

Quadrivalent Human Papillomavirus Vaccine (HPV4): Post-licensure Safety Update, Vaccine Adverse Event Reporting System (VAERS), United States

Advisory Committee on Immunization Practices, 10-22-08

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Overview

- VAERS background
- HPV4 data in VAERS
 - Methods
 - Adverse Events (AEs) following HPV4, general data
 - Selected serious conditions of clinical interest
 - Syncope
 - Venous Thromboembolism (VTE)
 - Guillain-Barre Syndrome (GBS)
 - Transverse Myelitis (TM)
 - Deaths
- Summary

VAERS

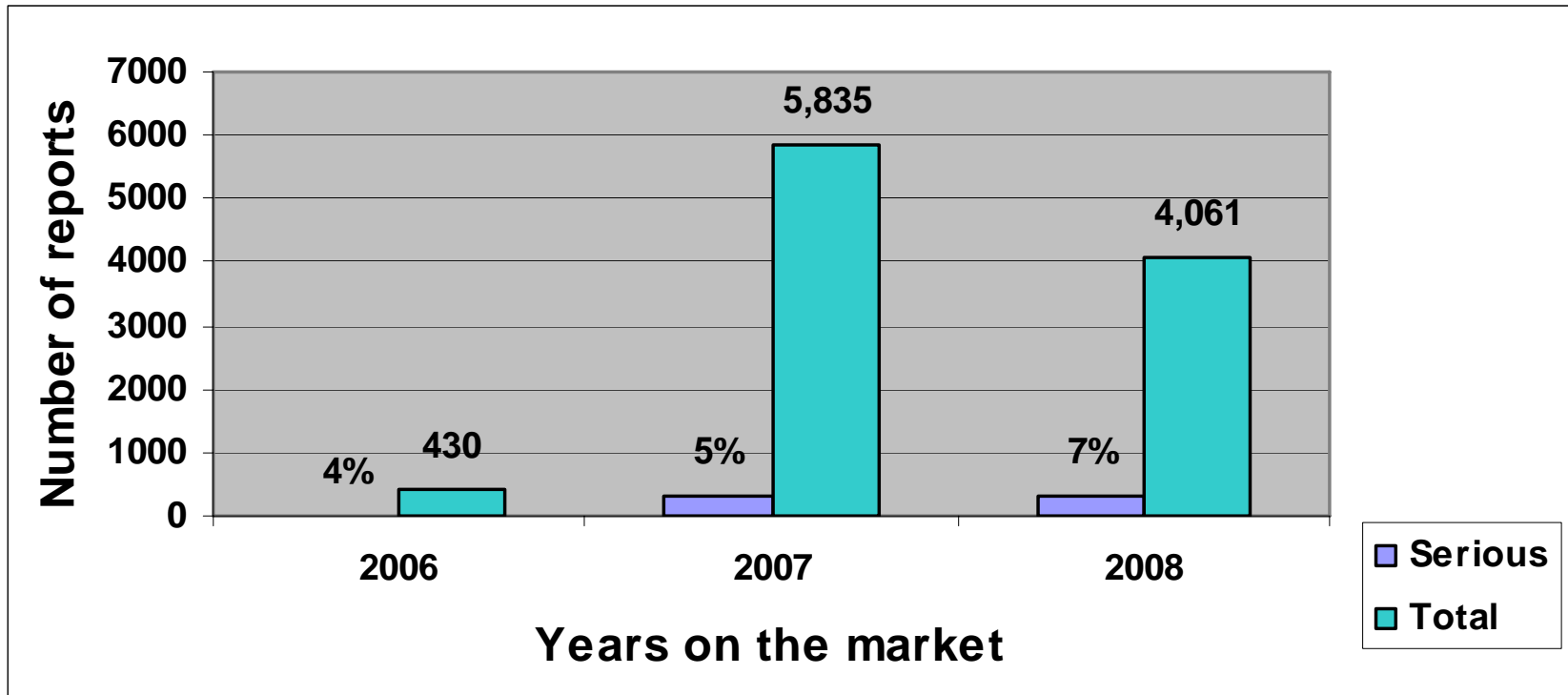
- National post-licensure passive surveillance system for vaccine adverse events operated by CDC and FDA
- Advantages
 - Covers US population
 - Permits monitoring for known AEs
 - Detects signals for previously unrecognized /rare AEs
 - Generates hypothesis
- Limitations
 - Risk of underreporting
 - Stimulated reporting due to media attention and other factors
 - Incomplete data
 - Lack of availability of denominator data

VAERS Reports Following HPV4 Vaccine Methods

- All primary US reports received between 06-30-06 and 8-31-08
 - Reviewed on 10-03-08
- Medical Dictionary for Regulatory Activities (MedDRA)
 - More than one code may be assigned to a single event and one VAERS report may include more than one symptom
- Brighton case definitions for AEs
- “Confirmed” case means that a report met the case definition, but was not necessarily causally associated with the vaccination
- Serious AEs are defined by Code of Federal Regulations as hospitalization, death, permanent disability, life threatening illness, or certain other medical important conditions

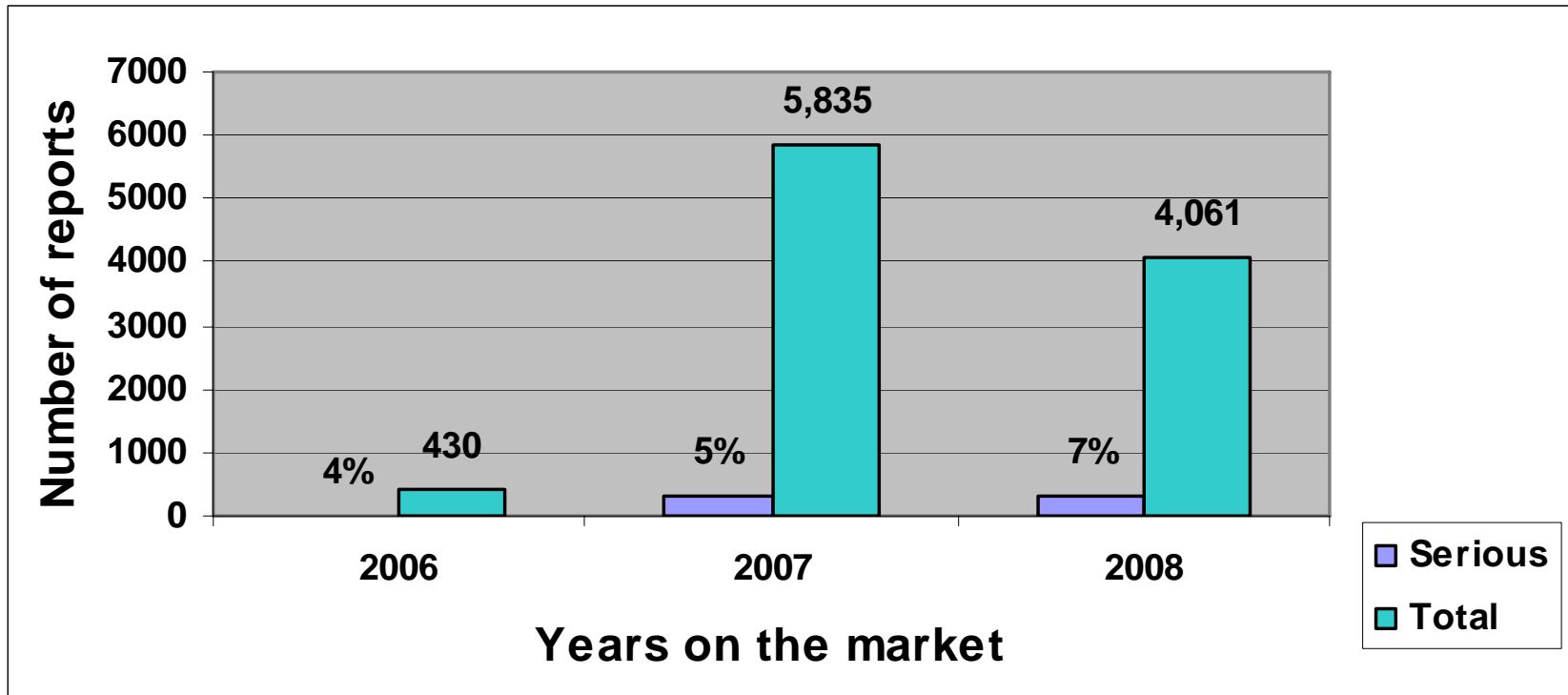
AEs Following HPV4

VAERS, June 30, 2006 – August 31, 2008



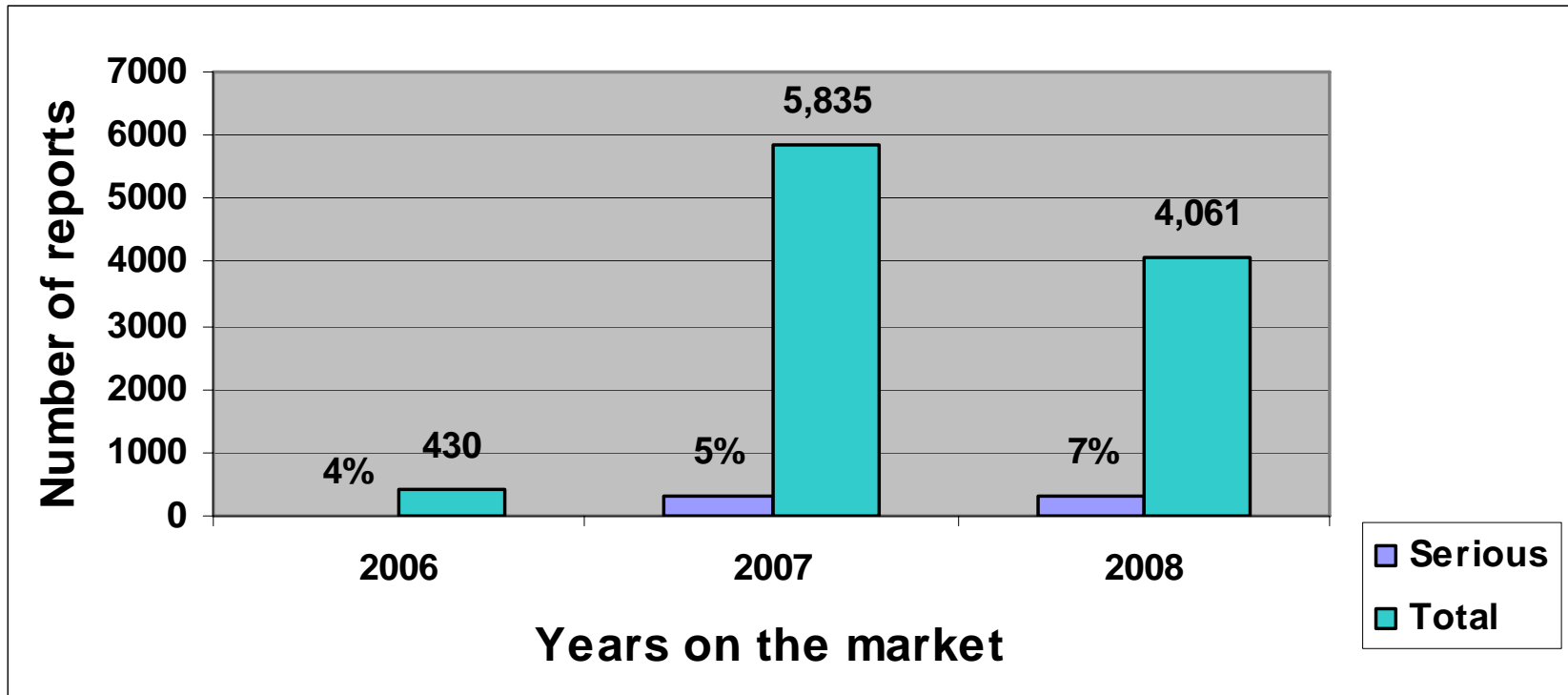
There were **10, 326** total VAERS reports following HPV4.

AEs Following HPV4 VAERS, June 30, 2006 – August 31, 2008



As of August 31, 20,383,145 doses of HPV4 have been distributed in the U.S. (Biologics Surveillance Data, unpublished, CDC)

AEs Following HPV4 VAERS, June 30, 2006 – August 31, 2008



HPV4 reports per 100,000 doses distributed

All reports: 50.7

Serious reports: 3.0

AEs Following HPV4 by Age Group

VAERS, June 30, 2006 – August 31, 2008

Age group (Years)	Reports (N)	Percent (%)
< 9	49	0.5%
9-10	143	1.4%
11-18	5,202	50.4%
19-26	2,535	24.5%
> 26	233	2.2%
Unk	2,164	21%
Total	10,326	100%

Most Frequent AEs Following HPV4 VAERS, June 30, 2006 – August 31, 2008

MedDra Coding Term	All AEs Following HPV4 (total N=10,326)	
	N	% of total
Syncope	1,564	15
Dizziness	1,469	14
Nausea	959	9
Injection site pain	818	8
Headache	731	7
Pyrexia	680	7
Rash	580	6

Serious AEs Following HPV4

Selected Conditions of Clinical Interest

VAERS, June 30, 2006 – August 31, 2008

- Syncope (n=70)
- VTE (n=41)
- Deaths (n=27)
- GBS (n=52)
- TM (n=10)

Serious AEs Following HPV4

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Serious AEs Following HPV4 Selected Conditions of Clinical Interest VAERS, June 30, 2006 – August 31, 2008

- Syncope (n=70)
- VTE (n=41)
- Deaths (n=27)
- **GBS (n=52)**
- **TM (n=10)**
 - Evaluated in detail by the Clinical Immunization Safety Assessment (CISA) Network
 - GBS included into the Vaccine Safety Datalink (VSD) study

Serious AEs of Syncope Following HPV4*

Total reports: 119

US reports: 70

- of the total US reports of syncope 5% are serious
- coded as “syncope” or “syncope vasovagal”
- occurred on the same day as vaccination: 38
- required hospitalization: 37
- Most commonly associated symptoms: loss of consciousness, dizziness, headache, nausea, vomiting, fall, and head injury.

*CDC. Syncope After Vaccination — United States, January 2005–July 2007; MMWR 2008; 57(17);457-460

Serious AEs of VTE Following HPV4

Total reports: 65

US reports: 41

- **Pending evaluation: 6**
- **Unable to follow-up or “no case”:** 17
- **Confirmed cases: 18**
 - Hormonal contraception current use (n=14)
 - 12 cases – Oral Contraceptive Pills
 - 2 cases on Nuvaring (increase risk of clots)
 - Some have additional risk factors
 - No hormonal contraception use (n=4)
 - 1 case of pregnancy
 - 1 case obesity, smoking, truck driver
 - 1 case long bus ride preceded to the VTE onset
 - 1 case had no reported risk factors

Reports of Death Following HPV4

Total: 31

US reports: 27

- Unable to follow-up: 7
- Pending evaluation: 3
- **Confirmed cases: 17**

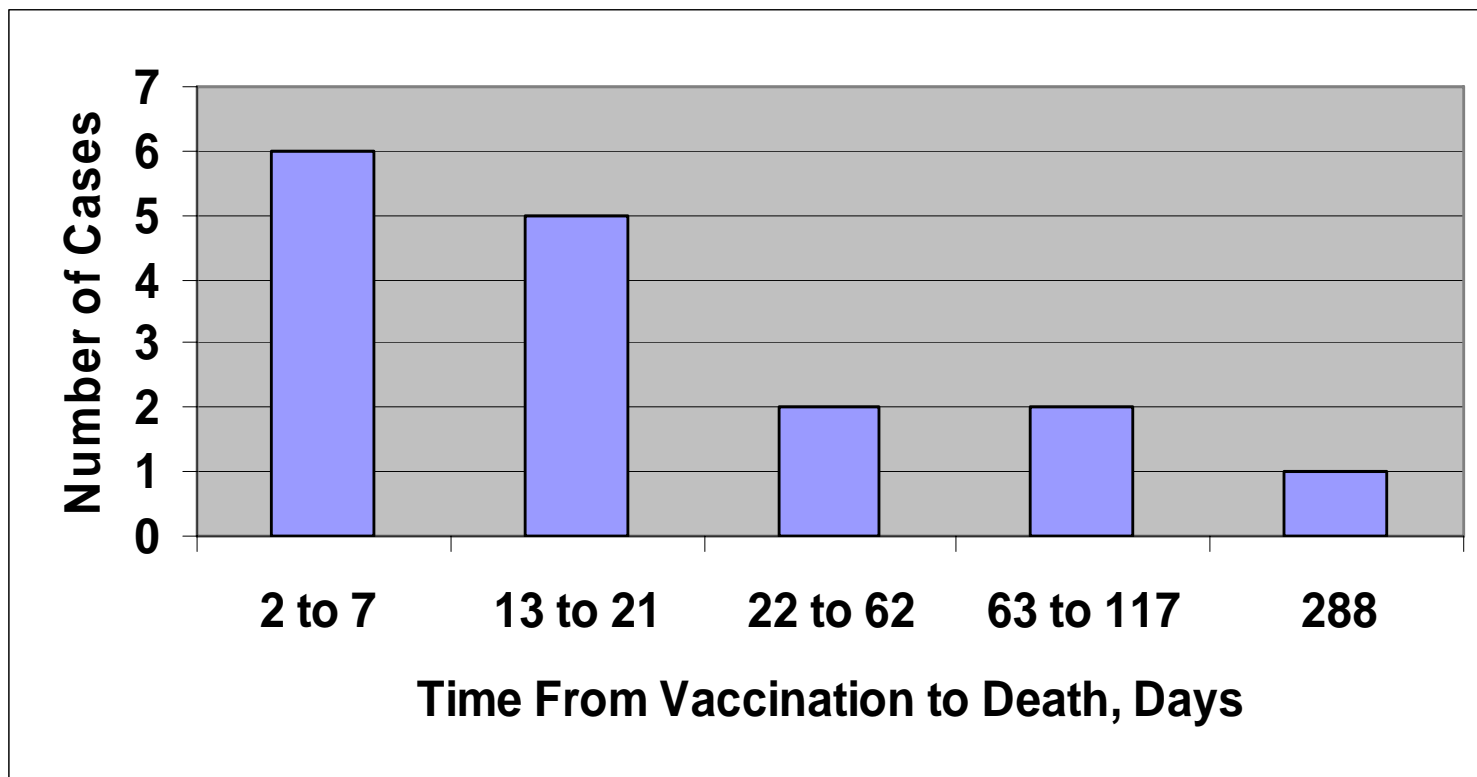
Cases of Death Following HPV4 by Age at Vaccination and Vaccine Dose

17 Confirmed Cases

	N (cases)
Ages (yrs)	
12-14	4
15-18	6
19-21	4
22-26	3
Dose number	
1	7
2	6
3	3
unknown	1

Cases of Death Following HPV4 by Time From Vaccination to Death

17 Confirmed cases, one case had unknown onset interval



Reports of Death Following HPV4

Total: 31

US reports: 27

- Unable to follow-up: 7
- **Pending evaluation: 3**
- **Confirmed cases: 17**

Considered for the Clinical Summary: 20

Clinical Summary, Reports of Death Following HPV4

- **Viral illnesses (n=3): acute myocarditis, meningoencephalitis, influenza B viral sepsis**
- **Pulmonary embolism (n=2)**
- **Cardiac events (n=2): arrhythmia due to cardiomyopathy, probable cardiac arrhythmia – patient had a history of**
- **Diabetic ketoacidosis (n=1)**
- **Idiopathic seizure disorder and history of seizures (n=1)**
- **Atypical GBS vs Juvenile ALS (n=1)**
- **Drug overdose (n=2)**
- **Unknown cause (n=3) and limited information for further evaluation (n=4)**

AEs Following HPV4 VAERS Data Summary

- More than 20 million doses distributed
 - 10, 326 overall HPV4 reports to VAERS
 - **Serious AEs (6%)**
- Syncope following vaccination could lead to serious outcomes; preventive measures are critical
- Predisposing factors in cases of VTE
 - Hormonal contraception use (n=14), co-morbidities, and life-style risks
- Deaths
 - No clustering by age groups, onset intervals, or dose number
 - No trends in clinical conditions which preceded or caused death
- VAERS is not designed to assess biological or epidemiological plausibility of AEs following vaccination

AEs Following HPV4 VAERS/ISO Activities

- Continue monitoring and evaluation of all serious AEs following HPV4
- Evaluate VAERS reports of inadvertent vaccination during pregnancy
- Communicate to the public and partners
- Update the ACIP HPV working group on a regular basis
- Collaborate with the VSD, CISA, NCHHSTP/CDC, FDA, and others

References and related links

- ***Reports of Adverse Events Following Gardasil* ®**
(on the CDC Vaccine safety web site):
<http://www.cdc.gov/vaccinesafety/vaers/gardasil.htm>
- VAERS information: <http://vaers.hhs.gov/info.htm>
- VAERS public search tool: <http://wonder.cdc.gov/vaers.html>
- Brighton Collaboration:
<http://www.cdc.gov/vaccinesafety/brighton/>
- ***Gardasil* ® Package Insert:**
<http://www.fda.gov/cber/label/gardasilLB.pdf>
- CDC. General Recommendations on Immunization; MMWR 2006; 55(RR15);1-48
<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5515a1.htm>

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