Meningococcal Conjugate Vaccine and Guillain Barré Syndrome

Advisory Committee on Immunization Practices

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Thomas Clark, MD, MPH

Meningitis and Vaccine Preventable Diseases Branch

National Center for Immunizations and Respiratory Diseases

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- Vaccine Adverse Events Reporting System team

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Guillain Barré Syndrome (GBS)

- Bilateral, symmetric, subacute, flaccid paralysis
- Autoimmune etiology
  - Cause identifiable in ~50% of childhood cases
  - Post-infectious causes (Campylobacter, CMV, EBV, Coxsackie virus)
  - Some cases vaccine associated
- No clear seasonality in Western countries
- Increasing incidence with increasing age
- Decreasing secular trend in U.S.*

*Frenzen et al. Neuroepidemiology 2007 Oct 8;29(1-2):83-88.

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GBS Prognosis

- Improved prognosis in children
  - 50% ambulatory at 6 months
  - 70% ambulatory at 1 year
  - 3-4% mortality

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A/New Jersey/1976 "Swine Flu" Vaccine and GBS

- Mass vaccination due to fear of flu pandemic
- Vaccine for most of adult population and at-risk children
- Program halted following reports of GBS after vaccine
- Later studies confirmed association between A/NJ/1976 vaccine and GBS
  - Attributable risk (AR) estimates in 6 weeks after vaccination - 4.9 to 11.7 cases per million*
- Institute of Medicine (IOM) subsequently determined evidence favored causal relationship

*Schonberger LB et al. Am J Epidemiol. 1979 Aug;110(2):105-23

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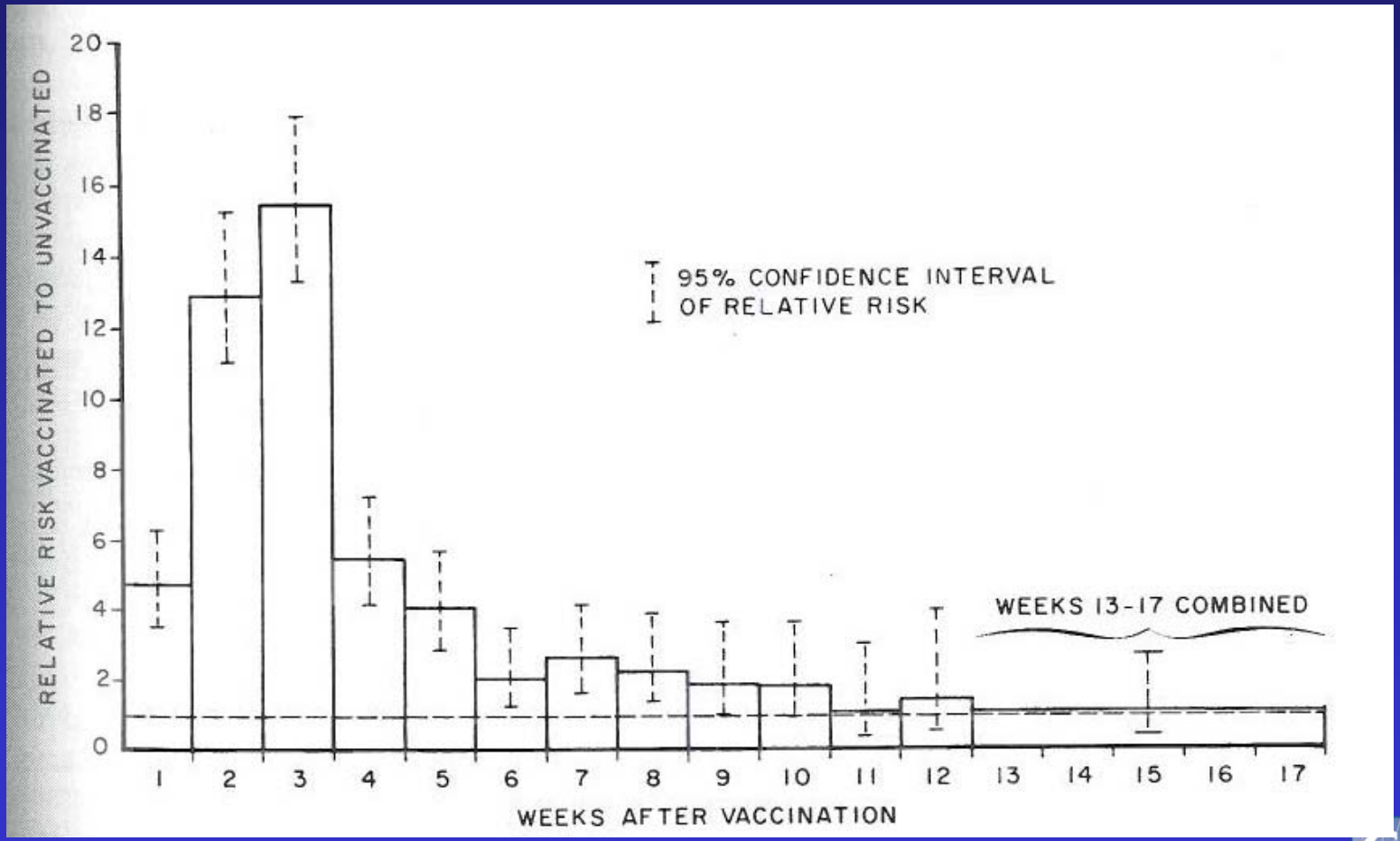
Elevated Risk of GBS after Swine Influenza



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GBS and Prior Seasonal Influenza Vaccines

- No association – 1978-79*, 1979-80**, 1980-81**
- Case-control study conducted due to doubling of GBS reports after influenza vaccine in 1993-94*
- No significant increase in risk in 92-93 or 93-94
- For both seasons combined, adjusted relative risk of 1.7 (95% CI 1.0-2.8)
  - Approximately 1 additional case per million vaccinees
- IOM subsequently concluded evidence inadequate to accept or reject causal relationship

*Hurwitz et al. NEJM. 1981 Jun 25;304(26);1557-61.
**Kaplan et al. JAMA. 1982 Aug 13;248(6):668-700.
***Lasky et al. NEJM. 1998 Dec 17;339(25):1797-802.

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ACIP Statement on Influenza Vaccine

- "If GBS is a side effect of influenza vaccines other than 1976 swine influenza vaccine, the estimated risk for GBS is based on the few studies that have demonstrated an association between vaccination and GBS is low (i.e., approximately one additional case per 1 million persons vaccinated). The potential benefits of influenza vaccination in preventing serious illness, hospitalization, and death substantially outweigh these estimates of risk for vaccine-associated GBS. No evidence indicates that the case fatality ratio for GBS differs among vaccinated persons and those not vaccinated."

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GBS and Meningococcal Vaccines

- No substantially increased incidence of GBS with British MenC vaccines*
- 1 case of GBS reported to VAERS after meningococcal polysaccharide vaccine (MPSV4) between 1990-1999**

*Salisbury DM, Personal Communication.

**Ball et al. Clin Infect Dis. 2001;32(9):1273-1280.

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Current Situation -October 2007

- Confirmed reports to VAERS = 24
  - 11-19 year-olds = 22
    - 11-14 year-olds = 2
    - 15-19 year-olds = 20
  - >19 year-olds = 2
- VSD Rapid Cycle analysis
  - 213,724 doses administered
  - 0 cases among 11-19 year-olds within 6 weeks
  - 0-1 case expected

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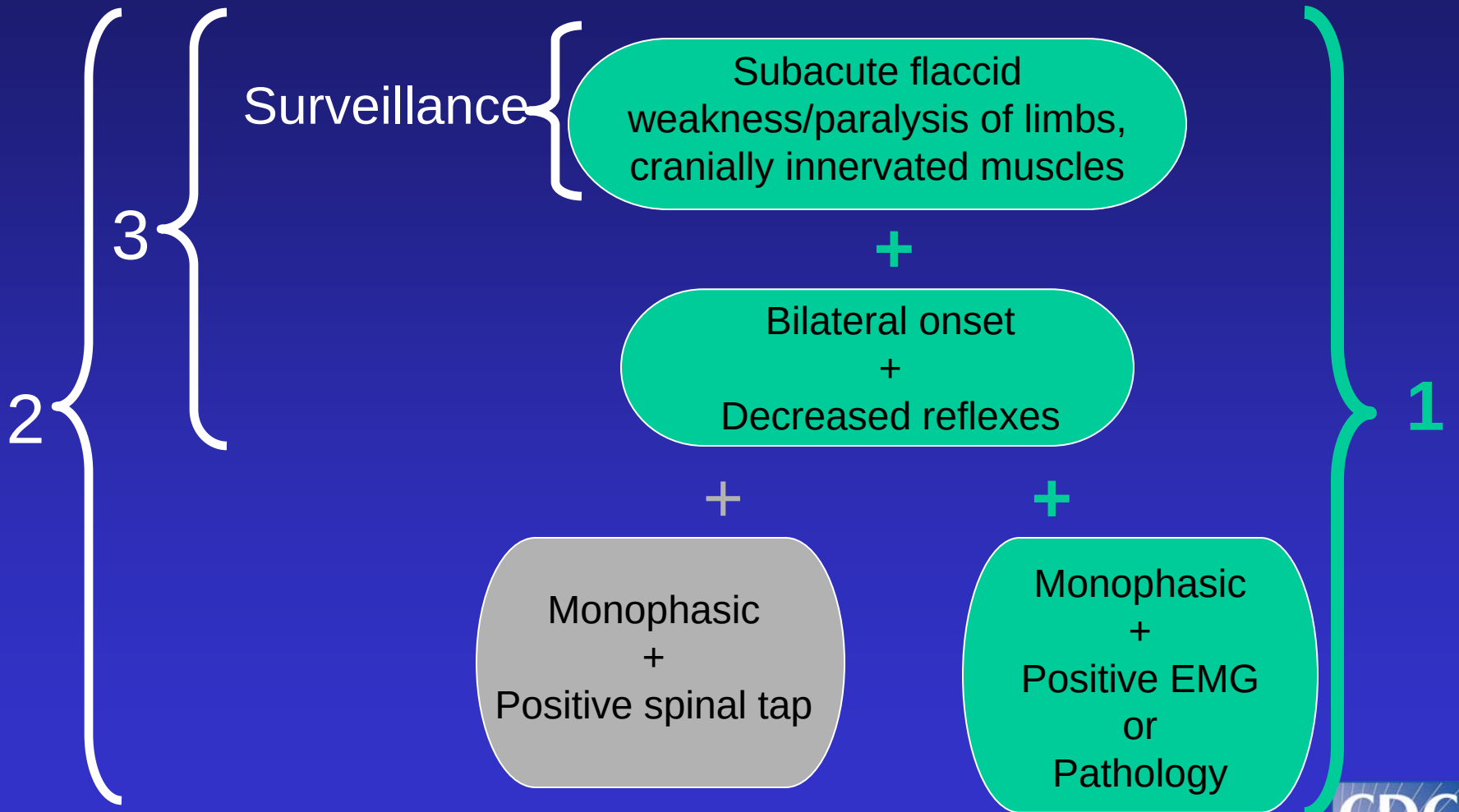
Brighton GBS Classification*



*Brighton Collaboration, provisional as of 6/22/2007

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Case Classification
(n=22)

Brighton GBS level	n	%
Level 1	7	32
Level 2	14	64
Level 3	1	4

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Case Summary

	+	n	%
Male	10	22	45
MCV4 alone	12	22	55
Hospitalized	19	22	86
Intensive care	9	21	43
Intubated	1	22	5
Plasmapheresis	3	22	14
IVIG	18	22	82

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Condition Upon Discharge

	+	n	%
Ambulatory	15	18	83
Disability affecting activities of daily living	8	18	44
Inpatient rehabilitation treatment	5	19	26

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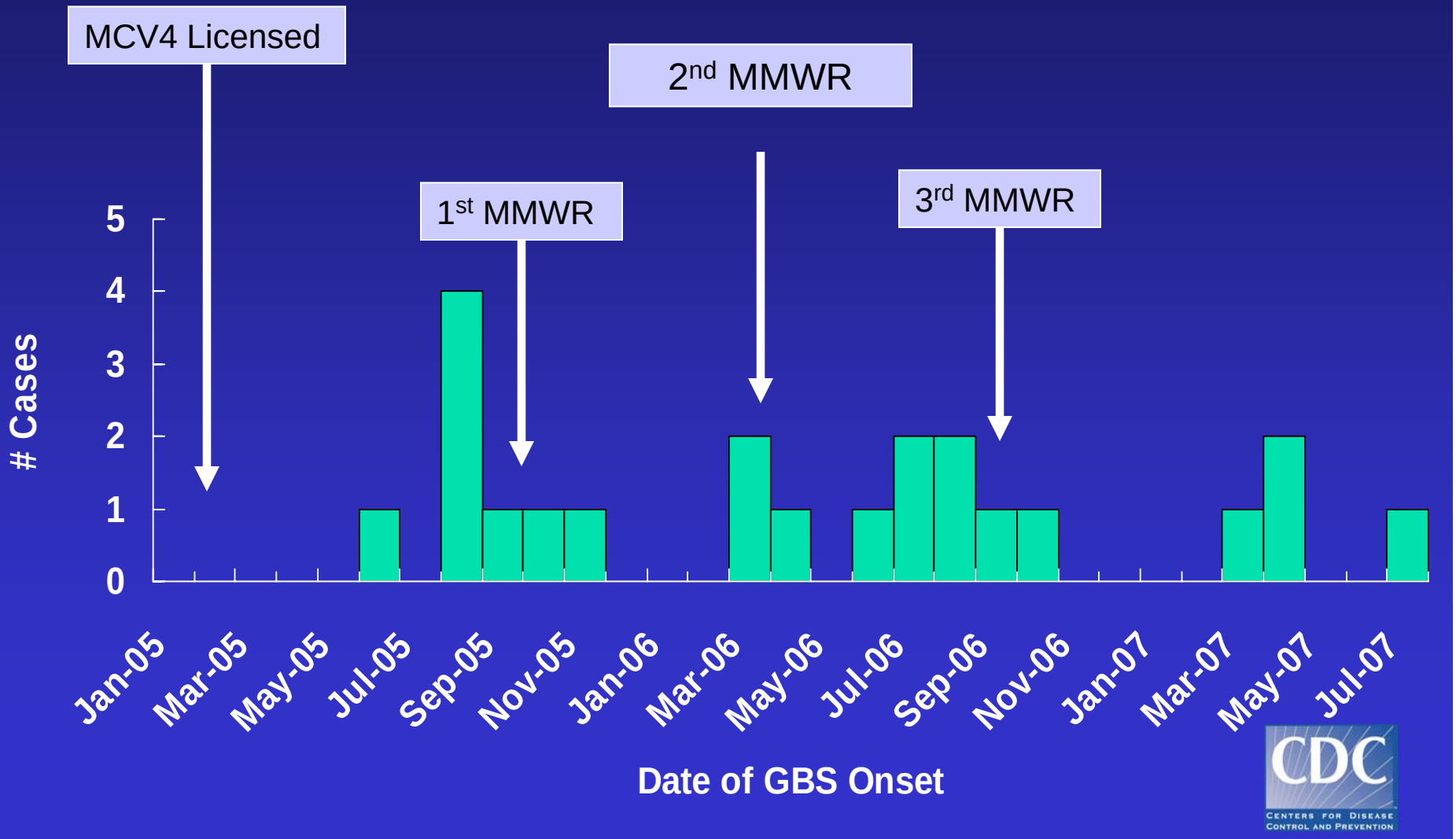
GBS cases among 11-19 year-olds within 6 weeks of receipt of MCV4, by month of onset (n=22)



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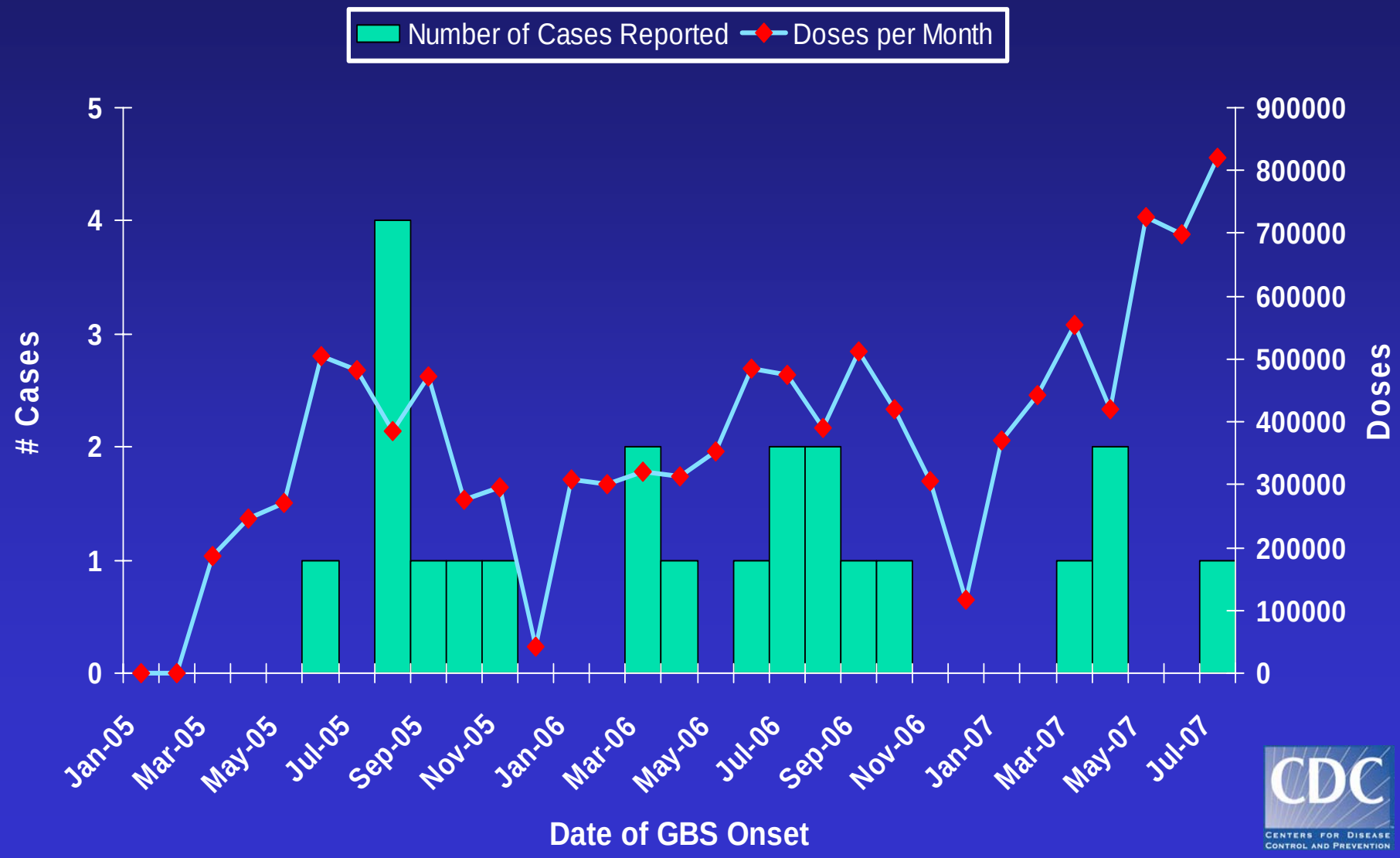
GBS cases (n=22) by month of onset and MCV4 doses distributed



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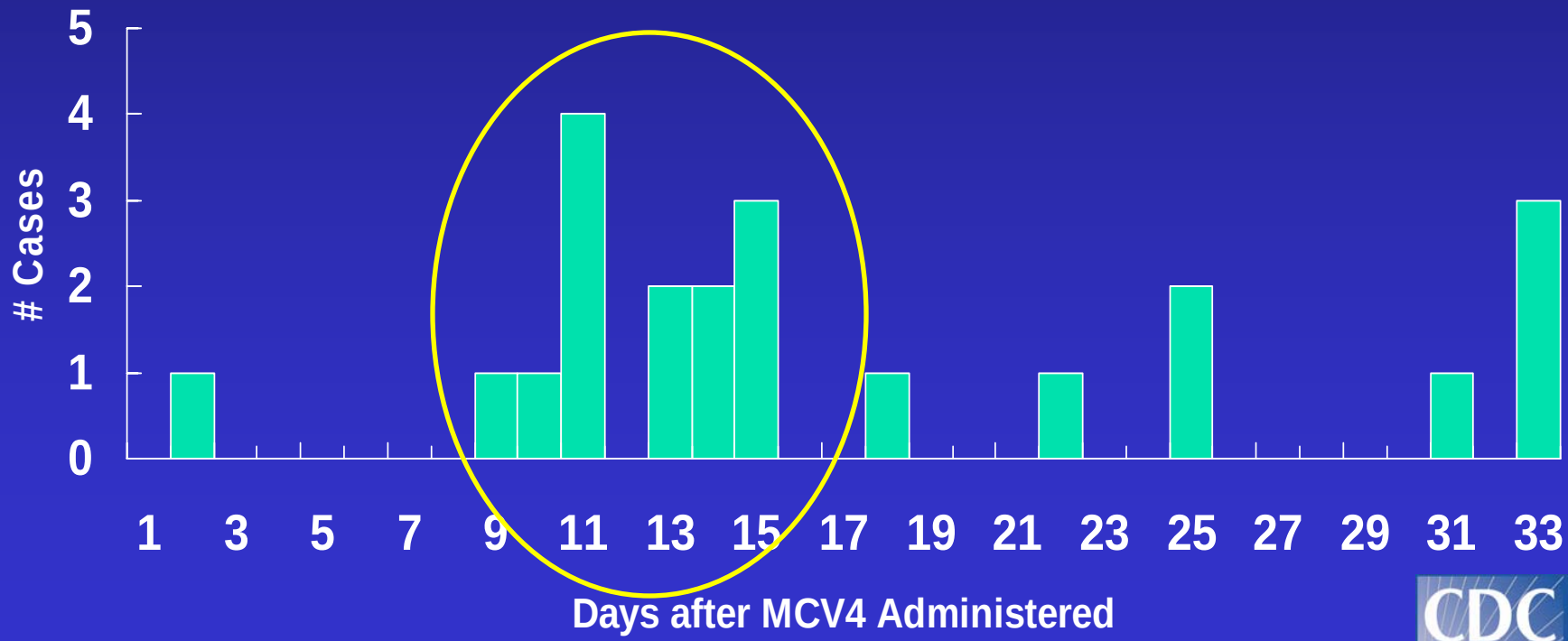
Timing of Onset
(n=22)

- Onset intervals 2-33 days
  - Mean 17.4 days
  - Median 14.5 days
  - Temporal Scan Statistic 9-16 days (p=0.006)



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Size of Association of GBS with MCV4

	Expected Cases	Cases Observed	IRR (95% CI)	Excess Risk per Million Doses
11-19 Year Olds	18	22	1.3 (0.8-1.9)	0.4
15-19 Year Olds	12	20	1.7 (1.0-2.5)	1.3

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Sensitivity Analysis
15-19 year-old patients

Incidence Rate Ratios			
	Reporting		
Doses administered	100%	70%	50%
100%	1.7	2.4	3.4
70%	2.4	3.4	4.8
50%	3.4	4.7	6.7

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Sensitivity Analysis
15-19 year-old patients

Excess Risk in cases per million vaccinated

Doses administered	Reporting 100%	70%	50%
100%	1.7	2.4	3.4
	1.3	2.6	4.6
70%	2.4	3.4	4.8
	2.7	4.7	7.4
50%	3.4	4.7	6.7
	4.6	5.9	11

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Decision Analysis

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Cohort Simulation Model

- To compare health outcomes of vaccination and no vaccination in the presence of GBS risk
- 11-yr-old birth cohort (= 4,076,600)
- 8-year period
- Perspective: Patients
- Outcomes
  - Cases of meningococcal disease and GBS
  - Death & Life-Years (LY) Lost
  - Quality Adjusted Life Years (QALY) Lost

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Assumptions and Parameters

- GBS
  - 5% (2.5% -- 10%) long-term morbidity among adolescents*
  - Incidence in unvaccinated 1.4/100,000 per year†
  - Incidence in vaccinated from VAERS reports 1.8/100,000 † †
- Meningococcal disease
  - Vaccine efficacy (VE)
    - 93% (78%-98%)
  - Disease incidence rate for the unvaccinated**
    - 0.77 per 100,000
  - Disease incidence rate for the vaccinated
    - 0.05 per 100,000 (0.02 per 100,000 – 0.17 per 100,000***)
  - Case Fatality Rate (CFR)**
    - CFR by age 11-19 yrs old
    - Overall 10.34%

Hahn AF. Lancet 1998
† †Trotter et al. Lancet 2004;364;365-367.
Arithmetic mean of Vaccine Safety Datalink and Healthcare Utilization Project rates
** Active Bacterial Core Surveillance (ABCs), unpublished data
*** Disease incidence rate for the vaccinated varies as VE changes

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Predicted Effect of MCV4

All 11-year-olds Vaccinated

	No Vaccination	Full Vaccination	Change (95% CI)
Guillain-Barre Syndrome			
Cases	494	499	5 (0, 14)
Moderate-Severe Disability	17	17	0.18
Meningococcal Disease			
Cases	388	29	- 359 (-376, -337)
Deaths	38	3	- 35 (-37, -33)
Amputations	20	2	-18
Neurologic Disability	14	1	-13
Hearing Loss	31	2	- 29
Total			
Discounted QALY Lost	2709	455	- 2254

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Predicted Effect of MCV4

All 11-year-olds Vaccinated

	No Vaccination	Full Vaccination	Change (95% CI)
Guillain-Barre Syndrome			
Cases	494	504	10 (0, 38)
Moderate-Severe Disability	18	18	0.37
Meningococcal Disease			
Cases	388	29	- 358 (-375, -336)
Deaths	38	3	- 35 (-37, -33)
Amputations	20	2	-18
Neurologic Disability	14	1	-13
Hearing Loss	31	2	- 29
Total			
Discounted QALY Lost	2707	460	- 2247

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Summary

- Estimated excess risk unchanged; analyses ongoing
- Clinical picture, outcomes typical
- Excess risk comparable to that seen for some prior seasonal influenza vaccines
- Vaccination favored, even with larger magnitude of risk
- Large controlled study being conducted by Harvard Pilgrim to assess causal relationship between GBS and MCV4

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Discussion

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