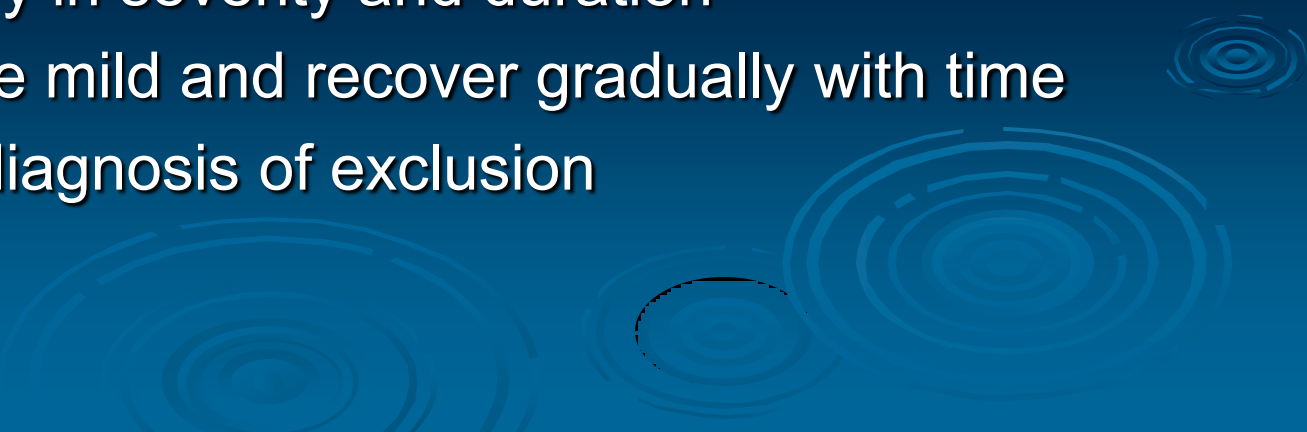
<sup>c</sup>Includes 4 twin pregnancies, resulting in 7 liveborn neonates.

1. Dana A et al. *Obstet Gynecol.* 2009;114:1170–1178.

# Complex Regional Pain Syndrome



# Complex Regional Pain Syndrome (CRPS)

- Chronic pain condition usually affecting one of the limbs
  - More than 90% cases associated with trauma or injury to the limb, usually a sprain or fracture, but cases have been reported following blood taking/blood donation
  - Represents an abnormal pain response that magnifies the effect of the injury – in effect like an allergy
  - Much more common in women than men
  - Symptoms vary in severity and duration
  - Most cases are mild and recover gradually with time
  - Essentially a diagnosis of exclusion
- 

# Notice from Japanese Ministry of Health, Labour and Welfare (MHLW) - 1

- In 2013, cases of complex regional pain syndrome were reported from Japan where over 8 million doses of HPV vaccines have been distributed.
- The Ministry of Health, Labor and Welfare (MHLW) in Japan issued an advisory to all municipalities on June 14 2013 to suspend active promotion of HPV vaccines, while continuing to keep the vaccines as part of the National Immunization Program (NIP).
- The MHLW advisory is based on the discussion at the second meeting of Health Science Council Immunization and Vaccines Adverse Reaction Evaluation Subcommittee that because a causal relationship with the vaccines cannot be excluded, active promotion of HPV vaccines should be suspended until reports of persistent pain are clarified and further information can be provided to the public.
- This is not a decision to stop routine HPV vaccination, according to the MHLW advisory.

# Notice from Japanese Ministry of Health, Labour and Welfare (MHLW) - 2

- During the sixth meeting of MHLW on December 25 2013, the committee discussed the following points:
  - (1) manifestation frequency of reported cases of extensive pain or motor dysfunction (about 1.5 per 100,000 vaccinations for the two HPV vaccines),
  - (2) temporal relationship between the cases and vaccination,
  - (3) factors for acute and chronic pain,
  - (4) the fact that there is no unified pattern of onset, symptom and course nor the presence of single disorder, suggesting no safety concern about the vaccines,
  - (5) chronic pain and various motor dysfunctions are not caused by brain disorder, and
  - (6) treatment has shown improvements in some cases.
  
- The committee has continued to meet and review the situation but has not yet reached a conclusion.

# Complex Regional Pain Syndrome



Centers for Disease Control and Prevention (CDC)<sup>1</sup>

- In the United States, VAERS has received only 14 reports of chronic regional pain syndrome after HPV vaccination as of March 2014.
- Because there was not a pattern among these reports, it is considered unlikely that chronic regional pain syndrome is a common risk after HPV vaccination.
- CDC continues to monitor closely the safety of all vaccines, including HPV.

# Complex Regional Pain Syndrome



World Health  
Organization

Global Advisory Committee on Vaccine Safety (GACVS)<sup>1,2</sup>

- Cases of complex regional pain syndrome (CPRS) were reported from Japan where over 8 million doses of HPV vaccines have been distributed.
- CRPS remains of unknown etiology and may occur in the absence of any documented injury.
- GACVS found no evidence to suggest a causal link with the HPV vaccine, and recommended careful documentation of each case and definition of diagnostic criteria to guide management and causality assessment.

(1) GACVS Safety update on HPV Vaccines. Released 13 June 2013. Accessed 10 November 2014 @ [http://www.who.int/vaccine\\_safety/committee/topics/hpv/130619HPV\\_VaccineGACVSstatement.pdf](http://www.who.int/vaccine_safety/committee/topics/hpv/130619HPV_VaccineGACVSstatement.pdf)

(2) GACVS Safety update on HPV vaccines. Released 12 March 2014. Accessed 10 November 2014 @ [http://www.who.int/vaccine\\_safety/committee/topics/hpv/GACVS\\_Statement\\_HP\\_V\\_12\\_Mar\\_2014.pdf?ua=1](http://www.who.int/vaccine_safety/committee/topics/hpv/GACVS_Statement_HP_V_12_Mar_2014.pdf?ua=1)

# WHO Position: Safety of HPV Vaccines – October 2014

2014, 89, 465-492

No. 43



World Health  
Organization

Organisation mondiale de la Santé

Weekly epidemiological record  
Relevé épidémiologique hebdomadaire

24 OCTOBER 2014, 89th YEAR / 24 OCTOBRE 2014, 89<sup>e</sup> ANNÉE

No. 43, 2014, 89, 465-492

<http://www.who.int/wer>

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## Human papillomavirus vaccines: WHO position paper, October 2014

### Introduction

In accordance with its mandate to provide guidance to Member States on health policy matters, WHO issues a series of regularly updated position papers on vaccines and vaccine combinations against diseases that have an international public health impact. These papers are concerned pri-

## Vaccins contre le papillomavirus humain: note de synthèse de l'OMS, octobre 2014

### Introduction

Conformément à son mandat qui est de fournir des conseils aux Etats Membres sur les questions relatives aux politiques sanitaires, l'OMS publie une série de notes de synthèse régulièrement actualisées sur les vaccins et les associations vaccinales contre les maladies qui ont des répercussions sur la santé publique

**“The WHO Global Advisory Committee for Vaccine Safety (GACVS) has regularly reviewed the evidence on the safety of HPV vaccines. GVCVS concluded in March 2014 that both HPV vaccines continue to have an excellent safety profile.”**

# Safety of HPV vaccines



Global Advisory Committee on Vaccine Safety (GACVS)<sup>1</sup>

4 years after the last review of HPV vaccine safety and with more than 170 million doses distributed worldwide and more countries offering the vaccine through national immunization programs, the Committee continues to be reassured by the safety profile of the available products.



Centers for Disease Control and Prevention (CDC)<sup>2</sup>

CDC continues to recommend the vaccination of 11 and 12 year old girls with 3 doses of vaccine to prevent the types of HPV that most commonly cause cervical cancer and genital warts. The vaccine is also recommended for girls and women ages 13 through 26 who did not get any or all of the doses when they were younger. Additionally, Gardasil<sup>®</sup> protects males against most genital warts. This vaccine is also recommended and available for boys and men, 9 through 26 years of age.



Federation of Gynecology and Obstetrics (FIGO)<sup>3</sup>

The Committee considered all available evidence on HPV vaccination and have concluded that both commercially available vaccines are safe. Having reviewed all available data, the FIGO Gynecologic Oncology Committee and the FIGO sub-committee for Cervical Cancer Prevention supports the continued administration of the HPV vaccines in appropriate populations.

(1) GACVS Safety update on HPV Vaccines. Released 13 June 2013. Accessed 10 November 2014 @ [http://www.who.int/vaccine\\_safety/committee/topics/hpv/130619HPV\\_VaccineGACVSstatement.pdf](http://www.who.int/vaccine_safety/committee/topics/hpv/130619HPV_VaccineGACVSstatement.pdf)

(2) CDC. Updated September 2014. Accessed 10 November 2014 @ [http://www.cdc.gov/vaccinesafety/Vaccines/HPV/hpv\\_faqs.html](http://www.cdc.gov/vaccinesafety/Vaccines/HPV/hpv_faqs.html)

(3) FIGO Statement. Int J Gynecol Obstetrics 2013; 123: 187-188

# Himalayan Women's Health Project







**WE PLEDGE TO SERVE**  
HEALTH DEPARTMENT (LADAKI LEH, LADAKH)  
NATIONAL RURAL HEALTH MISSION

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ہر روز 400 سے 450 گرام پھل و سبزی ضرور لیں۔  
Green vegetables and fruits  
are good for health.  
A daily intake of 400-450 gms  
of fruits everyday.



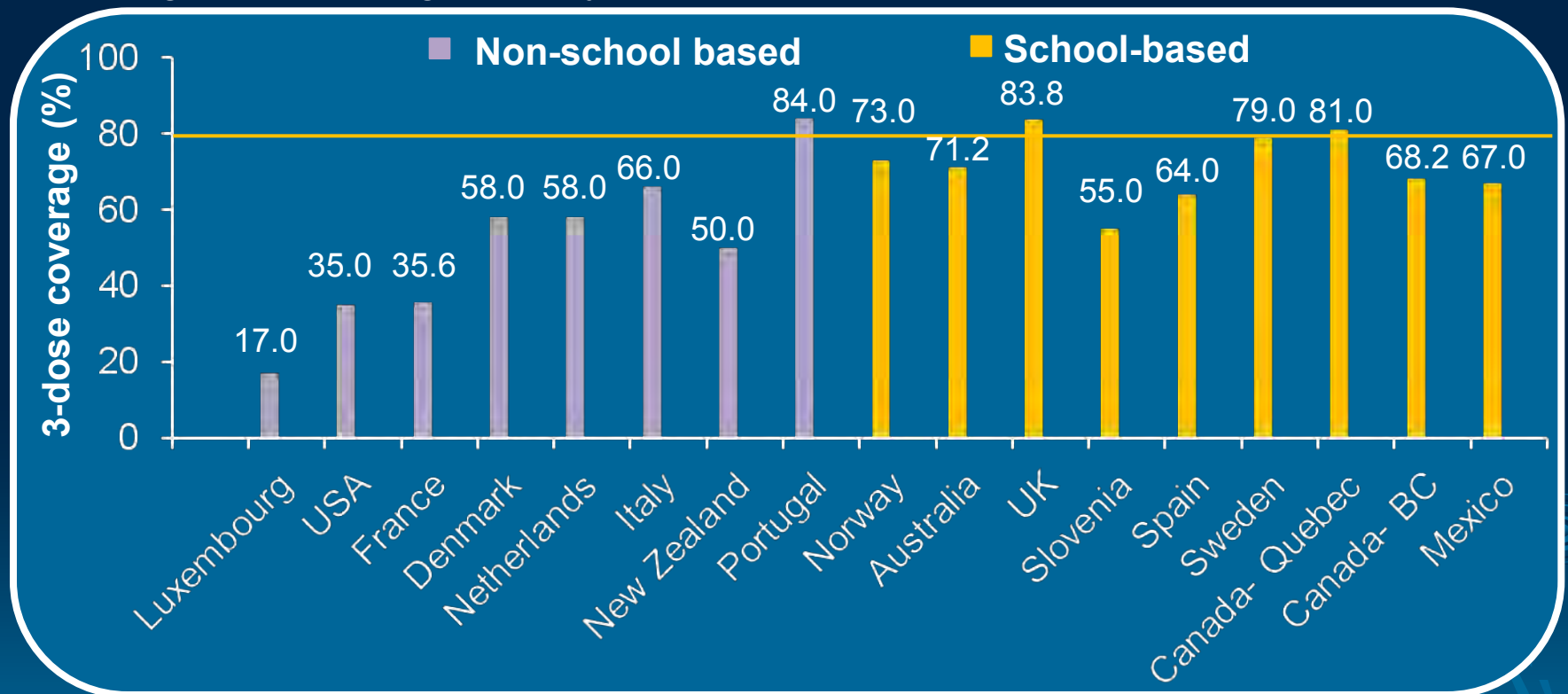
Courtesy of Swee Chong Quek.



Courtesy of Swee Chong Quek.

# Challenges for adolescent vaccination: achieving high coverage

- Highest coverage is typically achieved through school-based programmes
- The majority of national immunisation programmes are not achieving high enough coverage levels to significantly reduce the burden of cervical cancer



1. European Centre for Disease Prevention and Control. Introduction of HPV vaccines in EU countries – an update. Stockholm: ECDC; 2012.  
2. CDC. *MMWR* 2012;61:671–677. 3. Fagot JP, et al. *Vaccine* 2012;29:3610–3616. 4. Statens Serum Institut 2010. 5. Istituto Superiore di Sanità (ISS). 2012. 6. New Zealand Ministry of Health 2012. 7. Norwegian Institute for Public Health 2013;8. Department of Health and Ageing 2013. 9. Department of Health 2012. 10. Smittskyddsinstitutet 2013. 11. NCCID. 2011. 12. BCCDC. 2012. 13. CDC. *MMWR* 2011;60:1382–1384



Courtesy of Swee Chong Quek.

Thank You

