Rapid Cycle Analysis of the 9-valent Human Papillomavirus Vaccine (9vHPV) in the Vaccine Safety Datalink

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February 21, 2018

Outline

- Rapid Cycle Analysis (RCA) background
- RCA of 9-valent Human Papillomavirus Vaccine (9vHPV)
  - Objectives
  - Methods
  - Results
- Maintenance surveillance

Vaccine Safety Datalink and the Rapid Cycle Analysis Method

- VSD is a collaboration between CDC and 8 integrated healthcare plans to monitor vaccine safety using active surveillance and observational studies
- RCA was developed to permit more rapid assessment of vaccine safety using near-real time data
- Adverse event signals are interpreted as potential associations in an RCA
  - Medical record review or additional investigations are performed as appropriate
- RCA of 4vHPV (Gee J, et al. Vaccine 2011)
  - 600,000 doses. No statistically significant associations observed

Objectives of 9vHPV RCA

- Conduct near real-time surveillance (2015-2017) to assess the risks of pre-specified adverse events (AEs) after receipt of 9vHPV vaccine
- Monitor 9vHPV vaccine usage in VSD over time

9vHPV RCA Design and Population

- Prospective cohort
- Surveillance period: 10/4/2015—10/3/2017
- Enrolled in one of 6 participating VSD sites
- Males and females, 9-26 years old

9vHPV Recommendation

- Routine vaccination at age 11-12 years for males and females
- Females aged 13-26 years and males 13-21 years who were not adequately vaccinated
- Catch-up through age 26 years for certain other groups
- 3-dose series recommended until 2016
  - October 2016, ACIP recommended 2 dose series if receiving first dose before age 15 years (Meites E, et al. MMWR, 2016)
- More antigens and more adjuvant in 9vHPV compared to 4vHPV, but similar safety profile

Pre-specified Adverse Events Identified for Monitoring

- Clinically well defined, acute onset, results in a medical encounter, and biologically plausible
- All AEs in 4vHPV analysis (Gee, et al. Vaccine 2011)
- Additional AEs
  - Injection site reactions - more common among 9vHPV group compared to 4vHPV in pre-licensure trials
  - Pancreatitis - reported in VAERS following 4vHPV
- ICD-10 codes assigned at outpatient, inpatient, and/or ED encounters
- Post-vaccination risk window specified for each AE

Pre-specified Adverse Events

Adverse event	Setting	Post-vax window	Primary comparison group
Syncope	OP, ED, IP	Day 0	Concurrent
Injection site rxn, w/ and w/o day 0	OP, ED, IP	0-6, 1-6 days	Concurrent
Allergic Reactions	OP, ED, IP	0-2 ED, IP 1-2 for OP	Concurrent
Seizure	ED, IP	0-42 days	Concurrent
Anaphylaxis	OP, ED, IP	0-2 days	Concurrent
Appendicitis	ED, IP	1-42 days	Historic
Pancreatitis	ED, IP	1-42 days	Historic
Guillain-Barré Syndrome (GBS)	OP, ED, IP	1-42 days	Historic
Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)	OP, ED, IP	1-180 days	Historic
Stroke	ED, IP	1-42 days	Historic
Venous Thromboembolism (VTE)	OP, ED, IP	1-42 days	Historic

*Historical comparison is based on VSD data from 2007-2014. Concurrent comparison is based on non-HPV vaccination visits during the surveillance period.

General RCA Approach

- Near real-time surveillance of AEs using weekly aggregate data
- Compare observed vs. expected counts
  - Unexposed reference groups generate expected counts
- Sequential analyses used to detect signals while maintaining a pre-defined type I error rate
- For each AE, subgroups are defined by age, sex, and dose
- Medical record review or additional analyses as needed subsequent to a signal

Sequential Analytic Methods

- Maximized Sequential Probability Ratio Test (MaxSPRT) and Conditional MaxSPRT
  - Developed by VSD researchers (Kulldorff M, et al. 2011[1])
  - Uncommon or rare events: anaphylaxis, appendicitis, GBS, CIDP, pancreatitis, seizures, stroke, VTE
  - Expected counts from historical comparison groups (2007-14)
    - General VSD population (MaxSPRT)
    - Vaccinated VSD population (CMaxSPRT)
- Exact Sequential Analyses (ESA)
  - Developed by VSD researchers (Lewis E, et al. 2009[2])
  - Optimal for more common outcomes, but done for all
  - Expected counts from concurrent comparison group

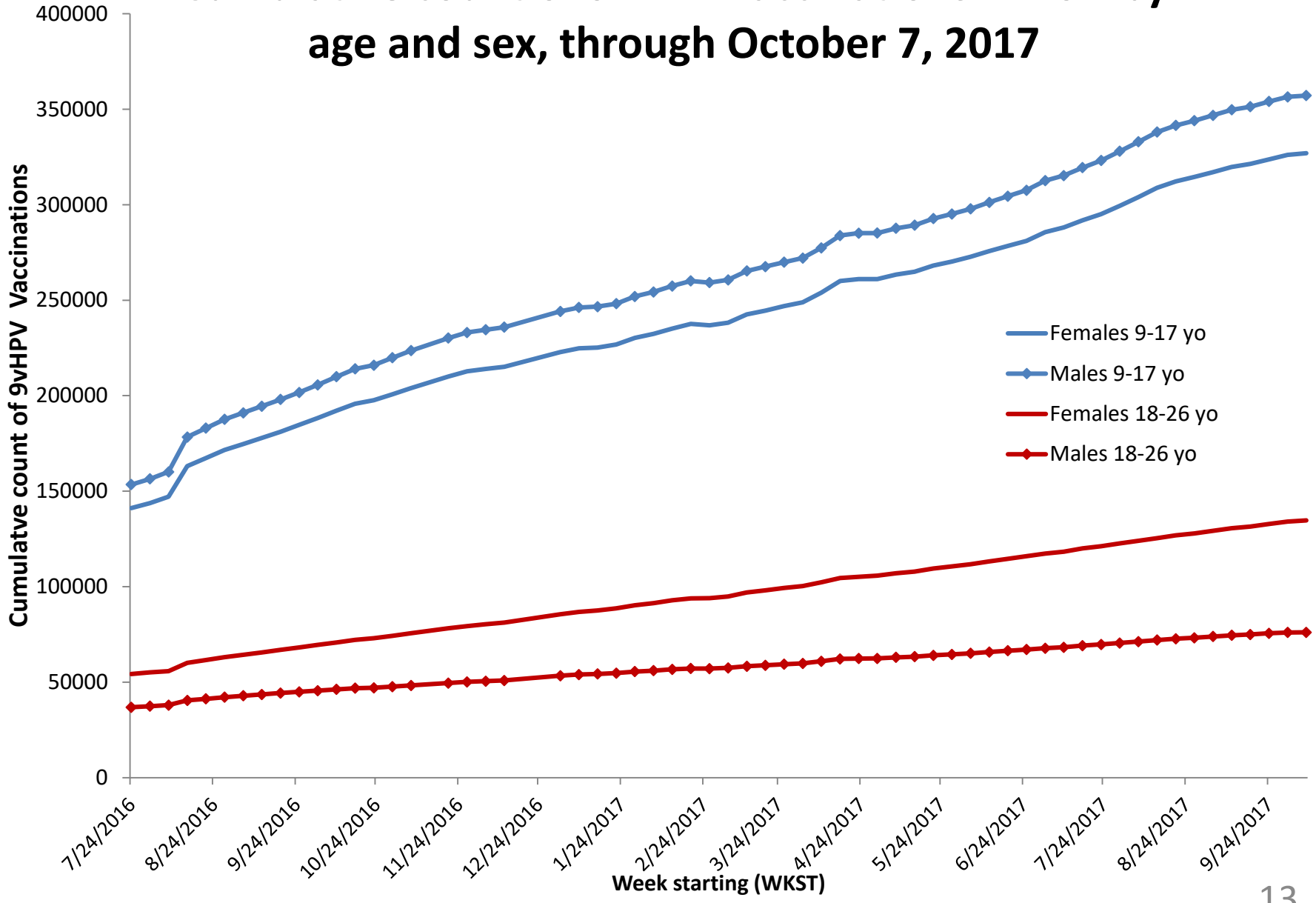
[1]Kulldorff M, et al. A maximized sequential probability ratio test for drug and vaccine safety surveillance. Seq. Anal. 2011;30:58-78.
[2]Lewis E, et al. Exact sequential analysis for vaccine safety surveillance. In: NFID 12th Annual Conference on Vaccine Research. 2009.

Follow-up of RCA signals

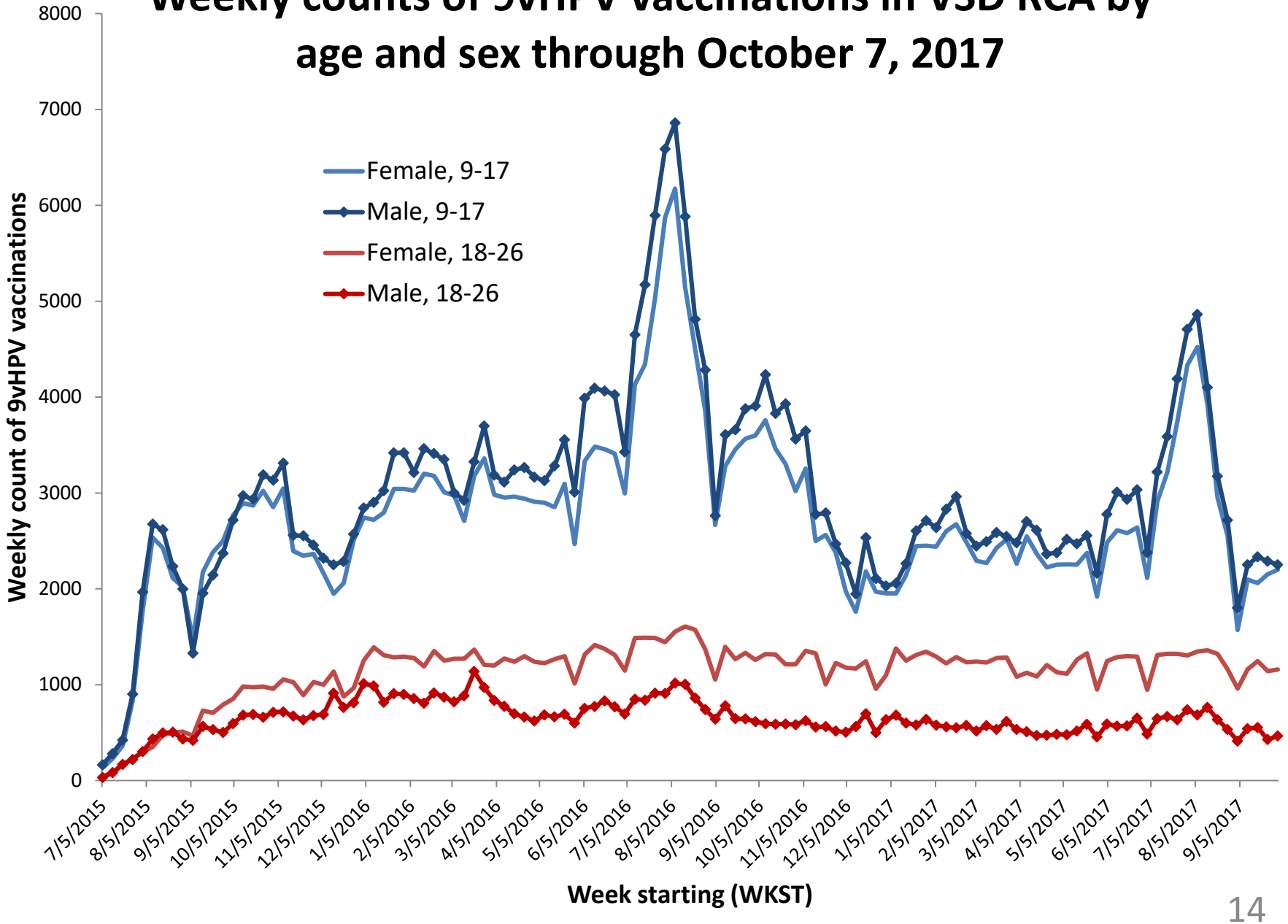
- Assess data quality for errors, anomalies, or unusual patterns
- Temporal scan analysis to identify clustering within the risk window
- Medical record review to confirm cases, especially if serious and uncommon
- Analytical epidemiology study if concern persists
  - Self-controlled case series (SCCS), self-controlled risk interval (SCRI), case-centered, case-control

RESULTS

Cumulative count of 9vHPV vaccinations in VSD by age and sex, through October 7, 2017



Weekly counts of 9vHPV vaccinations in VSD RCA by age and sex through October 7, 2017



Summary of MaxSPRT Results

NO SIGNAL	SIGNAL DETECTED
Anaphylaxis Guillain-Barre syndrome Appendicitis Seizures Stroke Venous thromboembolism Chronic inflammatory demyelinating polyneuropathy	**Pancreatitis in males, 18-26 years old**

Summary of Pancreatitis Signal

AE	Subgroup	RR	Exposed cases
Pancreatitis	Males 18-26	3.1	8

- Pancreatitis signaled in the MaxSPRT analysis only (RR=3.1, test statistic=3.71, critical value=2.87)
- No signal in the CMaxSPRT analysis (RR=1.84, test statistic=1.03, critical value=3.36)
- Pancreatitis was also evaluated in the ESA
  - RR=4.7, P=0.47
- 6 comparisons conducted each week for pancreatitis (sex, 2 age groups, 2 analytic methods)

Medical Record Review
Pancreatitis in Males 18-26 Years

- Eight cases exposed to 9vHPV
  - 6 had 1st dose, 2 had 2nd dose
- Diagnosis setting: 3 ED, 4 inpatient, 1 unknown
- Medical record review
  - 1 confirmed incident case without alternative cause or explanation for the diagnosis code
  - 1 possible case ('symptoms more likely to be GERD')
  - 6 other (alcohol, trauma, metastatic CA, not incident, etc.)
- No further investigation planned

Summary of ESA Results

NO SIGNAL	SIGNAL DETECTED
Anaphylaxis Guillain-Barre syndrome Pancreatitis Seizures Stroke Venous thromboembolism Chronic inflammatory demyelinating polyneuropathy	**Syncope** **Injection site reactions** (with and without day 0) **Allergic reactions** (ED/Inpatient, outpatient) **Appendicitis**

Summary of ESA Signals

Adverse event	Subgroup	RR	Cases (exp.)*
Syncope	Females, 18-26	1.9	98 (67)
	Females, 18-26, dose 1	2.2	65 (35)
	Females, 18-26, dose 2	2.0	60 (25)
Inj. site rxn, includes day 0	Males, 18-26, dose 3	95	3 (2)
	Males, 18-26, dose 1	11.1	14 (9)
	Females, 18-26, dose 1	1.8	71 (34)
Inj. site rxn, excludes day 0	Males, 9-17, dose 3	2.5	29 (18)
Allergic rxn, ED or inpatient	Females, 9-17	2.7	33 (26)
Allergic rxn, outpatient	Females, 18-26, dose 2	1.9	38 (15)
Appendicitis	Males, 9-17, dose 3	2.1	50 (30)

*Counts at first signal

Follow-up of ESA Signals: Syncope and Injection Site Reaction

- Both were expected based on clinical trials of 9vHPV and clinical experience with 4vHPV
- No formal follow-up studies planned

Follow-up of ESA Signals: Allergic Reaction (ED, Inpatient) in Females, 9-17 Years

- 26 cases exposed to 9vHPV
  - 18 after 1st dose, 8 after 2nd or 3rd dose
  - 6 vaccinated with 9vHPV only, 20 received 9vHPV + concomitant vaccine
- Medical record review
  - 8 allergic reaction with no alternative cause
  - 9 injection site or localized reaction
  - 9 other (reaction to food/drug, coding error, etc.)
- No signal in outpatient setting: RR=0.85, P=0.75
- No further investigation planned

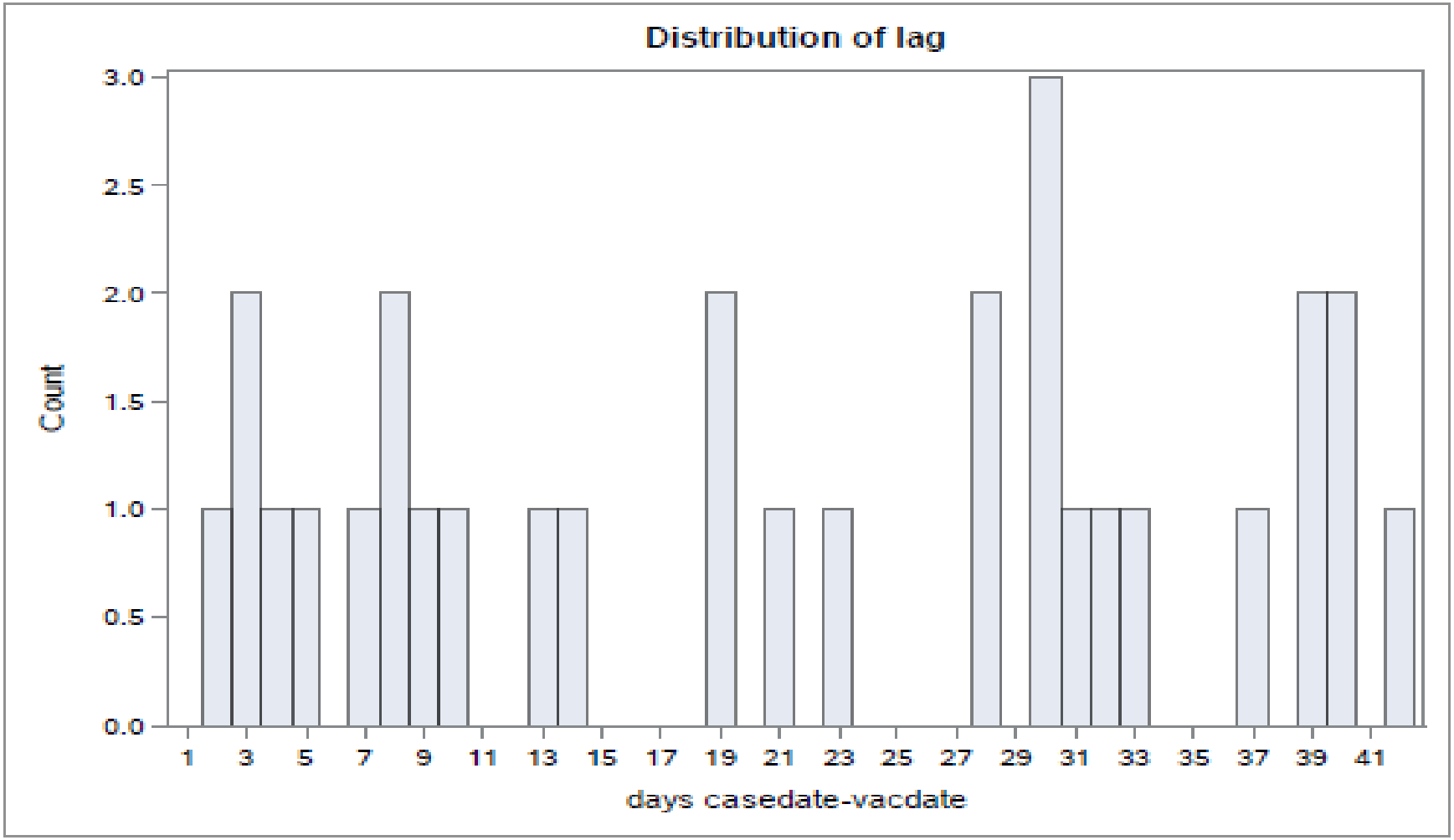
Follow-up of ESA Signals: Allergic Reaction (Outpt), Females, 18-26 Years, Dose 2

- 15 cases exposed to 9vHPV
  - 7 vaccinated with 9vHPV only, 8 received 9vHPV + concomitant vaccine
- Medical record review
  - 6 allergic reaction with no alternative cause
  - 9 other (reaction to food/drug, injection site reaction, etc.)
- No signal in the ED/IP setting: RR=0.4, P=0.75
- No further investigation planned

Follow-up of ESA Signals: Appendicitis in Males, 9-17 Years, Dose 3

- 30 cases exposed to 9vHPV
  - 20 vaccinated with 9vHPV only, 10 received 9vHPV + concomitant vaccine
- 14 ED, 15 inpatient, 1 unknown
- ESA results: RR=2.09, P=0.03
  - 10 comparisons conducted in the week in which appendicitis signaled
- MaxSPRT and CMaxSPRT results: **no increased risk** during the surveillance period (RR=1.3-1.6)

Appendicitis Temporal Scan Analysis: No Clustering within 1-42 days of 9vHPV vaccination



Range of P values for various scan widths in the temporal scan analysis: 0.78-0.98

Appendicitis Medical Record Review

- Appendicitis diagnosis confirmed in all 30 exposed cases
  - 30 appendectomies
  - 28 of 30 confirmed by pathology
- Days between 9vHPV vaccination and illness onset:
  - Median 22 days (range, 0-42 days)

Follow-up of ESA Signal for Appendicitis: Self-Controlled Risk-Interval (SCRI) Analysis

- Study sample: All cases occurring 180 days post-vaccination
- Risk window 1 to 42 days post-vaccination
- Main unexposed window 43-84 days
  - Medical record review to confirm diagnosis in unexposed risk window (n=30)
  - RR=1.42 (95%CI 0.77 to 2.62)
- No evidence of elevated risk

Strengths and Limitations of the 9vHPV RCA

- Strengths
  - Near real-time access to electronic medical record data
  - Capacity to conduct medical record review as needed
  - Nearly 900,000 vaccinations documented
  - Complementary analytic methods
- Limitations
  - Near real-time data can be unstable
  - Miscoding or secular trends in coding
  - Secular trends in disease incidence
  - Seasonality of vaccination and disease

Conclusions

- RCA signaled for several adverse events after 9vHPV
  - Syncope and injection site reactions were expected
  - All other signals were further investigated
- Signals for allergic reaction, pancreatitis, and appendicitis were not confirmed after further evaluation

Maintenance Surveillance

- Weekly surveillance has concluded for 9vHPV
- Periodic analysis to ensure continued safety
  - Examine observed and expected counts, risk estimates, and exposures
- Surveillance for serious and uncommon outcomes after 9vHPV
  - Anaphylaxis, GBS, CIDP, stroke, venous thromboembolism

Acknowledgements

- VSD Investigators
  - Ned Lewis and Bruce Fireman at NCK, Martin Kulldorff (Harvard), PIs, research coordinators, and program managers at participating VSD sites
- CDC
  - Eric Weintraub, Julianne Gee, Natalie McCarthy, Lori Phillips, Frank DeStefano
- Marshfield Clinic Research Institute
  - Erica Scotty, Kayla Hanson