Clinical Immunization Safety Assessment (CISA) Network: Activities Related to Human Papillomavirus Vaccine (HPV4)

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Background: CISA

- **Network of six academic centers with vaccine safety subject matter experts**
  - Boston Medical Center, Columbia University Medical Center, Johns Hopkins University, Northern California Kaiser Permanente, Stanford University Medical Center, Vanderbilt University Medical Center
- **Established in 2001 to:**
  - Investigate the pathophysiologic mechanisms and biologic basis of adverse events following immunization (AEFIs) and
  - Provide selected clinical consultations
- **Established collaborations with other clinical specialists (e.g., neurologists, allergists, geneticists, metabolic/mitochondrial experts)**

CISA Activities Related to HPV4

- **Clinical consultation on rare, serious adverse events following HPV4**
- **Transverse myelitis (TM) review**
  - **Led by Johns Hopkins**
  - **Licensure through August 2008**
- **Guillain Barré Syndrome (GBS) review**
  - **Led by Boston Medical Center**
  - **Licensure through August 2008**

Methods

- Cases identified through review of VAERS database for reports of TM and GBS
- Reports received between 6-01-06 and 8-31-08
- Medical records on cases reviewed by CISA investigators and clinical expert neurologists
- Proposed Brighton case definition used for confirmation of GBS cases*
  - Level 1 represents highest level of certainty
- Theoretical window of biological plausibility for immune-mediated neurologic events is 4 – 42 days after vaccination

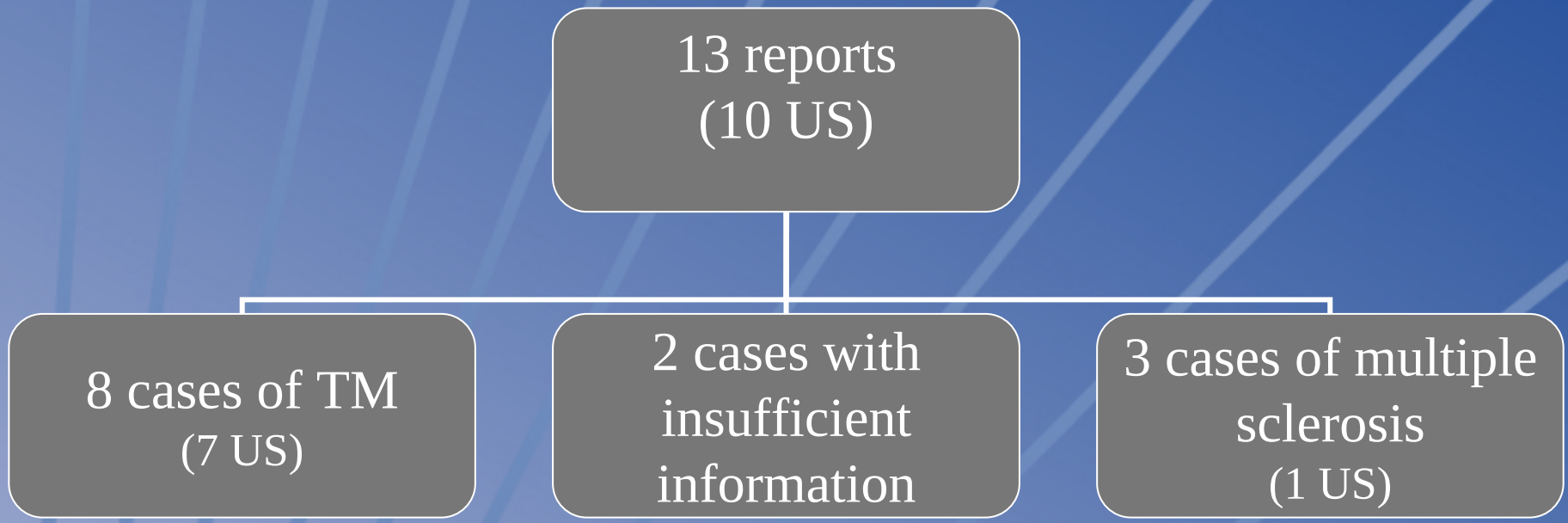
*http://www.brightoncollaboration.org/internet/en/index/definition___guidelines.html

Background: Transverse Myelitis(TM):

- TM is a rare neurological disorder caused by inflammation across both sides of one or more adjacent levels, or segments, of the spinal cord that can cause axonal demyelination.
- 75 cases reported in the literature (1964 to 2008) following vaccinations (temporal association only).
- Conservative estimates of TM incidence per year vary from 1 to 5 per million population.*
- The peak ages for a TM diagnosis appear to be between 10 to 19 years and after 40 years of age.†

* Jeffery et.al., Arch Neurol, 1993
† Berman, Neurology, 1981

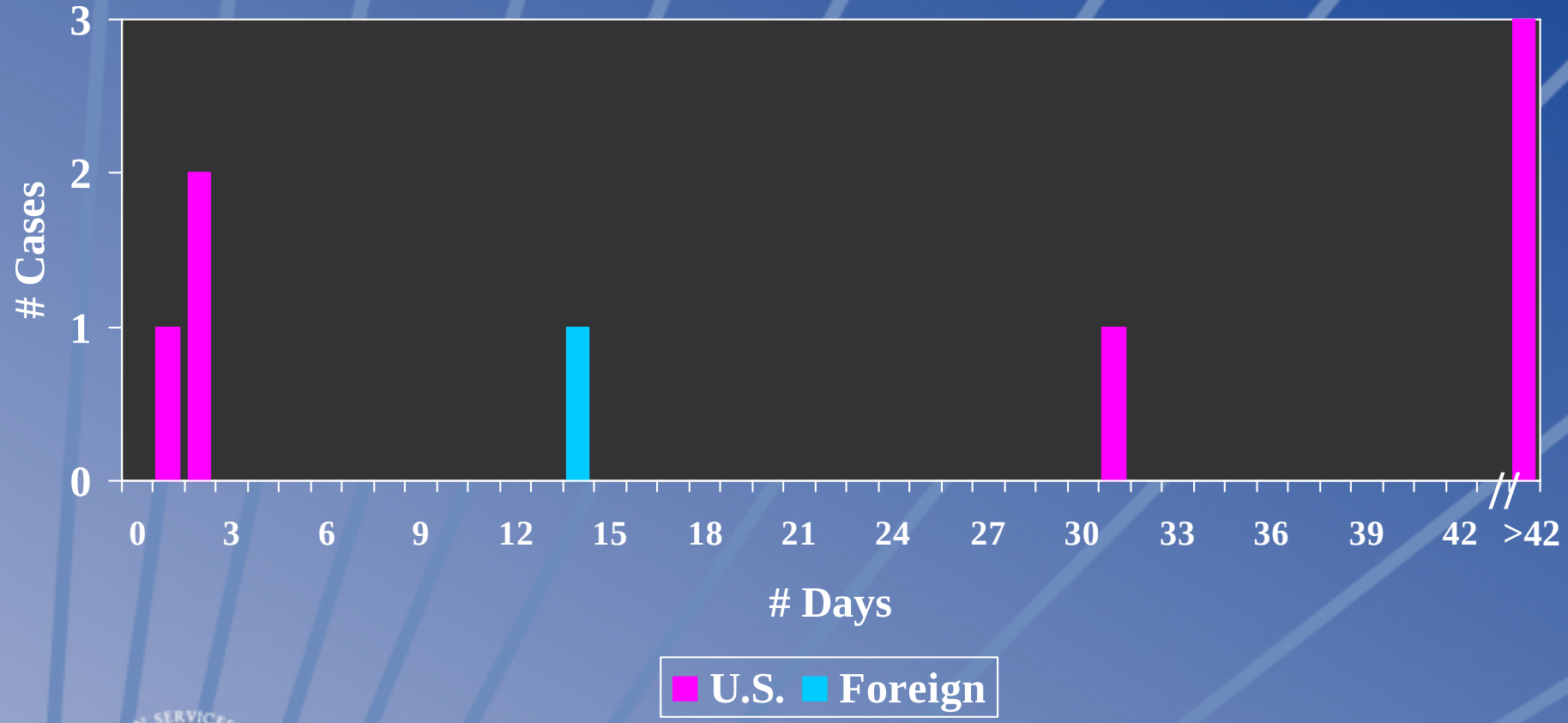
Clinical Review of TM Cases Reported to VAERS after HPV4 Immunization



Medical Record Review of 8 TM Case Reports

- **Level of lesion**
  - Cervical: 4
  - Thoracic: 4
- **Range of ages (years): 11 to 26**
- **Sex: all females**
- **Vaccines involved:** HPV4 vaccine only
- **Review for confounding conditions**
  - Infectious symptoms = 2
  - Other diseases = 0
  - History of allergy = 1
- **Number of dose preceding symptom onset**
  - 1 dose = 2
  - 2 doses = 6

Number of Days: HPV4 Immunization to First Symptoms of TM



Intervals > 42 days = 52, >60, 150 days

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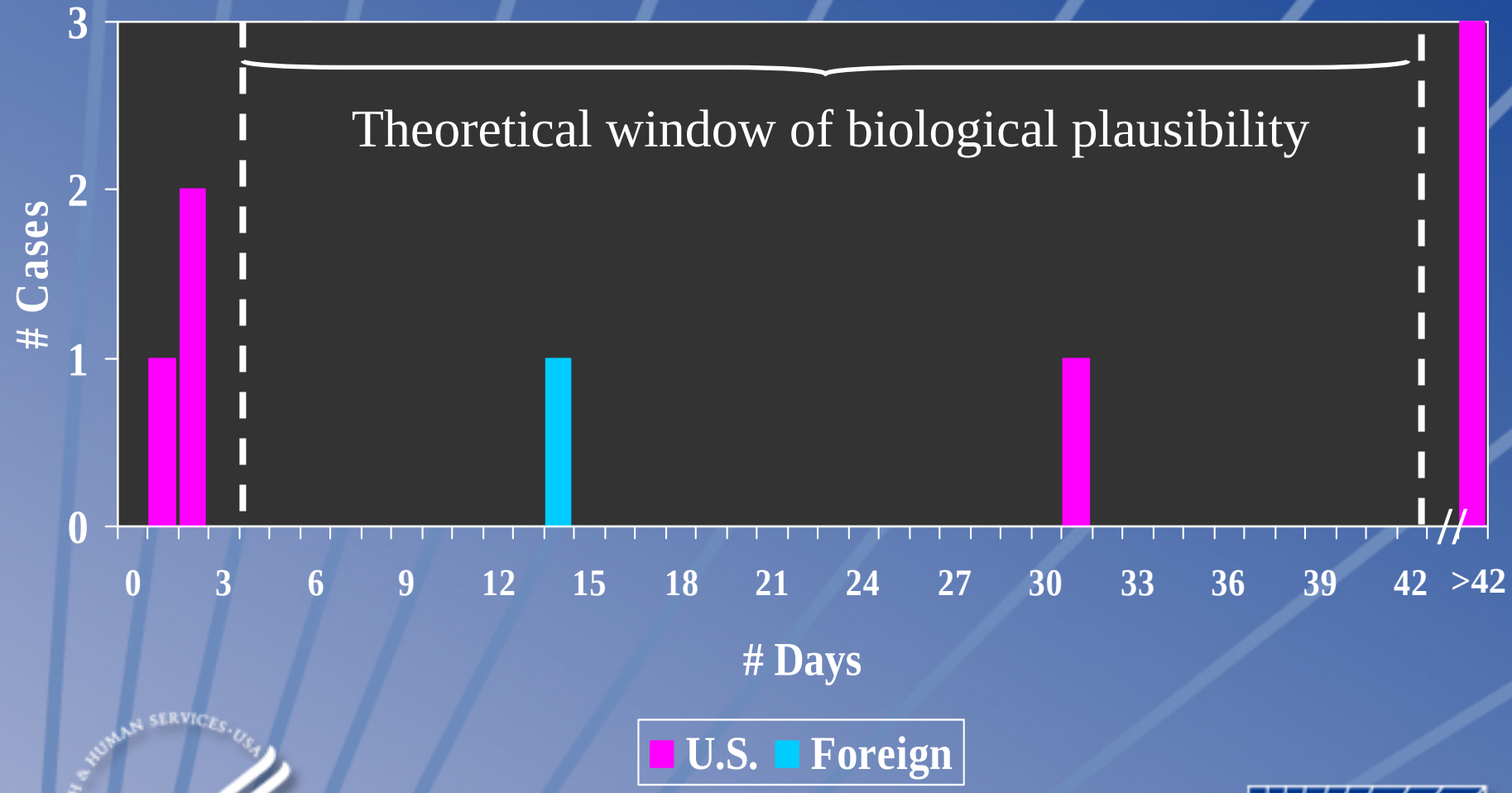


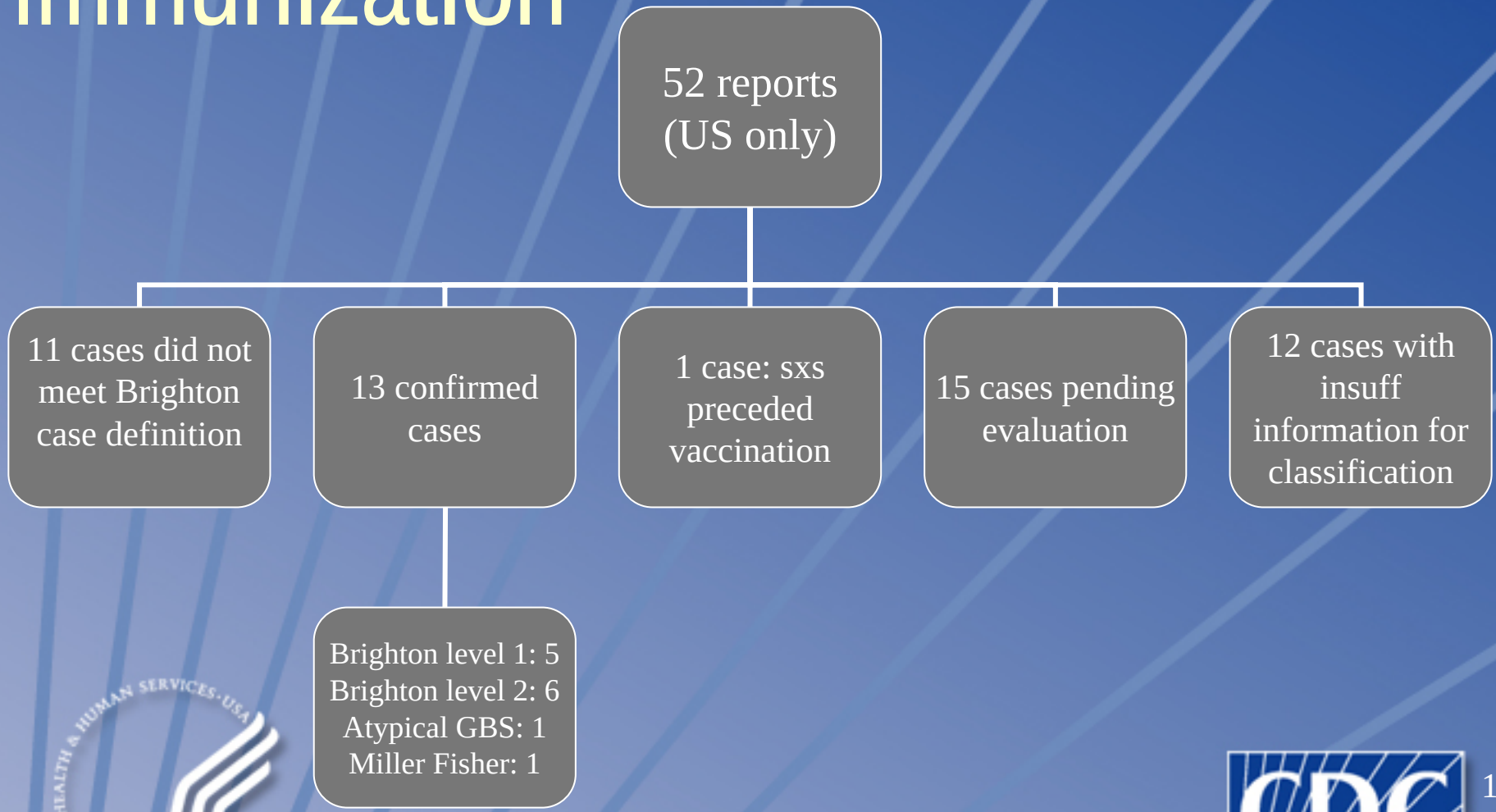
Intervals > 42 days = 52, >60, 150 days

Background: Guillain-Barré Syndrome (GBS)

- GBS is an immune-mediated acute demyelinating polyneuropathy affecting the peripheral nervous system.
- The estimated annual incidence rate of GBS is 1 case per 100,000 population
- To date, with rare exceptions, associations between vaccines and GBS have been based only upon temporal associations with limited epidemiologic evidence.
- Evidence for a causal association with immunization is strongest for the swine influenza vaccine (1976-77). Studies of subsequent influenza vaccines have found small or no increased risk of GBS.*

*Institute of Medicine. Influenza Vaccines and Neurological Complications, 2004.

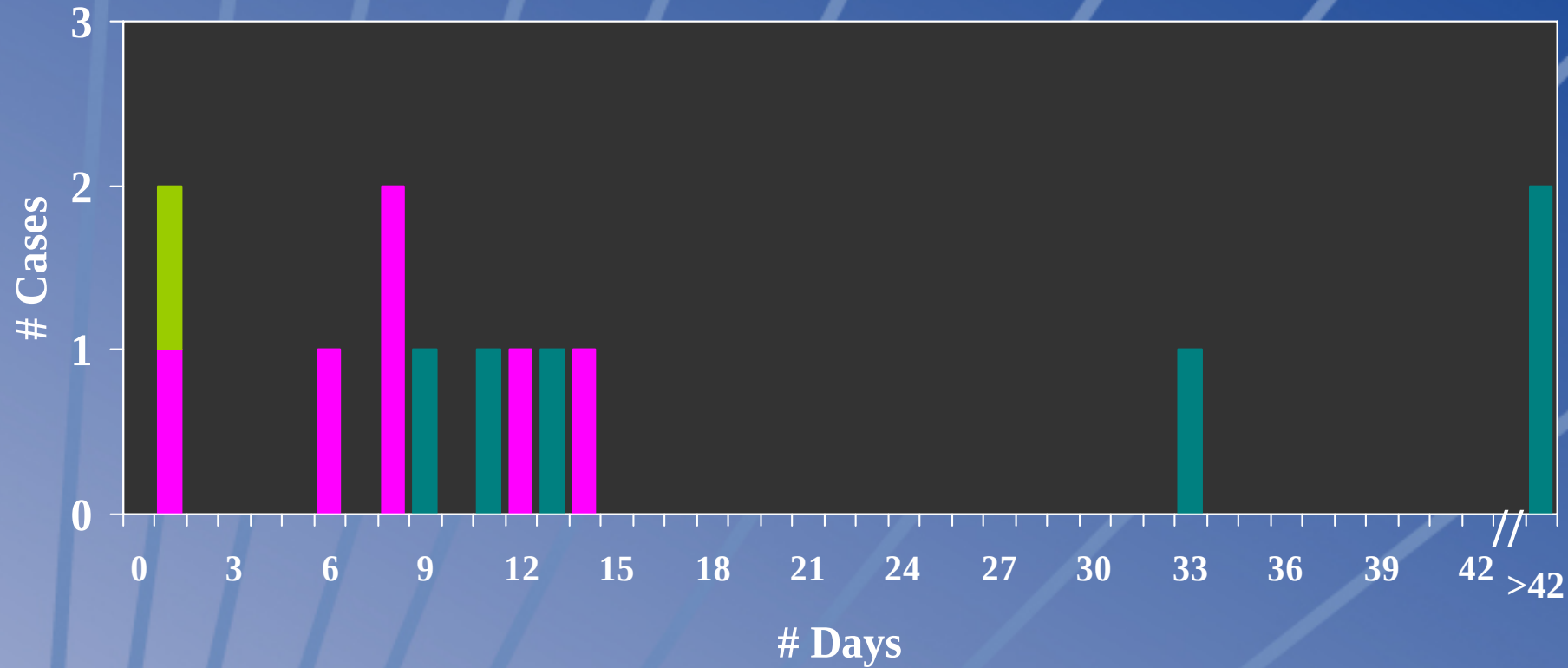
Clinical Review of GBS Cases Reported to VAERS after HPV4 Immunization



Medical Record Review of 13 GBS Cases after HPV4

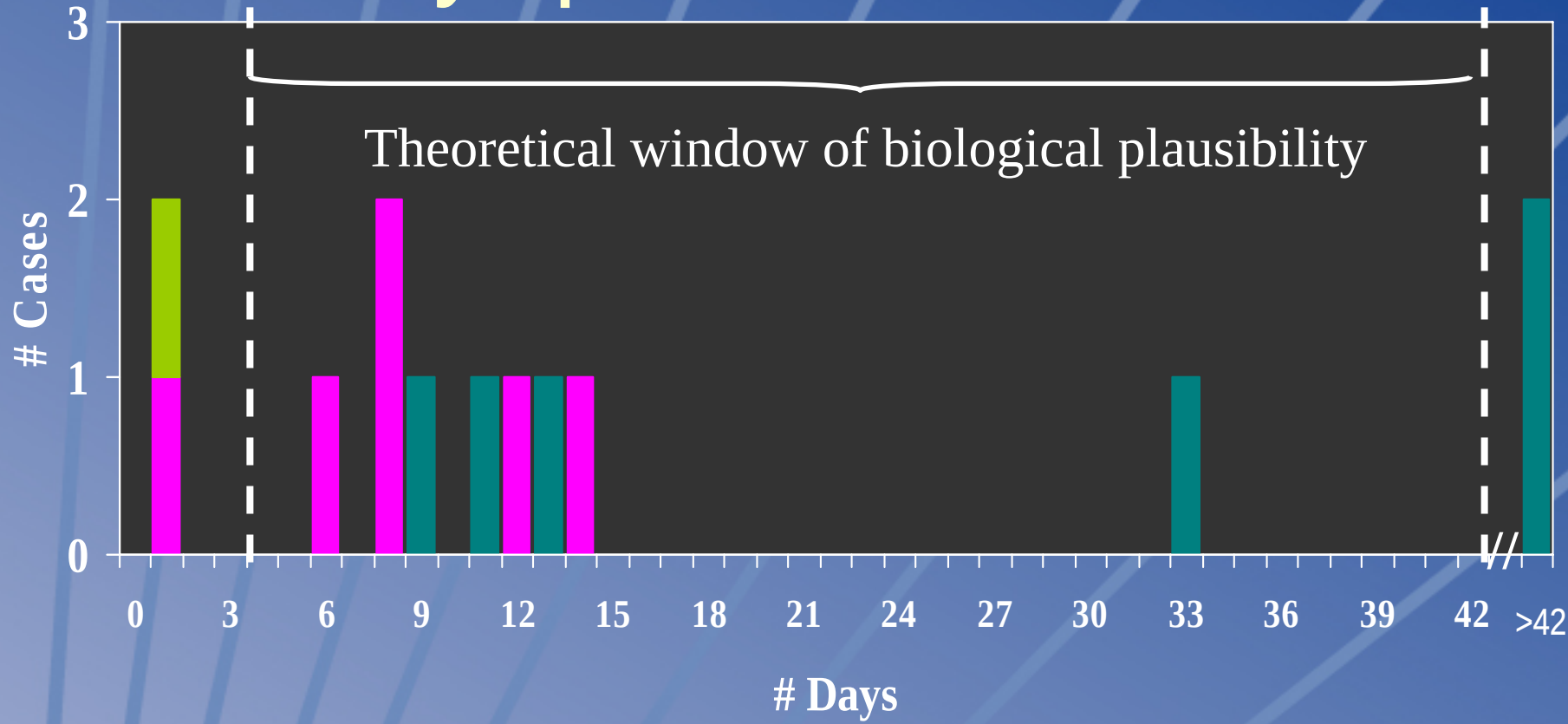
- **Vaccines involved:**
  - HPV4 vaccine only: 6
  - HPV4 vaccine + Menactra® (MCV4): 6
  - HPV4 + other vaccines: 1
- Demographic characteristics
  - 12 cases: 13 – 20 years of age, female
  - 1 case: 56 y.o. male
- Number of doses preceding onset of symptoms:
  - 1 dose: 9
  - 2 doses: 3
  - 3 doses: 0
  - Unknown: 1

Number of Days: HPV4 Immunization to First Symptoms of GBS



Intervals > 42 days = 86 and 144 days

Number of Days: HPV4 Immunization to First Symptoms of GBS



Intervals > 42 days = 86, 144 days

Limitations of Studies

- Usual limitations of VAERS data
- Analysis based on medical record review only; available records may be incomplete
- No denominator data for doses given, so cannot calculate post-immunization rates of TM or GBS

Summary

- 2 cases (1 US) of TM after HPV4 within 4 to 42 days, both received HPV4 vaccination alone
- 9 cases of confirmed GBS within 4 to 42 days after HPV4, 4 also received MCV4
- Reports show temporal association only
  - Evidence insufficient to support causal relationship
- Most reports of GBS submitted to VAERS not confirmed
  - 50% with adequate medical records met case definition criteria
- CDC and FDA continue to carefully analyze all reports of GBS and TM submitted to VAERS

Ongoing CISA Studies

- Transverse Myelitis
  - Comparison of Idiopathic Acute Transverse Myelitis With and Without Receipt of a Vaccine*
  - Risk Factors for Acute Transverse Myelitis: A Self-Controlled Case Series Approach
- Guillain Barrė Syndrome
  - Genetics of GBS: Investigation of Vaccine-Associated and Non-Vaccine-Associated GBS
  - Post-MCV4 GBS Case Series
  - Does Re-Vaccination of Patients with a History of GBS Result in a Relapse?

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