# Adverse events following 9-valent human papillomavirus vaccine (9vHPV) reported to the Vaccine Adverse Event Reporting System (VAERS)

**Jorge Arana, MD, MPH**
**Immunization Safety Office**
**Centers for Disease Control and Prevention (CDC)**

Advisory Committee on Immunization Practices
February 21, 2018

# Disclaimer

- The findings and conclusions in this presentation are those of the authors and do not necessarily represent the official position of the CDC or FDA

# Background: 9vHPV

- December 2014: 9vHPV vaccine licensed in United States[1]
- February 2015: ACIP recommends 9vHPV as one of three HPV vaccines that can be used for routine vaccination[2]
- By the end of 2016: Manufacturers stopped marketing 2vHPV and 4vHPV in the United States
  - Only 9vHPV is available in the United States[2]
- December 2014 – December 2017: ~29 million 9vHPV doses distributed in the United States[3]

[1] https://www.cdc.gov/hpv/downloads/9vhpv-fda.pdf
[2] https://www.cdc.gov/hpv/downloads/9vhpv-guidance.pdf
[3] Kuter B (Merck), personal communication, 25th January 2018

# Background: 9vHPV vaccine safety pre-licensure studies

- 7 pre-licensure studies[1,2]
- Well tolerated in >15,000 study participants
  - Adverse event profile similar to that of 4vHPV
  - More injection site-related swelling and erythema
  - Among inadvertent vaccination in pregnancy[3] during clinical studies
    - Proportion of adverse outcomes observed was consistent with pregnancy outcomes observed in the general population
    - There was an imbalance in spontaneous abortion (SAB) following 9vHPV during pregnancy compared to 4vHPV
      - Rates of SAB in the 9vHPV group not elevated compared to background rates[4]

[1] http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM426457.pdf
[2] https://clinicaltrials.gov/ct2/show/NCT01651949?term=v503&rank=3
[3] 9vHPV is FDA Category B for pregnancy
[4] Wilcox A et al. Incidence of early loss of pregnancy. NEJM 1988

# Objective

- Describe the safety profile of reports submitted to the Vaccine Adverse Event Reporting System (VAERS) after 9vHPV vaccine

# Vaccine Adverse Event Reporting System (VAERS)[1]

## Strengths

- National data
- Accepts reports from anyone
- Rapidly detects safety signals
- Can detect rare adverse events
- Data available to public

## Limitations

- Reporting bias
- Inconsistent data quality and completeness
- Lack of unvaccinated comparison group
- Generally cannot assess causality

As a hypothesis generating system, VAERS identifies potential vaccine safety concerns that can be studied in more robust data systems

[1] VAERS jointly managed by CDC and FDA (http://vaers.hhs.gov)

# Methods: VAERS Data

- U.S. 9vHPV reports received from December 1, 2014 – December 31, 2017
  - Excluded pregnancy reports
- Serious[1] report defined as death, life-threatening illness, hospitalization, prolongation of hospitalization, or permanent disability
- Signs and symptoms of the adverse event coded using Medical Dictionary for Regulatory Activities (MedDRA)[2] Preferred Terms (PTs)
  - PTs are not mutually exclusive
    - A single report may be assigned more than one PT

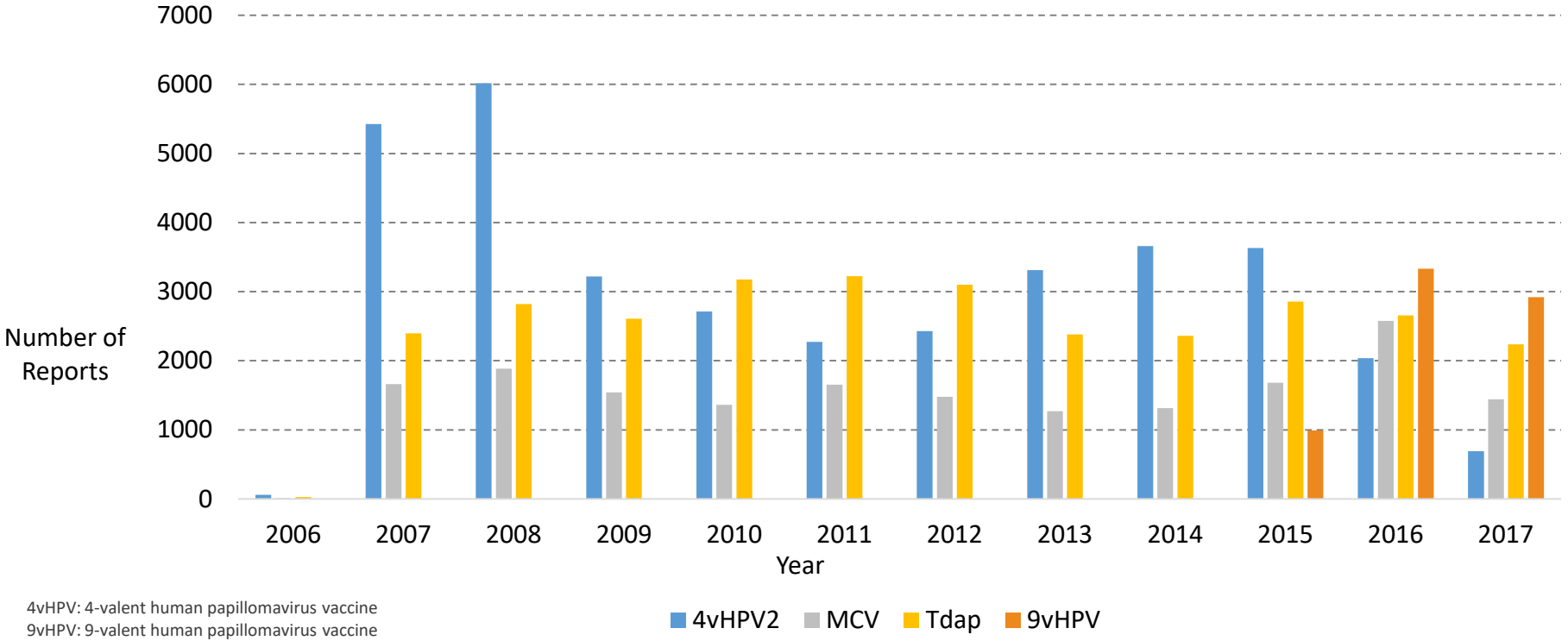
[1] Based on the Code of Federal Regulations 21 CFR 600.80
[2] Medical Dictionary for Regulatory Activities (https://www.meddra.org/)

# Methods (cont.)

- Automated analysis of 9vHPV reports
- Clinical review of reports for select conditions of clinical interest
  - Historical interest: anaphylaxis, Guillain-Barré syndrome, and death
  - Recent interest: complex regional pain syndrome, postural orthostatic tachycardia syndrome, and primary ovarian insufficiency
- Empirica Bayesian[1] data mining
  - Used to detect disproportionate reporting in the VAERS database for adverse events after 9vHPV
  - Identifies adverse events reported more frequently than expected after 9vHPV compared with other vaccines in the VAERS database

[1]Bate, A. Quantitative signal detection using spontaneous ADR reporting. Pharmacoepidemiology and Drug Safety, 2009:18: 427-436

# Reports to VAERS following human papillomavirus, meningococcal, and Tdap vaccines by year, 2006-2017




4vHPV: 4-valent human papillomavirus vaccine
9vHPV: 9-valent human papillomavirus vaccine
MCV: meningococcal conjugated vaccine
Tdap: tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine.
VAERS: Vaccine Adverse Event Reporting System

# Summary of 9vHPV Reports in VAERS, Dec 2014-Dec 2017

| Characteristics | N (%) |
|---|---|
| Total reports[1] | 7,244 |
| Female | 2,258 (31) |
| Male | 1,566 (22) |
| Unknown | 3,420 (47) |
| Serious reports[2] | 186 (3) |
| Deaths | 7 (0.1) |
| Reported by manufacturer | 4,650 (64) |
| Age range, years [median] | 0-73 [14] |
| Onset interval, days [median] | 0-751[0] |
| Received 9vHPV alone | 5,411 (75) |

[1] US primary reports (foreign reports excluded)
[2] Based on the Code of Federal Regulations if one of the following is reported: death, life-threatening illness, hospitalization or prolongation of hospitalization or permanent disability

# Top 10 reported signs and symptoms[1] after 9vHPV in VAERS, Dec 2014-Dec 2017

| Non-serious (n=7,058) | N (%) |
|---|---|
| Dizziness | 529 (7) |
| Syncope | 488 (7) |
| Headache | 355 (5) |
| Injection site pain | 316 (4) |
| Injection site erythema | 314 (4) |
| Nausea | 313 (4) |
| Pyrexia (fever) | 283 (4) |
| Loss of consciousness | 273 (4) |
| Injection site swelling | 266 (4) |
| Pallor | 235 (3) |

| Serious[2] (n=186) | N (%) |
|---|---|
| Headache | 63 (34) |
| Dizziness | 50 (27) |
| Nausea | 48 (26) |
| Fatigue | 42 (23) |
| Pyrexia (fever) | 35 (19) |
| Asthenia (weakness) | 34 (18) |
| Vomiting | 33 (18) |
| Syncope | 29 (16) |
| Abdominal pain | 26 (14) |
| Loss of consciousness | 26 (14) |

[1] As coded using the MedDRA preferred terms (PT); more than one code may be assigned to a single event
[2] Based on the Code of Federal Regulations if one of the following is reported: death, life-threatening illness, hospitalization or prolongation of hospitalization or permanent disability

# Clinical review of select conditions

- Conditions of historical interest
  - Anaphylaxis: 9 reports
    - 3 confirmed[1]
      - 2 received 9vHPV only
  - Guillain-Barré Syndrome (GBS): 8 reports
    - 4 confirmed[2]
      - 3 describe a viral respiratory illness two to four weeks prior to presentation of GBS symptoms
  - Death: 7 reports
    - 5 “hearsay” reports based on indirect information
    - 2 verified by autopsy and/or certificate of death
      - Cause of death: cardiac arrest; cerebellar aneurysm

[1] Ruggeberg et al. Anaphylaxis: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data Vaccine. 2007 Aug 1;25(31):5675-84.
[2] Sejvar et al. Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2011 Jan 10;29(3):599-612.

# Clinical review of select conditions (cont.)

- Conditions of recent interest
  - Complex regional pain syndrome (CRPS)
    - 1 report of possible[1] CRPS; insufficient information
  - Postural orthostatic tachycardia syndrome (POTS)
    - 17 reports of possible POTS cases
      - 6 partially met diagnostic criteria[2]
      - No pattern of concern was noted
  - Primary ovarian insufficiency (POI)
    - 3 reports of possible POI cases did not meet diagnostic criteria[3]; insufficient information

[1] Harden et al. Validation of proposed diagnostic criteria (the "Budapest Criteria") for Complex Regional Pain Syndrome. Pain. 2010; 150(2):268-274
[2] Arana et al. Reports of Postural Orthostatic Tachycardia Syndrome After Human Papillomavirus Vaccination in the Vaccine Adverse Event Reporting System. J Adolescent Health. 2017 Nov;61(5):577-582
[3] The American College of Obstetricians and Gynecologist. Committee on Adolescent Health. Primary Ovarian Insufficiency in Adolescents and Young Adults. Committee Opinion. July 2014 Number 605

# Empirica Bayesian data mining

- Disproportional reporting of “syncope” was noted[1]
  - “Syncope” historically was disproportionally reported for 4vHPV
  - Syncope is a labeled adverse event
- Other PTs signaled but do not represent an adverse event (i.e., drug administered to patient of inappropriate age, and other administration errors)
- No other disproportional reporting for 9vHPV has been noted

[1] Data provided by FDA/CBER Division of Epidemiology

[2] Adverse Effects of Vaccines: Evidence and Causality, Institute of Medicine, Aug 2011 (http://www.iom.edu/Reports/2011/Adverse-Effects-of-Vaccines-Evidence-and-Causality.aspx)

# Summary

- VAERS received 7,244 reports following 9vHPV during the study period, December 1, 2014 – December 31, 2017
  - Most (97%) reports were non-serious
  - Most frequently reported adverse events after 9vHPV were dizziness, syncope, headache and injection site reactions
  - ~29 million 9vHPV doses were distributed in the United States
- No new safety signals or unexpected patterns were observed
- The safety profile of 9vHPV is consistent with data from pre-licensure trials and post-licensure data on 4vHPV
- CDC and FDA will continue to monitor and evaluate the safety of 9vHPV

# Acknowledgements

**CDC**

Tom Shimabukuro
Maria Cano
Julianne Gee
John Su
Paige Lewis
Pedro Moro
Lakshmi Sukumaran
Karen Broder
William Vaughn
Frank DeStefano

**FDA**

Adamma Mba-Jonas

# Thank you

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.