

**Influenza Vaccine and
Neurological Adverse Events:
VAERS 7/1990 - 1/2003
Institute of Medicine (IOM) - 3/13/03**

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

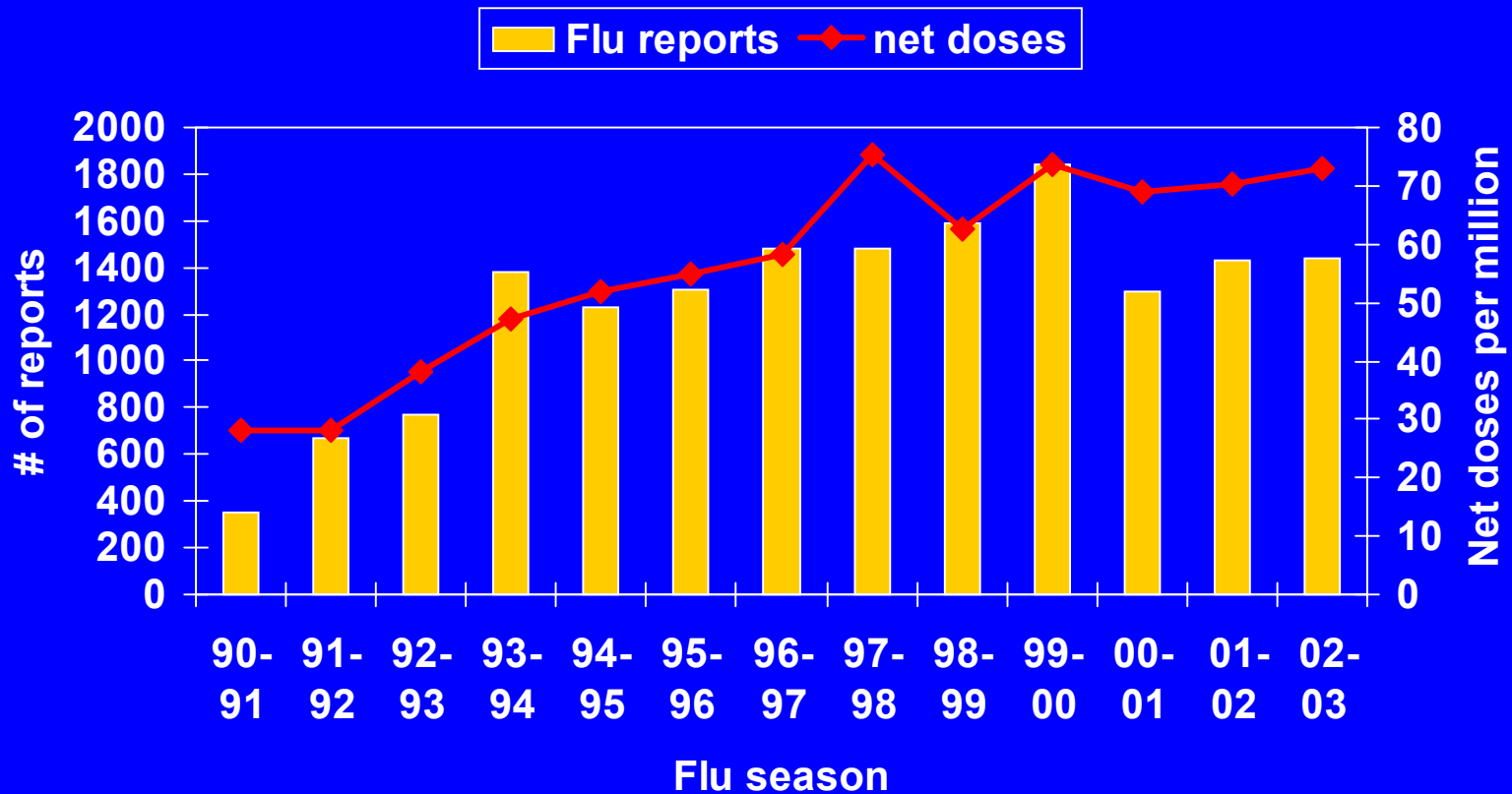
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Outline

- Overview: influenza adverse event reports to VAERS, 7/1990-1/2003
- Selected neurological adverse events
 - A priori interest for IOM
 - GBS
- Special studies:
 - Flu / GBS VAERS Follow-up: 1994 – 2003
 - Proportional Reporting Ratio (PRR)
 - Bell's palsy
 - Positive re-challenge

All Influenza Vaccine Reports By Season*, VAERS 7/1990-1/2003



* Year calculated by vaccination date, all ages

Influenza Vaccine Reports by Severity level, VAERS 7/1990 – 1/ 2003

Severity level	% of all reports- Flu	% of all Flu reports
Fatal	1.4	1.7
Non-fatal Serious*	9.6	11.8
Non-serious**	89.0	86.5

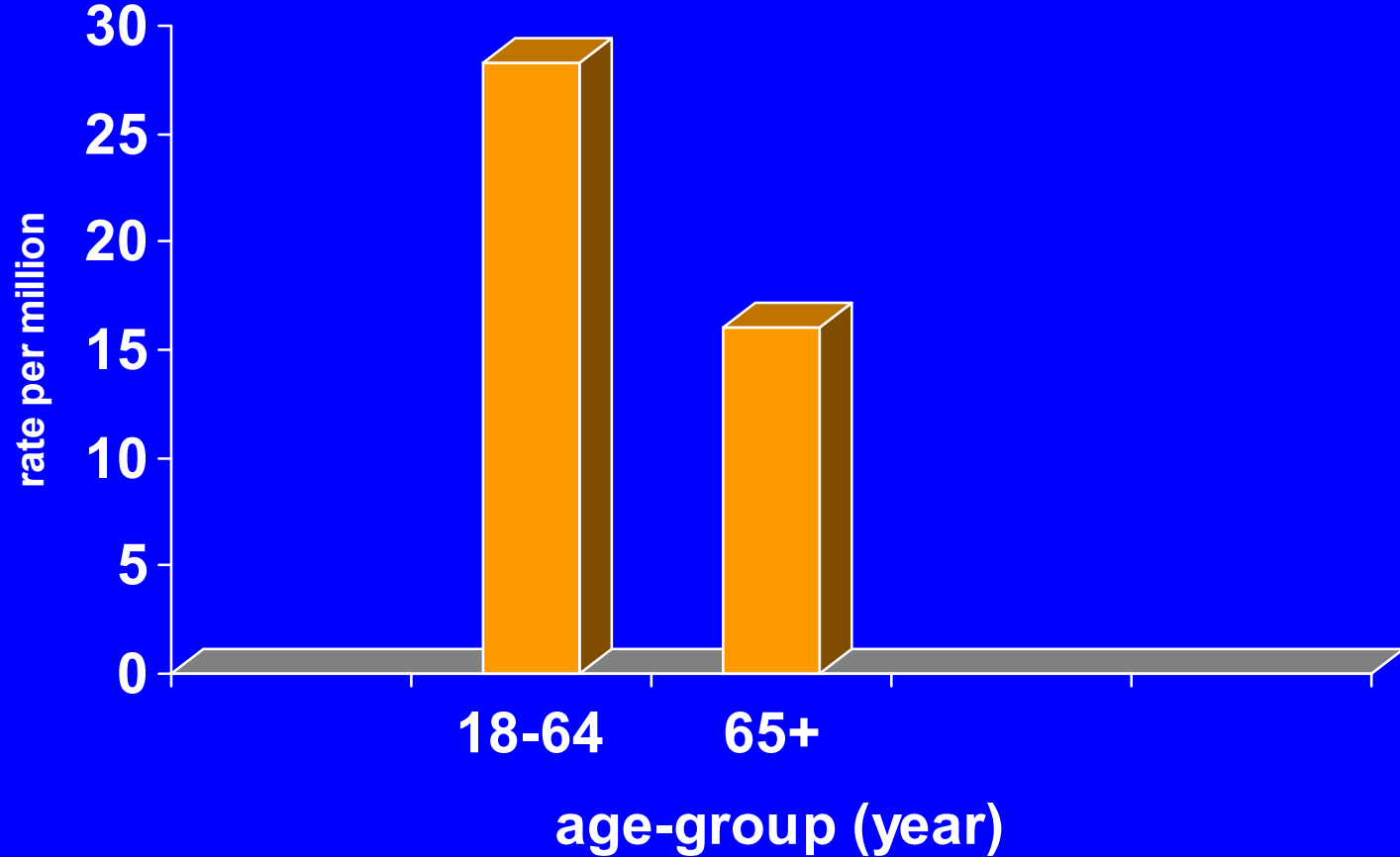
•Non-fatal serious if vaccinee reported one or more of the following: Hospitalization, life-threatening illness, extended hospital stay and / or disability.

Influenza Vaccine Reports to VAERS, Compared with PPV and TD

	Flu alone N=14,203	PPV alone N=4,289	Td alone N=7,196
% administered alone	81	59	68
Reporting rate*	23.7	106	62.5
% serious	14.4	9.6	4.2
Ratio F : M	2.7 : 1	2.2 : 1	3.3 : 1

* Per million doses distributed

Reporting Rates Following Influenza Vaccine By Age-Group



Selected Neurological Adverse Events* Following Influenza Vaccine, VAERS 7/1990-1/2003

Age-group	Encephalitis N=42 N (rate)	Encephalopathy N=26 N (rate)	Peripheral neuritis N=14 N (rate)	Neuritis N=38 N (rate)
0-17	2 (NA)	5 (NA)	-	-
18-64	26 (.07)	10 (.03)	10 (.03)	29 (.07)
65+	10 (.04)	10 (.03)	4 (.02)	7 (.03)
Unknown	5 (NA)	1 (NA)	-	2 (NA)

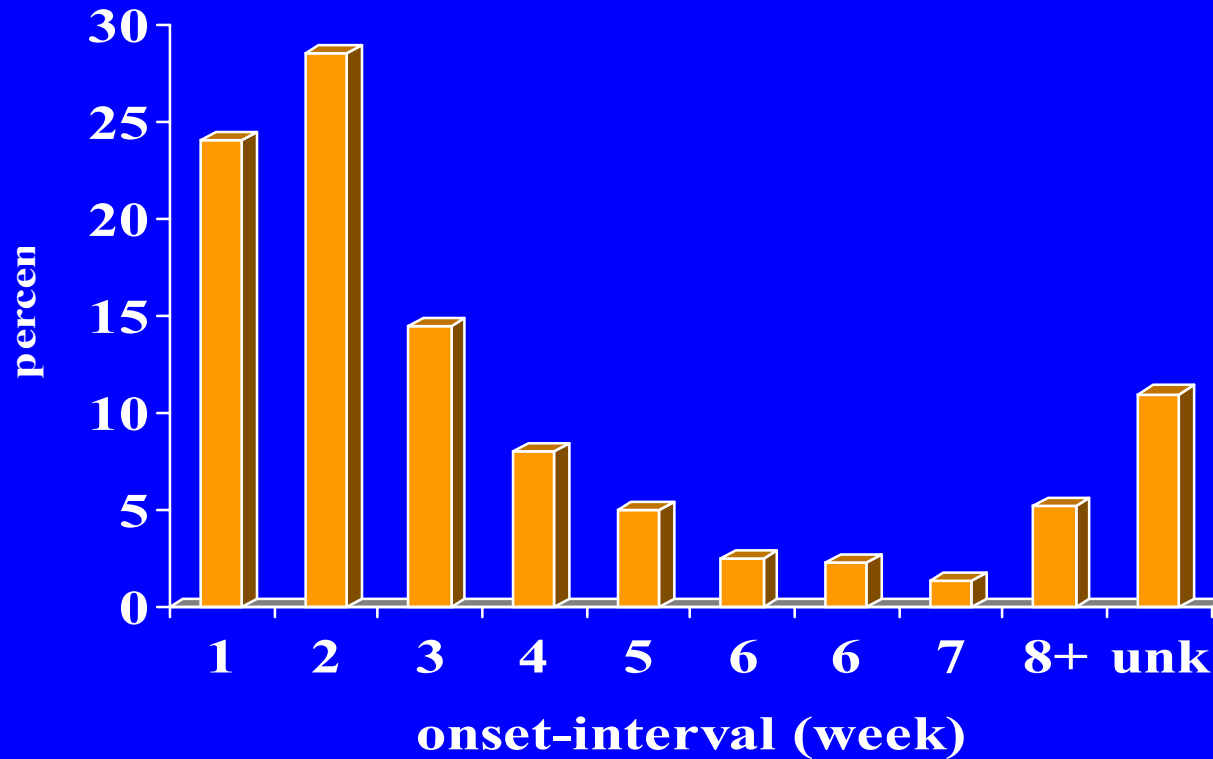
* Excluding GBS reports; COSTARTS codes are not mutually exclusive. # NHIS data reporting rate per million doses administered.

Selected Neurological Adverse Events* Following Influenza Vaccine, VAERS 1/1990-1/2003

Age-group	Optic Neuritis N=26 N (rate)	Facial paralysis N=175 N (rate)	Multiple sclerosis N=24 N (rate)	Myelitis N=46 N (rate)
0-17	-	6 (NA)	-	-
18-64	22 (.06)	113 (3.3)	20 (.05)	30 (.08)
65+	2 (.008)	38 (.2)	1 (.004)	8 (.03)
unknown	2 (NA)	18 (NA)	3 (NA)	8 (NA)

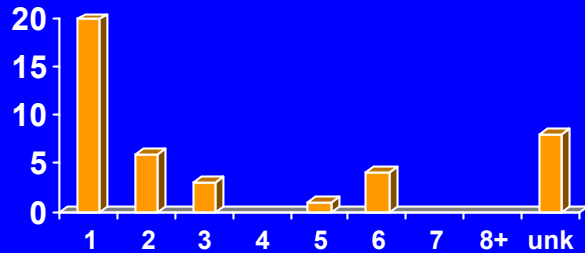
•Excluding GBS reports; COSTARTS codes are not mutually exclusive. # NHIS data reporting rate per million doses administered

GBS Reports following Influenza Vaccination by Onset-Interval

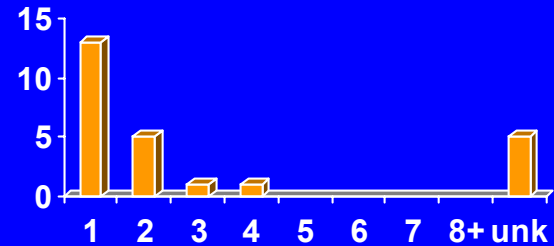


Neurological Adverse Events following Influenza Vaccine by Onset Week

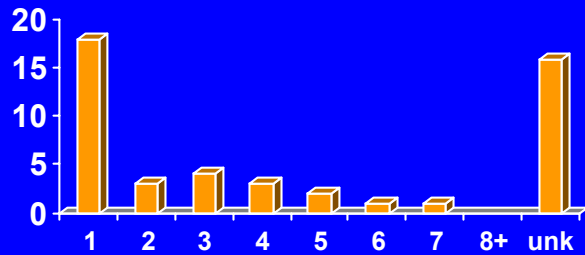
Encephalitis



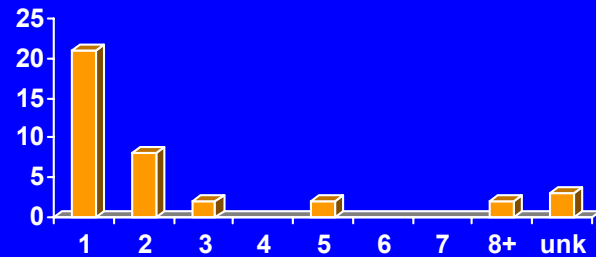
encephalopathy



Myelitis

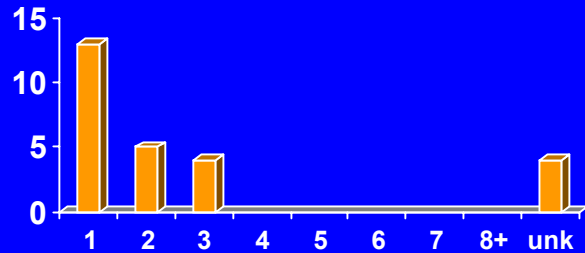


Neuritis

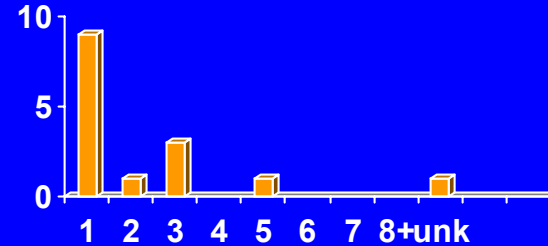


Neurological Adverse Events following Influenza Vaccine by Onset Week

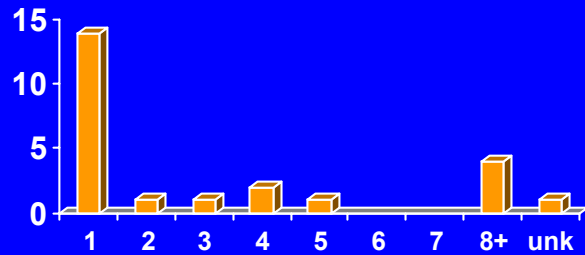
optic neuritis



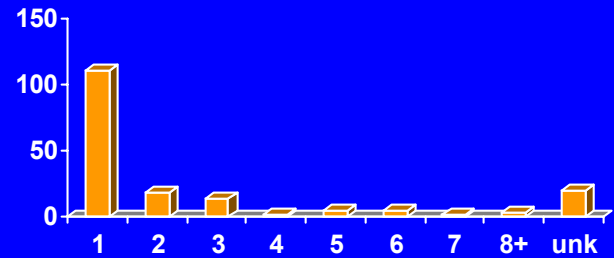
peripheral neuritis



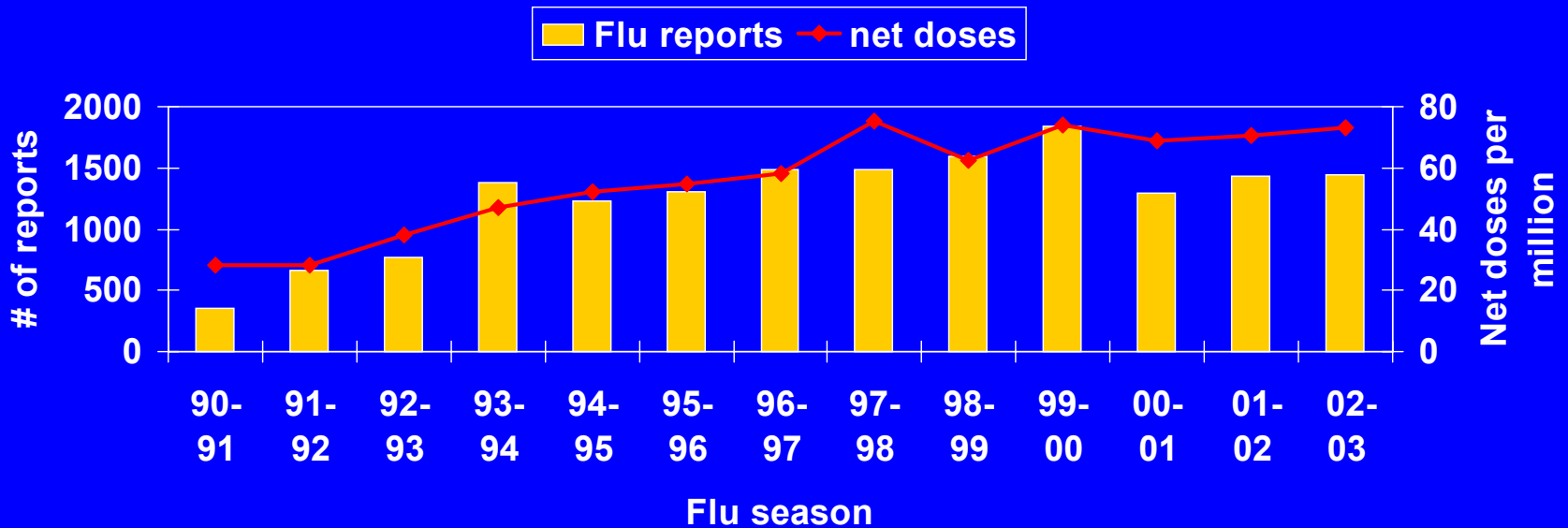
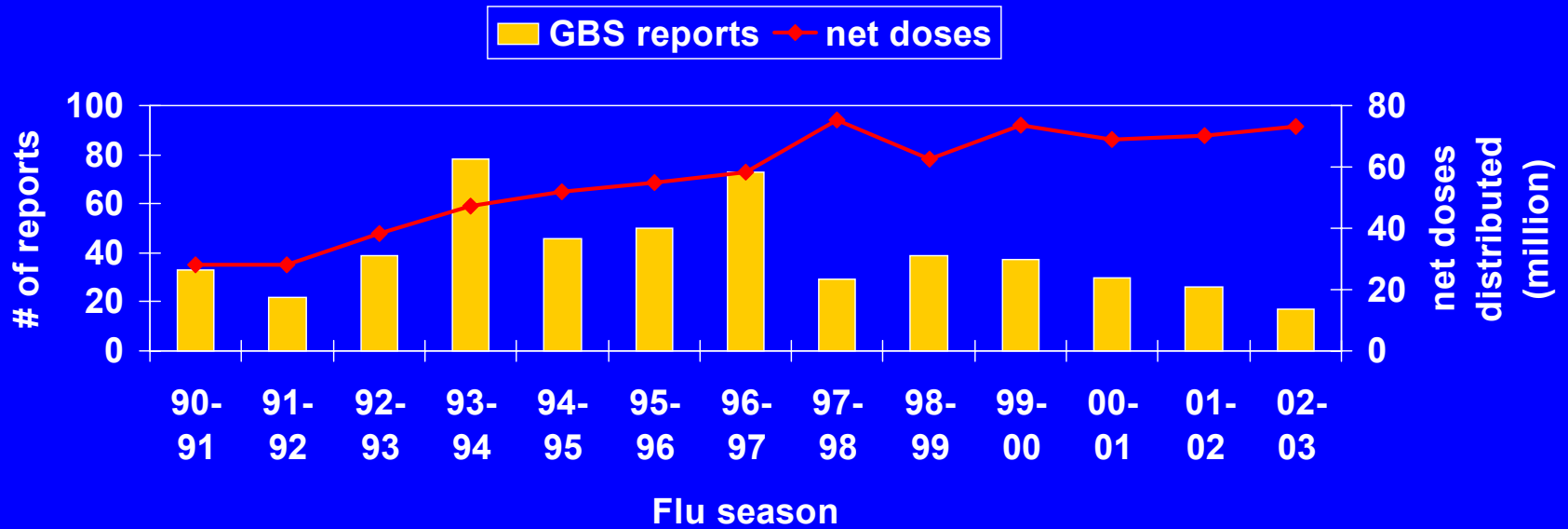
multiple sclerosis



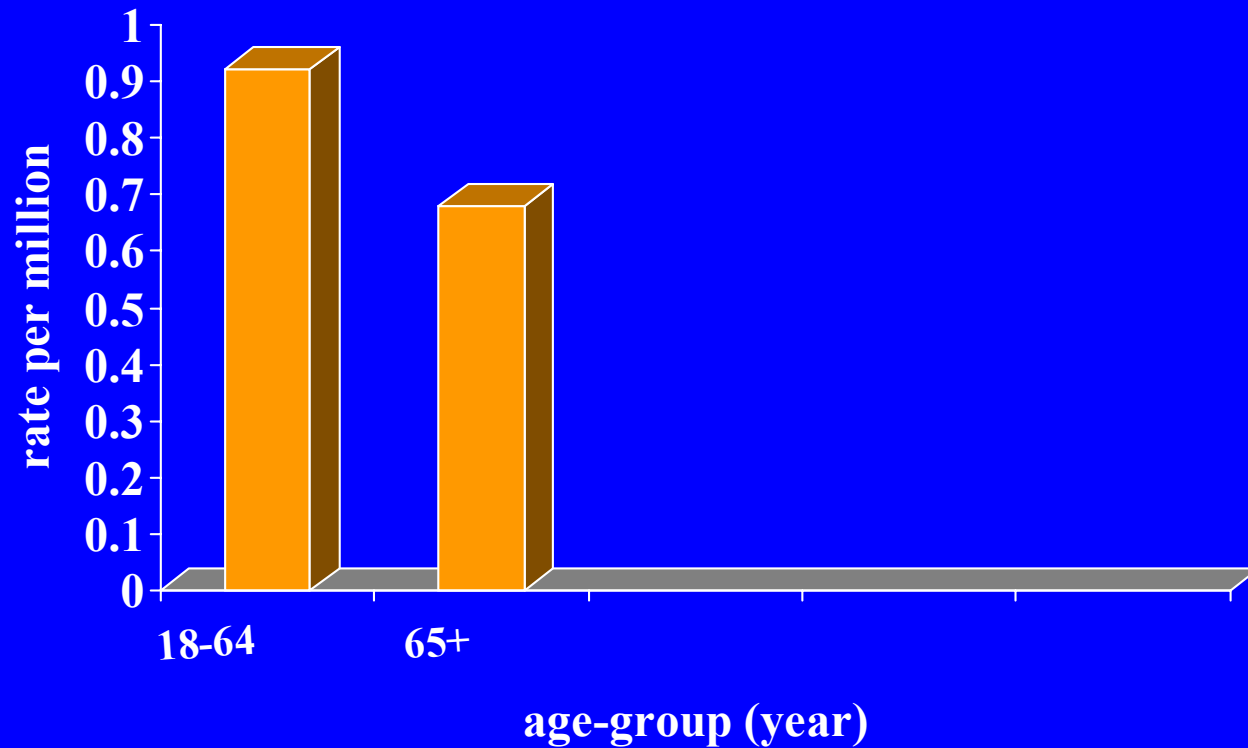
facial paralysis



GBS Reports Influenza Season



Reporting Rate of GBS followig Influenza Vaccination by Age -Group*



* Denominator data from NHIS survey ; data for age-group 0-17 old NA



RECEIVED FEB 27 1996

Centers for Disease Control and Prevention (CDC)
Atlanta GA 30333

REPORTED GUILLAIN-BARRE SYNDROME (GBS) FOLLOW-UP SURVEY

Please circle or enter the appropriate information.

1. Is the final diagnosis still Guillain-Barre Syndrome (GBS)? Yes No Unknown
2. Was the diagnosis of GBS made by a neurologist? Yes No Unknown
3. Did the patient experience any other illness within the four weeks before the onset of GBS symptoms? Yes No Unknown
- If yes, please describe Sinusitis, Laryngitis

4. Did the patient ever previously have GBS or a related illness? ^{CONGENITAL} ~~CMT~~ Yes No Unknown
5. Has the patient ever previously received influenza vaccination(s)? Yes No Unknown
6. Person providing verified final diagnosis (please print legibly):

Name/Title _____ Phone number (____) _____

Mailing Address _____

VACCINE ADVERSE EVENT REPORTING SYSTEM
PO Box 1100, Rockville, MD 20849-1100
24 Hour Toll-free Information 1-800-822-7967
Fax: 301-309-8495

PATIENT IDENTITY KEPT CONFIDENTIAL

**GBS following Influenza Vaccine : Active Follow-up
VAERS 7/1994- 6/2002**

Penina Haber

Results:	% verified
GBS diagnosis -yes	81%
Non-GBS	9%
Lost to F/U	10%
Prior GBS history	1%
Prior illness w 4 wks	18%
Prior flu vaccination	40%-yes, 43%-unk, 16%- no

Non-GBS Reports following Influenza Vaccine

- *Other diagnoses:*
 - Examples: Transverse myelitis, CIDP, chronic inflammatory demyelinating polyneuropathy, viral myelitis, brachial neuritis, sepsis, viral myelitis, sepsis, paralysis.
 - *Illness 4 weeks prior to vaccination:* asthma, pharyngitis, sinusitis, fever, chills, diarrhea, upper respirator infection, bronchitis, lung infection, surgery, gastritis, bronchitis, pneumonia.

Proportional Reporting Ratio (PRR) Definition

- PRR is the ratio of the proportion of reports of a particular adverse event for a given vaccine to the proportion of that adverse event following other vaccines
- Defined numerically as follows:

	Specific event	All other events
Vaccine of interest	a	b
All other vaccines	c	d

$$\text{PRR} = (a / (a+b)) / (c / (c+d))$$

PRR \geq 2 potential 'signal'

Proportional Reporting Ratio (PRR) of GBS following Influenza Vaccine By Age-Group

Age-group (year)	N	PRR
0-17	15	12.5
18-64	320	10.2
65+	163	6.6

Proportional Reporting Ratio (PRR) following Influenza Vaccine in Children 0-17 years

COSTART codes*	N	PRR
Paresthesia	22	3.9
Facial paralysis	6	3.3
Coma	5	3
Headache	61	2.5
Encephalopathy	5	2.4
Asthenia	39	2.2

•excluding GBS reports ; COSTART codes not mutually exclusive;
included PRR values of N=> 5

Proportional Reporting Ratio (PRR)

Following Influenza Vaccine in Adults 18-64 Years

COSTART codes*	N	PRR
Coma	15	2.9
Depressed CNS	11	2.6
Myelitis	43	2.5
Facial paralysis	101	2.3

* Excluding GBS reports ; COSTART codes not mutually exclusive ; including PRR values of N => 5

Proportional Reporting Ratio (PRR)

Following Influenza Vaccine in Adults 65+ years

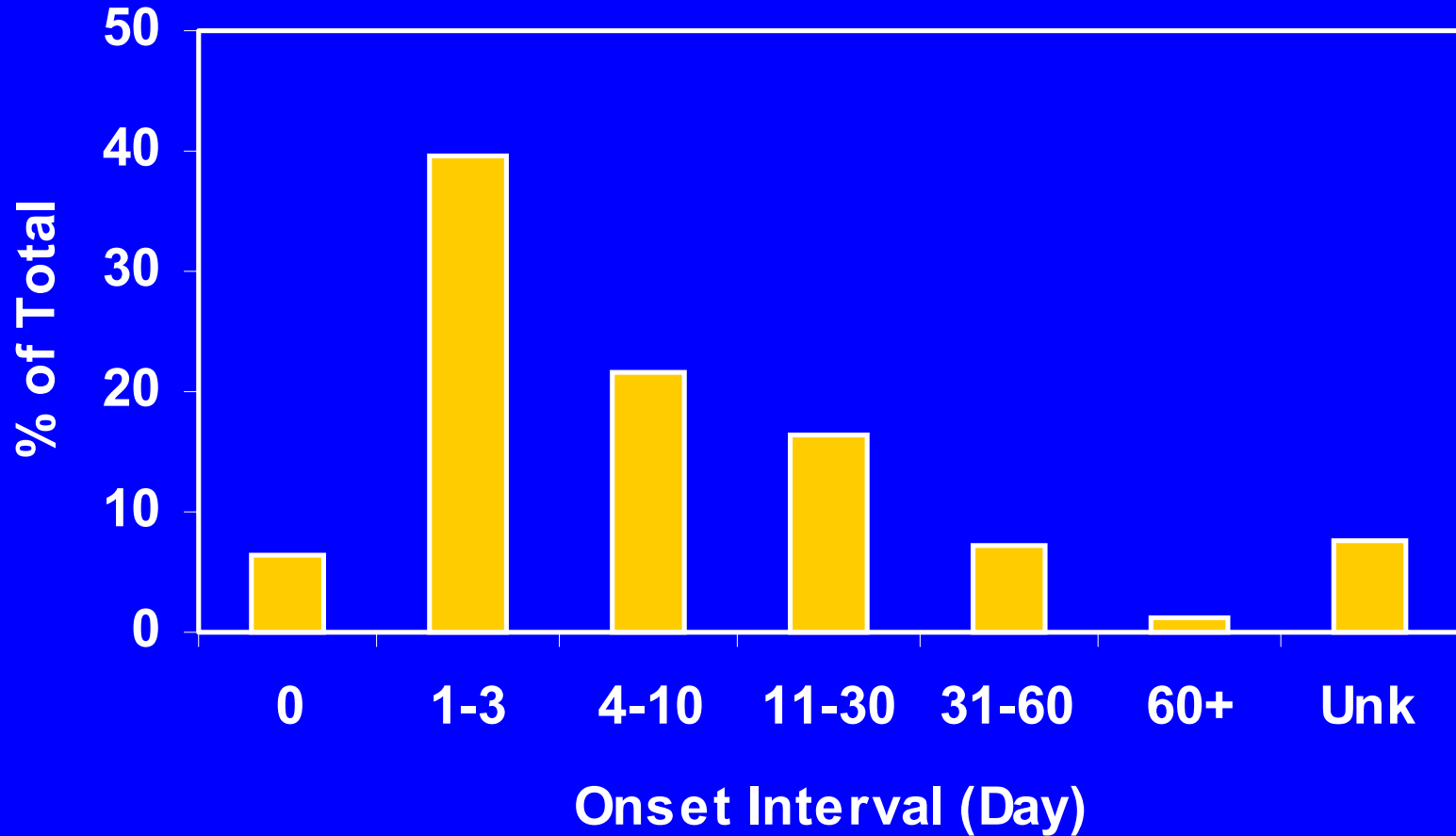
COSTART code*	N	PRR
Encephalitis	13	5.2
Facial paralysis	38	3.8
Speech Disorder	30	3.4
Dysphagia	25	3.3
Vertigo	24	3.2
Amblyopia	19	3
Myelitis	17	2.7
Somnolence	68	2.7

* excluding GBS reports ; COSTART codes not mutually exclusive;
including PRR values of N => 5

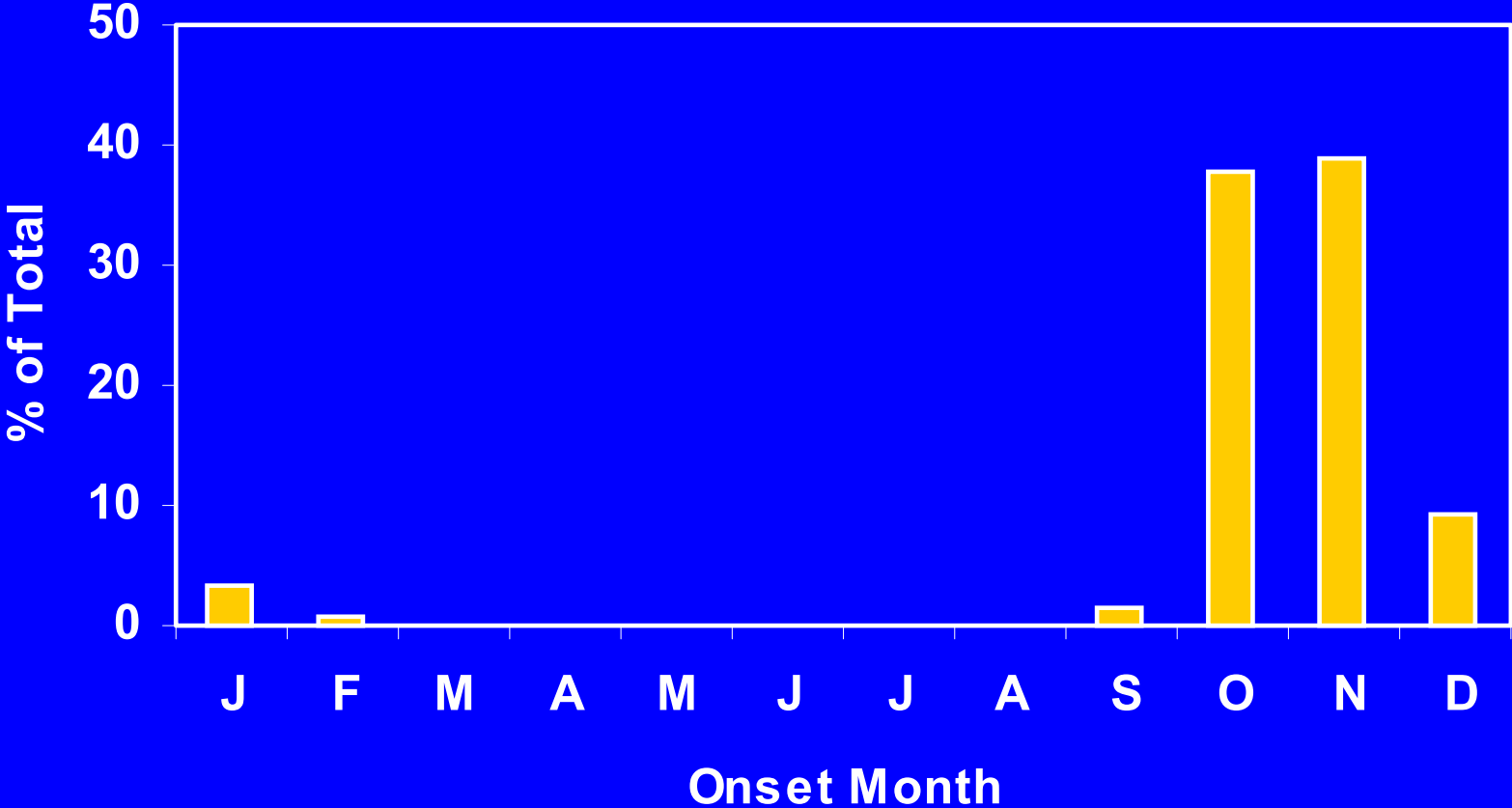
**Review of Bell's Palsy
VAERS 1/1991-12/2001
Weigong Zhou**

- COSTART term for “ Facial Paralysis”
- Combined with text string search of “ Bell's palsy”
- Total of 154 reports
- PRR =4 suggests Bell's palsy is a possible signal

Onset Interval of Bell's Palsy after Influenza Vaccines



Onset month of Bell's Palsy after Influenza Vaccines



Positive Re-challenge

- Same adverse event occurred previously after the same vaccine
- Positive re-challenge COSTART code added end of 1994
- Four GBS reports: 1994, 2000, 2001 & 2002
- Four reports of paresthesia, myasthenia and hypotonia
- One report of neuralgia
- The above five reports aggravated / severe following 2nd dose

Summary

- Influenza vaccine most common “ exposure” annually (70 millions N x 3 next vaccine >Hep B)
- Reporting rate for influenza vaccine to VAERS is low vs. all other vaccines
- Annual variation in GBS reports after flu vaccination
- Diagnoses verified in 81%
 - Non random distribution onset intervals
 - Prevalence antecedent illness: 18%
 - Several other neurological outcomes after flu vaccination have PRR =>2
 - Controlled studies needed to further assess causality

Acknowledgement

Weigong Zhou
Frank Destefano
James Singleton
Robert Chen

Thank You

Summary

GBS / Selected Neurological Outcomes

- 565 GBS reports after flu; 64% of all GBS reports to VAERS;
- Reporting rate of 0.76 per million flu doses sold < estimated risk of 1-2 per 1,000,000 flu vaccinations per year
- 94% following a single vaccine
- 23.8% of all serious flu reports
- 60% in 18-64 age-group – same as all flu reports
31% within 1 week post vaccination; 32% within 2 weeks

Summary of GBS Re-challenge Reports following Influenza Vaccine

- 1994/1995: Mfg. report. No confirm information in follow-up
- 2000/2001: HX of GBS per patient following flu shot in 1999; final DX not by a neurologist
- 2001/2002: prior GBS in 1995/1996; Vax in December 1995; 2nd GBS in 1999; same neurologist during both episodes
- 2002/2001: Pt. states GBS 12 years ago; no confirm data; no confirm data; story confirmed by aunt and brother

VAERS limitations

- Underreporting (severity, timing, publicity, etc.)
- Biased reporting (severity, timing publicity, etc.)
- Complexity>> traditional PH surveillance
 - Multiple “ exposures” + “ outcomes”
 - Detect “ new” + change “ known “ AE’s
 - Mix of causal and coincidental events
 - Inadequate report quality
 - Lack of denominator and control group
 - Generally unable to assess causality

Reporting Rates* by Influenza Season

Season	All Flu	GBS
1990-91	12.3	1.2
1991-92	23.6	0.8
1992-93	20.2	1.0
1993-94	29.4	1.7
1994-95	23.7	0.9
1995-96	23.7	0.9
1996-97	25.5	1.3
1997-98	19.7	0.4
1998-99	25.3	0.6
1999-2000	24.9	0.5
2000-2001	18.8	0.4
2001-2002	20.3	0.4
2002-2003	19.9	0.2

* Per million doses distributed

GBS Reports in VAERS

Vaccine	% total
Flu	65.6
Hep B	9.4
Flu+ PPV	3.0
MMR	2.7
Td	2.7
PPV	1.9
TTOX	1.3
MMR+ Td	0.7
Rubella	0.6
TYP	0.6