



# **Safety of closely spaced Tdap vaccines in the catch-up immunization schedule**

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Pedro L. Moro, MD, MPH  
Immunization Safety Office  
Centers for Disease Control and Prevention (CDC)

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## Disclaimer

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

**Background**

# Catch-up schedule: current and proposed

**Current** adolescent and adult catch-up schedule series for those with incomplete or unknown vaccine history



**Proposed** policy option under consideration



# Catch-up schedule: current and proposed

- Limited data exist on the safety of the current vs. the proposed catch-up schedule for adolescents and adults
- An approach to address this issue is to look at published and unpublished data on the safety of:
  - Immunization regimens similar to proposed schedule
  - Administering closely spaced ( $\leq 12$  months) Tdap doses

# Objectives

- Review published literature on studies that have assessed the safety of closely spaced Tdap:
  - Compared to closely spaced Td doses
  - Non-comparative, descriptive
- Review unpublished safety data on closely spaced Tdap from CDC's vaccine safety monitoring systems:
  - Vaccine Adverse Event Reporting System (VAERS)
  - Vaccine Safety Datalink (VSD)

**Published studies**

# Study of Tdap vs. Td<sup>1</sup>

- Study design: double-blind, randomized, controlled clinical trial
- Study population: 460 adults  $\geq 40$  years from 3 European countries with no Td vaccine for 20 years or unknown vaccination history
- Study arms: received the following in a 0-1-6 month schedule:
  - 3 doses of Tdap
  - 1 dose of Tdap-IPV followed by 2 doses of Td, or
  - 3 doses of Td vaccine (control)
- Outcomes: immunogenicity and reactogenicity
- Results: No statistically significant differences in local or general symptoms between groups were observed

<sup>1</sup>Theeten H, et al. Current Medical Research and Opinion. 2007;23:11,2729-2739

# Study of maternal Tdap reactogenicity<sup>1</sup>

- Study design: cohort study
- Study population: 374 pregnant women; 225 nonpregnant women
- Study sub-population of interest: 8 pregnant women who had more than one Tdap within the past 12 months
- Comparison groups: none
- Outcomes: injection site and systemic reactions
- Results: no severe local or systemic reactions
- Conclusion: no adverse event of concern but small number of subjects

<sup>1</sup> Fortner K, et al. Reactogenicity and immunogenicity of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant and non-pregnant women. *Vaccine*. 2018 Oct 8;36(42):6354-6360

# Vaccine Adverse Event Reporting System (VAERS)

Unpublished analysis

# Vaccine Adverse Event Reporting System (VAERS)

## Strengths

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

## Limitations

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

- VAERS accepts all reports from all reporters without making judgments on causality, irrespective of clinical seriousness
- As a hypothesis generating system, VAERS identifies potential vaccine safety concerns that can be studied in more robust data systems

# Closely spaced Tdap reports in VAERS - Methods (unpublished data)

- Search VAERS database for U.S. reports of all persons who received more than one dose of Tdap
  - Jan 1, 1990 – June 30<sup>th</sup>, 2019
- Review of VAERS reports and any medical records to assess for the length of interval between doses and the adverse event (AE), if any
- Reports where interval of two Tdap doses  $\leq 12$  months included in final analysis

# Closely spaced Tdap reports in VAERS – Findings (unpublished data)

- Among 34,804 reports of Tdap submitted to VAERS during the search period, 342 involved multiple doses of Tdap
- In 88 reports interval of two Tdap doses  $\leq 12$  months
  - 67 (76.1%) did not describe an AE (vaccination errors)
  - 21 (23.9%) described an AE
- The most common AEs were injection site reactions in 8 reports

# Vaccine Safety Datalink (VSD)

Unpublished analysis

# Retrospective Cohort Study assessing repeated doses of Tdap vs. Td – unpublished analysis

- Data source: unpublished data from VSD retrospective cohort study evaluating repeated Tdap doses
  - Supplementary analysis on existing dataset<sup>1</sup>
- Study sub-population of interest (unpublished data): 13,599 non-pregnant adolescents and adults 11-64 years who received Tdap or Td within 12 months of prior Tdap
- Comparison groups:
  - 11,687 Tdap vs. 1,912 Td vaccines given within 12 months of prior Tdap
- Outcomes: pre-specified local reactions and neurologic adverse events<sup>2</sup>
- Results: Repeated Tdap was not associated with an increase in any adverse event compared to Td within 12 months of prior Tdap

<sup>1</sup> Jackson M, et al. Pharmacoepidemiol Drug Saf. 2018;27:921-925

<sup>2</sup> Cellulitis, Limb swelling, Pain in limb, Encephalopathy, encephalitis and/or meningitis, Paralytic syndromes, Seizure, Cranial nerve disorders, Guillain-Barre Syndrome

# Maternal Tdap safety in the VSD – unpublished analysis

- Data source: unpublished data from VSD retrospective cohort study evaluating maternal Tdap safety
- Study sub-population of interest (unpublished data): 187 women with multiple Tdap vaccines during the same pregnancy (excluded from larger published study<sup>1</sup>)
- Comparison group: None
- Outcomes: acute adverse events (fever, allergy, and local reactions) and adverse birth outcomes (small for gestational age, preterm delivery, and low birth weight)

<sup>1</sup> Sukumaran L et al. JAMA. 314(15):1581-1587

## Maternal Tdap safety in the VSD – unpublished analysis (cont.)

- Only 1/187 with acute event following multiple Tdap vaccines in same pregnancy
  - ICD-9 code of limb pain and limb swelling 7 days after vaccination
  - Occurred on the day of delivery
  - Affected limb(s) unspecified
  - Baby born at 39 weeks
- Birth outcome rates were similar to pregnant women exposed to a single Tdap dose during the same pregnancy<sup>1</sup>

<sup>1</sup> Sukumaran L et al. JAMA. 2015;314(15):1581-7

# Summary and Conclusions

## Summary - Published Studies

Studies	Design	Setting	N	Findings
<u>Theeten et al. 2007</u>	RCT comparing: -Tdap x 3 -Tdap-IPV, Td, Td -Td x 3	Europe	460	No differences in reactogenicity between Tdap vs Td
Fortner et al, 2018	Cohort retrospective no comparison	USA	8 <sup>1</sup>	No severe local or systemic reactions

RCT: Randomized clinical trial; <sup>1</sup> Number with closely spaced Tdap ( $\leq 12$  months)

# Summary - unpublished data

## VAERS:

- Most reports (76%) of excess doses of Tdap in VAERS did not describe an AE
- Among reports with AEs (n=21), local reactions were most commonly reported (n=8)

## VSD:

- Among subjects who received a Tdap dose  $\leq 12$  months compared to Td, no increased rates of AEs were observed
- Among 187 women in the VSD who received multiple Tdap doses in the same pregnancy, one presented with limb pain and limb swelling 7 days after vaccination (unclear if related)

# Conclusions

- Published data on closely spaced Tdap doses shows no increase in AEs when Tdap or Td was administered as a second or third dose
  - Regimens similar to the current and proposed catch-up schedule did not show differences in reactogenicity
- Unpublished data of closely spaced Tdap doses shows no unusual or increased reporting of any AE
- While data on multiple Tdap doses is limited, our review of published and unpublished safety data is reassuring

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# Thank you

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

