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Case-Control Studies in Infectious Diseases

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Case Control Studies in Infectious Disease Epidemiology

- May be very important in outbreaks of acute infectious disease to define:
 - Relationship of an infectious agent to a clinical syndrome
 - Important risk factors operative in infectious disease outbreaks
- Often must be done quickly during an acute infectious disease in order to control the epidemic
- Careful attention must be given to reliable measurement of relevant variables and selection of an appropriate control group



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Section A

Toxic Shock Syndrome (TSS)

Background — Toxic Shock Syndrome (TSS)

- A new illness reported in 1978 affecting 8–17-year-old children
- Multisystem illness with fever, hypotension or shock, vomiting/diarrhea, scarlet-fever-like rash
- Illness followed a staphylococcal infection—but no sepsis, blood cultures were negative
- Believed due to an *S. aureus* toxin called “toxic shock syndrome”

Background—Toxic Shock Syndrome (TSS)

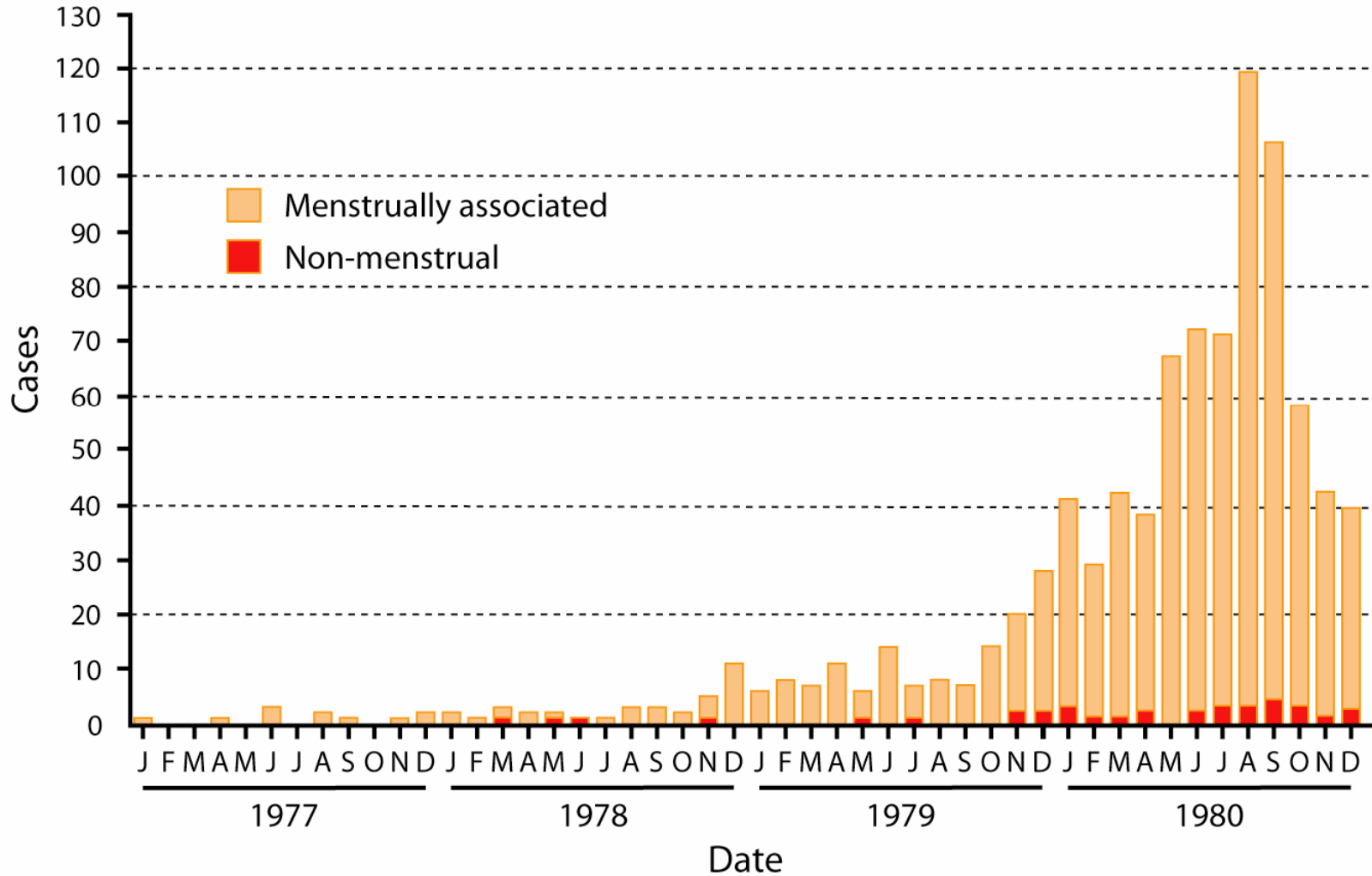
- January 1980
 - Epidemiologists in Wisconsin and Minnesota reported several cases of a similar illness to the TSS cases in children among young women
- Symptoms were shock, multisystem illness, and rash of sudden onset during menstrual period, without known cause

Toxic Shock Syndrome Case Definition (CDC)

1. Fever $\geq 102^{\circ}\text{F}$
2. Rash diffuse, macular, erythema
3. Desquamation (after 1–2 weeks)
4. Hypotension (Bp < 90 mm) or shock
5. Multisystem illness (GI, Renal, Hem, CNS)
6. Negative work-up for known causes

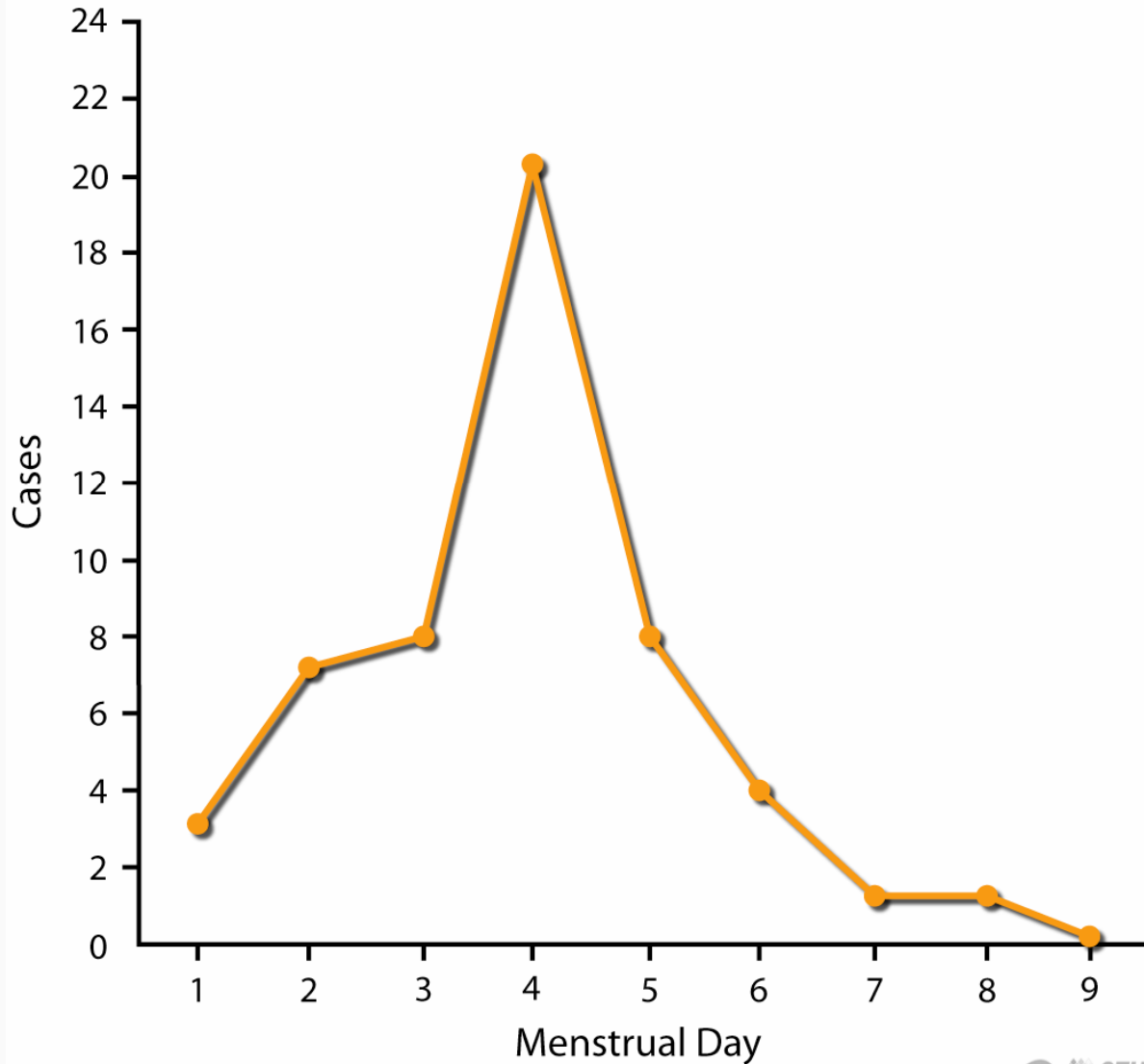
Reported Cases of Toxic Shock Syndrome, U.S. 1970–80

Reported Cases of Toxic-Shock Syndrome by Date of Onset, United States, January 1970 – December 1980



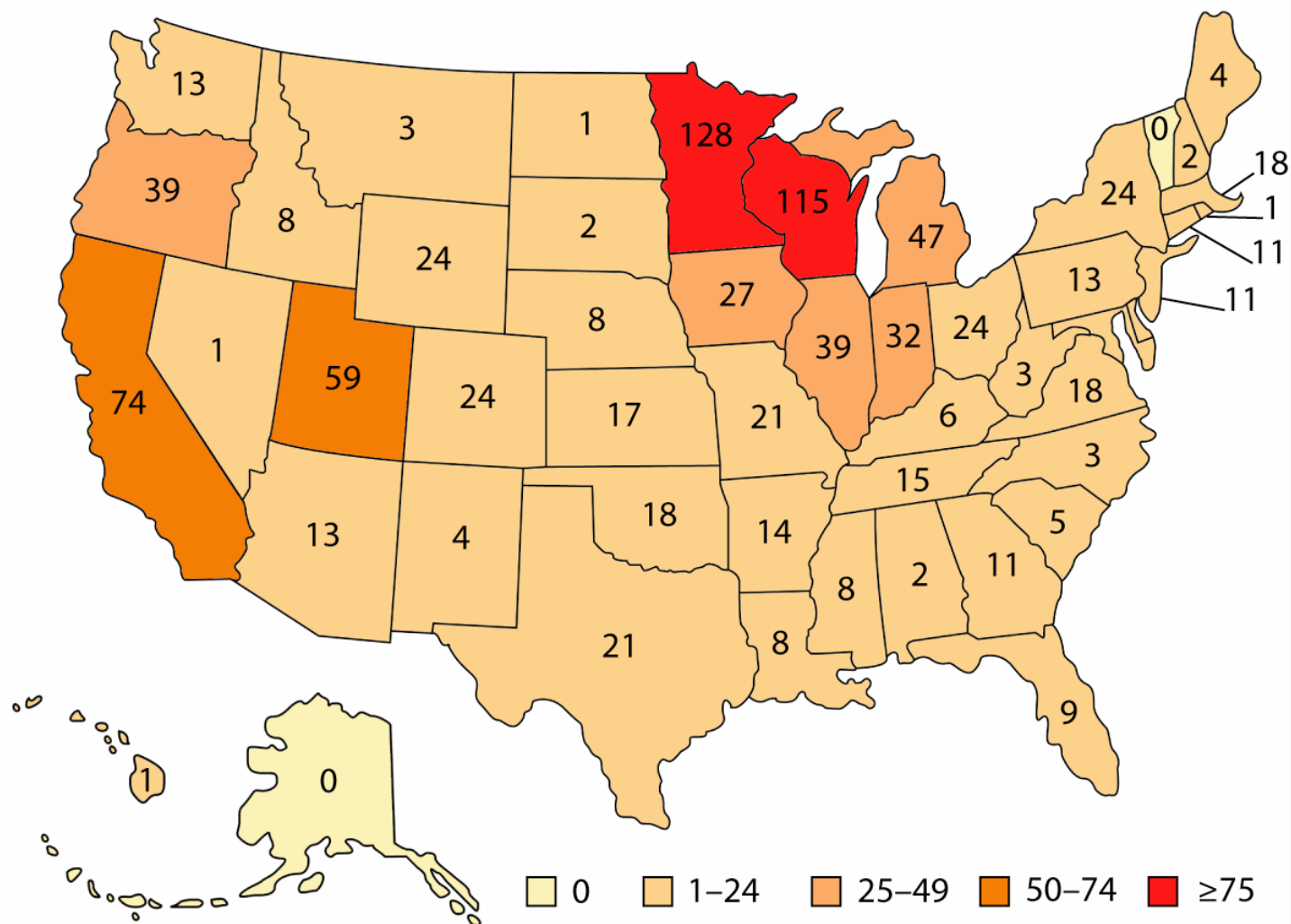
Toxic Shock Syndrome: Menstrual Cycle

Day of Menstrual Period on Which Clinical Illness Began
(Toxic-Shock Syndrome)



Reported Cases of Toxic Shock Syndrome, U.S., 1970–80

Distribution of Reported Cases of Toxic-Shock Syndrome,
United States, January 1970 – December 1980



Wisconsin Case-Control Study of Toxic Shock Syndrome

- Thirty-eight cases of toxic shock syndrome reported to Wisconsin State Health dept. before 30 June 1980
 - 37 cases were women and 35 cases occurred during menses
- Three controls per case (N = 105) were selected from a population of non-pregnant women presenting for routine gynecologic care to a clinic in Madison, Wisconsin, matched for age (± 2 years) to the case

Wisconsin Case-Control Study of Toxic Shock Syndrome

- Telephone interviews for marital status, duration and intensity of menstrual flow, patterns of tampon and napkin use, brand of tampon, use of contraceptives, sexual activity, evidence of vaginal infection
- Significant findings:
 - Use of contraceptives ($p < 0.001$)
 - Tampon use ($p < 0.01$)

First CDC Study of Toxic Shock Syndrome

- Fifty-two cases of toxic shock syndrome that met the CDC definition (fever, rash, hypotension, desquamation, multisystem involvement, and other specific rash-type illnesses excluded)
- All cases were menstruating women reported to CDC between January 25, 1980, and June 13, 1980
- One control was matched to each case: a female friend within three years of age and willing to be interviewed

First CDC Study of Toxic Shock Syndrome

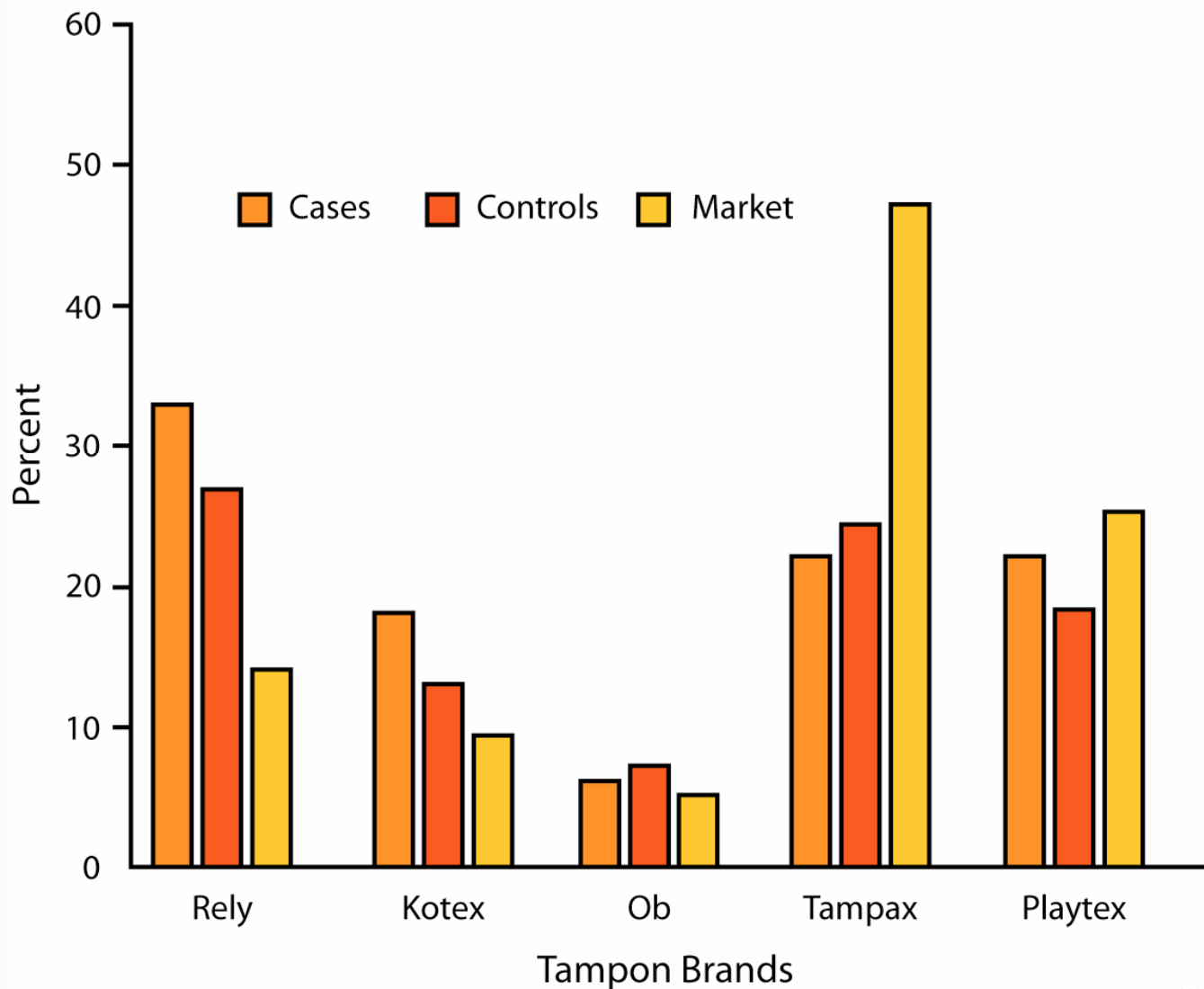
- Cases and controls asked about marital status, fecundity, contraceptive methods, frequency of sexual intercourse, intercourse during menstruation, use of tampons or sanitary napkins—type, brand, absorbency and continuity of use
- Cases questioned about index menses prior to illness, controls questioned about most recent menses
- Interviews done June 13–19, 1980

First CDC Study: Findings

1. Significant association with tampon use 100% (cases) vs. 85% (controls)
2. Significant continuous use of tampons, i.e., through day and night, among cases
3. No differences in cases and controls in amount or duration of menses
4. Significantly fewer cases (35%) than controls (47%) were contraceptive users
5. No association of toxic shock syndrome with any particular brand of tampon

Distribution of Tampon Brands

Distribution of Tampon Brands in the Centers for Disease Control Study I of June 1980 (Single Brand Users Only)



Second CDC Study: Findings

- Cases reported to CDC between July 1 and September 5, 1980, that met case definition of toxic shock syndrome occurring during menses and had not been included in another survey (N = 50)
- Three controls (friends of case) chosen for each case and matched for age (+/- 3) years (N = 150)
- Telephone interviews September 5–8, 1980
- All participants asked to check the tampon box and read label to investigator
- Significant association with:
 - Tampon use (cases = 100%, controls = 83%)
 - Use of Rely tampons (cases = 75%, controls = 26%)
- Rely tampons withdrawn from market on September 22, 1980

Tampon Distribution

Distribution of Tampon Brands Among Users of a Single Brand of Tampon*		
Brands	Patients ($n = 42$) %	Control Subjects ($n = 113$) %
Rely (Proctor & Gamble)	71	26
Playtex (Playtex International, Ltd.)	19	26
Tampax (Tampax)	5	26
Kotex (Kimberly-Clark)	2.5	11
o.b. (Johnson & Johnson)	2.5	11

* Centers for Disease Control Study II

Tampon Characteristics

- Before 1977, all tampon products were made of rayon or a blend of rayon and cotton
- Since 1977, 44% of tampon products, representing 65% of the estimated market, have contained more absorbent synthetic materials, including poly-acrylate fibers, carboxymethyl cellulose, high-absorbency rayon cellulose, and polyester foam (“super tampons,” e.g., Rely)
- Not sterile, but contained toxin-producing *S. aureus* on culture at CDC
- Very absorbent—can be left in place for longer periods
- More prone than rayon-cotton tampons to produce mucosal abrasions (and possible absorption of toxins)

Tampon Use in Case-Control Pairs

	Yes	No
Yes	44	0
Controls		
No	<u>8</u>	<u>0</u>
	52	0

OR = 8/0 (8/0.5 Approx) = 16, $p = < 0.02$

Tampon Use in Studies of Toxic Shock Syndrome

	Cases	Controls	OR
1. CDC #1: June 1980	52/52 (100%)	43/52 (85%)	20.1*
2. Wisconsin Health Department: 1980	34/35 (97%)	80/105 (76%)	7.3*
3. CDC #2: September 1980	50/50 (100%)	125/150 (83%)	21.5*
4. Utah: August 1980	29/29 (100%)	70/91 (77%)	18.0*
5. Tri-State: October–November 1980	75/76 (99%)	123/152 (81%)	12.0*
6. Oregon: January–March 1981	18/18 (100%)	14/18 (78%) 16/18 (89%)	11.5* 5.6*

*p < .05

Effect of Treatment with BLRA

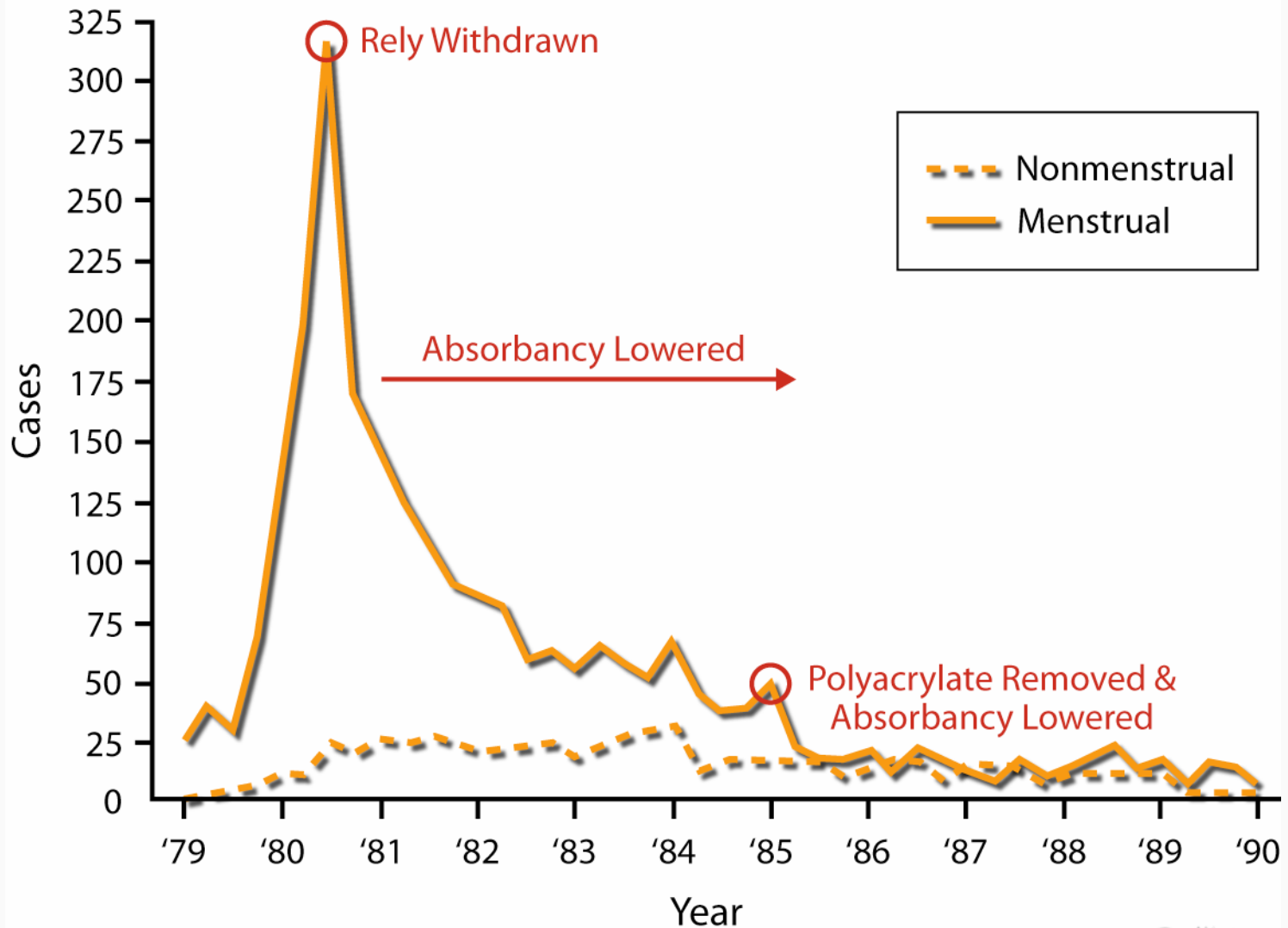
- Effect of treatment with beta-lactamase-resistant antibiotics (BLRA) during the initial episode of TSS on the rate of recurrence of TSS

Mos. after 1 st episode	Treated with BLRA		Not treated with BLRA		P Value*
	No. of patients	Cumulative No. with recurrences	No. of patients	Cumulative No. with recurrences	
1	19	0	13	8	0.0001
2	19	1	13	9	0.0002
3	16	1	13	9	0.0004

*All were statistically significant by Fisher's exact test.

Reported Cases of TSS by Quarter, U.S., 1979–1990

Reported Cases of Toxic-Shock Syndrome, United States
January 1, 1979 – March 31, 1990





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Section B

Reye's Syndrome (RS): Background

Reye's Syndrome Background

1. In 1963, Reye et al. described a syndrome of acute encephalopathy with fatty degeneration of the liver following a febrile illness
2. Patients had no inflammation of liver or brain. Cerebral edema was the main pathological finding.
3. Patients with RS had elevated transaminase with hypoglycemia

Reye's Syndrome Background

4. Patients became drowsy or comatose, clinically
5. RS resembled intoxication
6. In October 1963, outbreaks of RS following an Influenza B epidemic in North Carolina
7. Subsequently, outbreaks of RS frequently followed Influenza epidemics (1963–1981)

TABLE 1

Epidemiologic case definition of Reye's syndrome, Centers for Disease Control, Atlanta, Georgia, 1980*

1. Acute noninflammatory encephalopathy with
 - Microvesicular fatty metamorphosis of the liver confirmed by biopsy or autopsy, or
 - A serum glutamic oxaloacetic transaminase (SGOT), a serum glutamic pyruvic transaminase (SGPT), or a serum ammonia (NH_3) greater than three times normal.
2. If cerebrospinal fluid is obtained, it must have <8 leukocytes/ mm^3
3. In addition, there should be no other more reasonable explanation for the neurologic or hepatic abnormalities

* Source: Reference 70.

TABLE 6

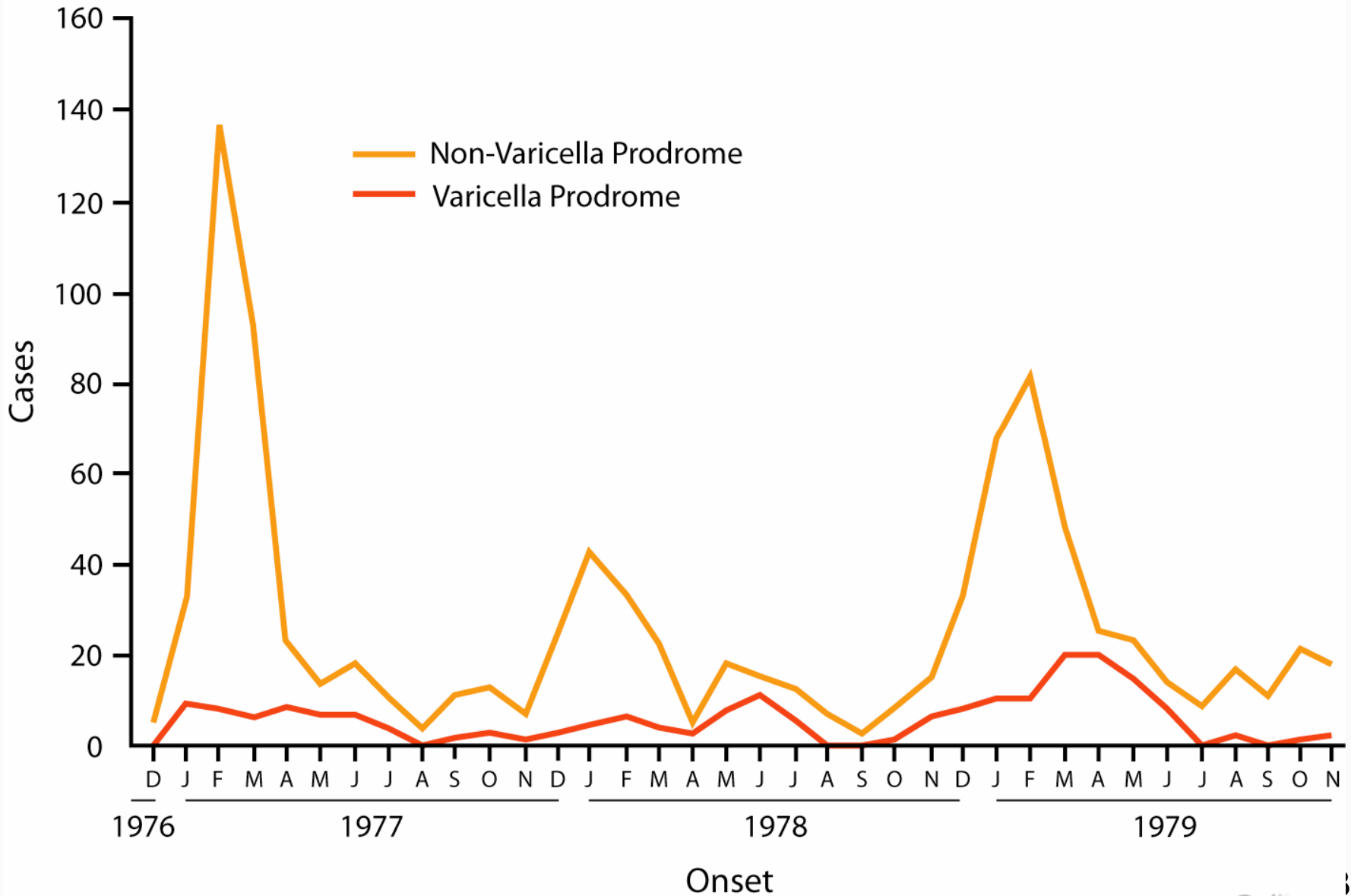
Toxins and medications suspected of being associated with Reye's syndrome-like illnesses

Agent	Reference no.
Aflatoxins	31, 67, 69, 75, 80, 113–118
Endotoxin	124
Hypoglycin	2
Insecticides and insecticide-related chemicals	75, 119-121
Isopropyl alcohol	104
Antiemetics	19, 30, 58
Pteridine	125
Salicylates	19, 58, 129–132
Valproic acid	126, 127
Warfarin	128

CDC RS Table: Viruses Associated with RS

Virus	Type	Reference no.
Adenovirus	2,3	139, 58
Coxsackie A	9, 10, untyped	47, 58, 113
Coxsackie B	1, 4, 5	3, 47, 140
Cytomegalovirus		29, 89
Dengue	1	90
Echo	8, 11	3, 141
Epstein-Barr		142
Herpes simplex	Untyped	69, 140
Influenza	A, B	3, 29, 30, 43, 52, 53, 55-58, 70, 87, 93, 94, 99, 139, 144, 152-160
Mumps		36, 58
Parainfluenza	1, 2, 3, 4A	36, 58, 143, 144
Poliomyelitis	1, vaccine-like, untyped	145, 146
Reovirus	1, 2, 3	113, 147
Respiratory syncytial		139, 144, 148
Rotavirus		149
Rubella	Vaccine	42
Rubeola	Wild, vaccine	42, 146, 150, 151
Vaccinia		30, 36, 58
Varicella-zoster		30, 43, 52, 53

Epidemiology of Reye Syndrome



CDC RS Table: Reported Cases of RS, U.S., 1967-80

Year	No. of reported cases/100,000 persons
1967	11
1968	17
1969	41
1970	13
1971	83
1972	30
1973	32
1974	379†
1975	‡
1976	‡
1977	454§
1978	240
1979	389
1980	443*

Sources: CDC. Unpublished data. Atlanta, GA, 1980, and references 30, 52, 53.

† December 15, 1973, to June 30, 1974

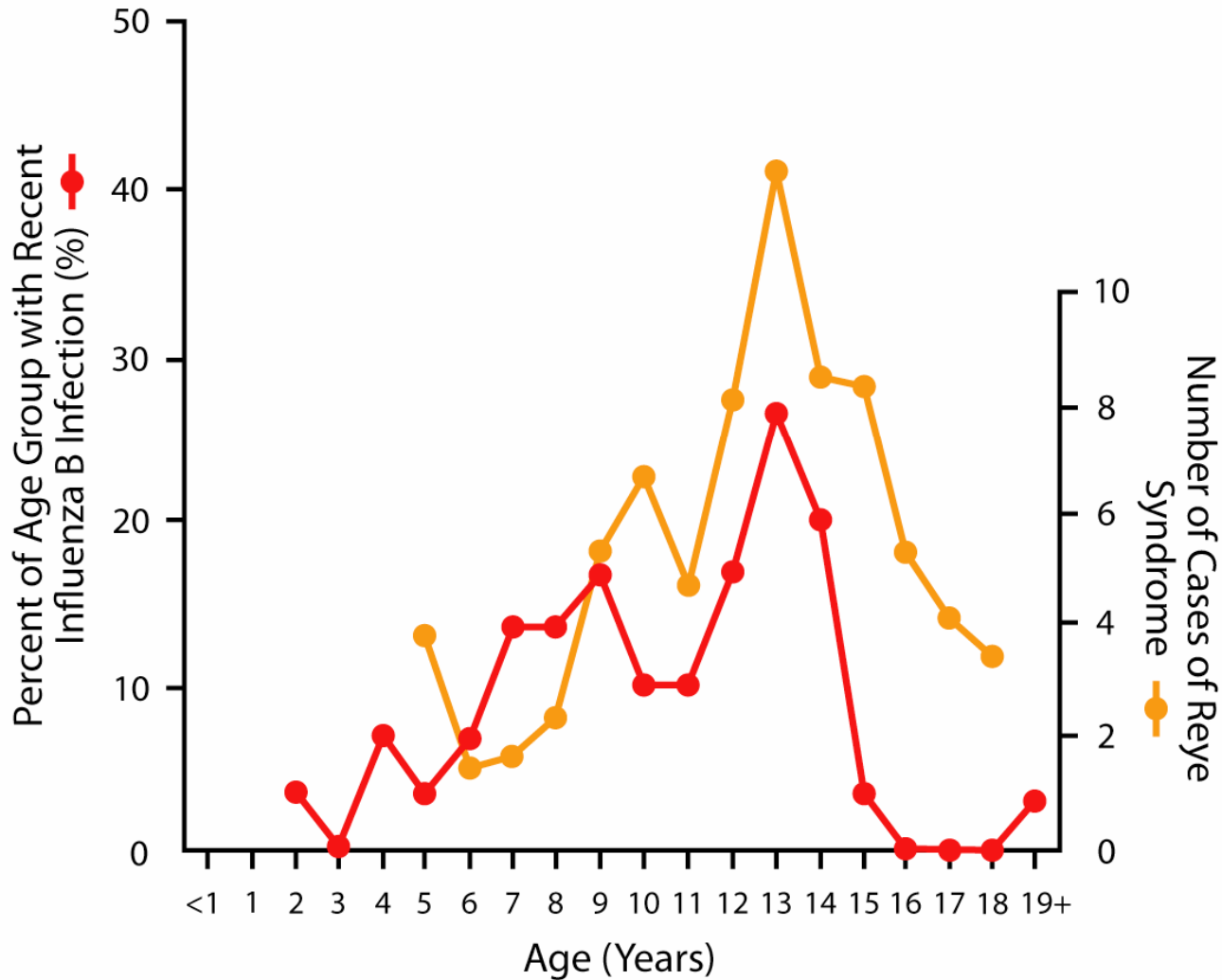
‡ Data unavailable

§ December 1976 to November 1977: dates for all subsequent 12-month periods are similar.

* Through August 31, 1980

Age Association

Incidence of Influenza B and Influenza B-Associated Reye Syndrome, by Age
Michigan, January 1–June 30, 1974



Clinical Stages of RS

■ In the National Reye's Syndrome Surveillance System

Stage	Characteristics
0	Alert, wakeful
1	Difficult to arouse, lethargic, sleepy
2	Delirious, combative, with purposeful or semipurposeful motor responses
3	Unarousable, with predominantly flexor motor responses, decorticate
4	Unarousable, with predominantly extensor motor responses, decerebrate
5	Unarousable, with flaccid paralysis, reflexes, and pupils unresponsive
6	Treated with curare or equivalent drug, and therefore, unclassifiable



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Section C

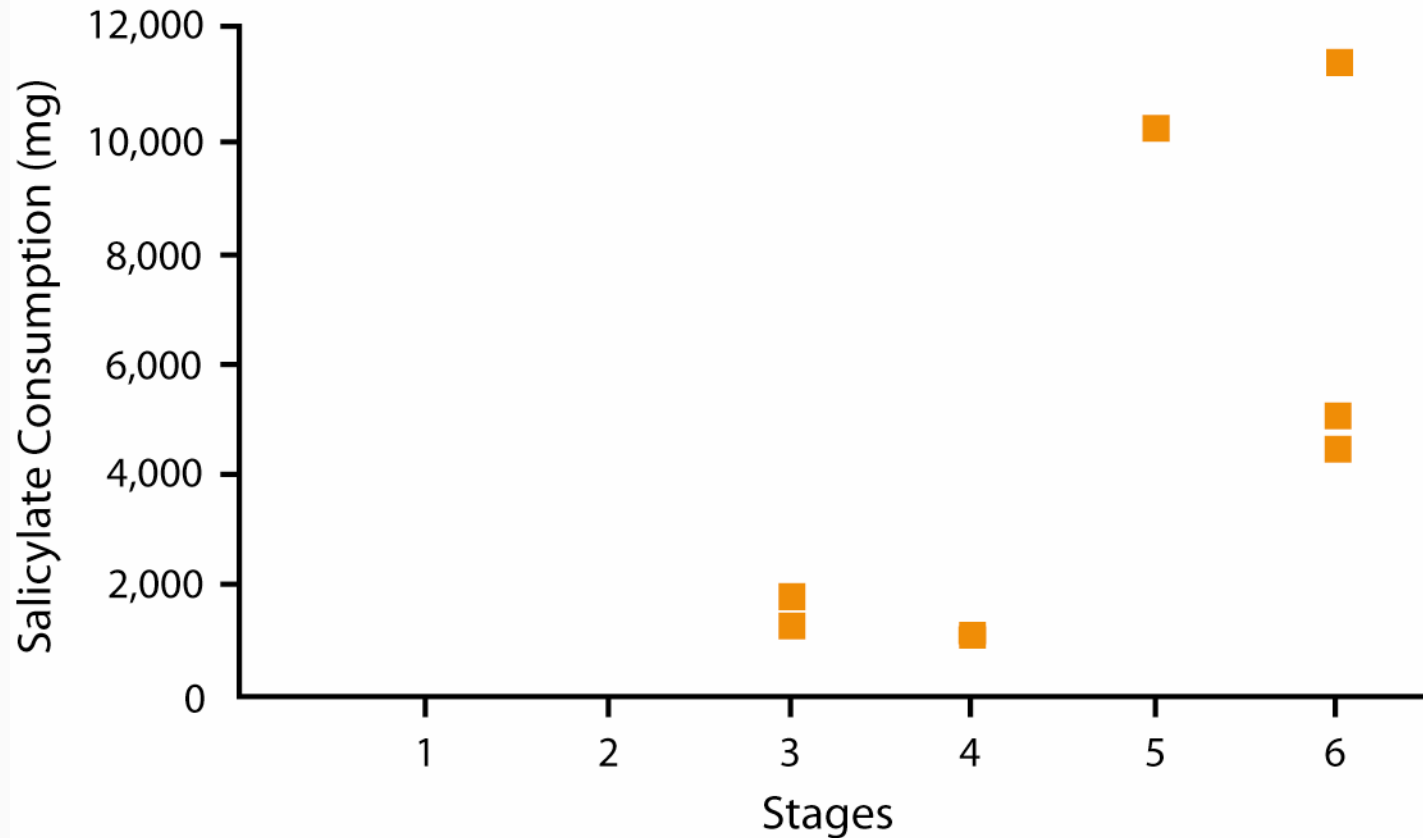
Case-Controlled Studies of Reye's Syndrome

Arizona Study, 1978

- During an outbreak of Influenza A in Arizona in 1978, seven children developed RS
- School absenteeism 25–52%
- Cases of RS matched with 16 controls of same age and same schools who had also been infected with Influenza A during epidemic but had no evidence of RS
- All seven cases and 8 of 16 (50%) controls took salicylates prior to onset of RS
- There was a dose relationship between salicylates and severity of RS

Stages of Reye's Syndrome

Salicylate Consumption by Children with Reye's Syndrome, Related to Stage of Reye's Syndrome at Most Severe Point



Adapted by CTLT from PEDIATRICS Vol. 102 No. 1 Supplement July 1998, pp. 259-262



Sources of Bias

1. Selection bias

- Physicians might be more likely to report RS if aspirin was used to treat influenza and encephalopathy ensued because of publicity concerning this association

2. Confounding bias

- Aspirin might be more likely to be used if influenza illness was more severe, e.g., high fever, more myalgia, headaches, etc.

3. Observational bias

- A child or parent would be more likely to remember aspirin use if encephalopathy ensued

Ohio Study, 1978–1980

- Ninety-seven cases of RS in Ohio with onsets from December 1978–March 1980 matched with 156 controls; matched for age, same school, similar type of precipitating febrile illness to the case of RS
- Aspirin was used by 97% of cases and 78% of controls; 16% of cases and 33% of controls had received acetaminophen

Cases and Controls

Ten Medication Components Most Frequently Used by Study Subjects,* Ohio, December 1978 through March 1980

Medication	Cases, % (n = 97)	Controls, % (n = 156)
Aspirin	97	71
Alcohol	42	43
Vitamins	35	35
Acetaminophen	16	33
Phenothiazines	21†	4
Phenylpropanolamine hydrochloride	25	28
Guaifenesin	28	27
Dextromethorphan hydrobromide	16	22
Miscellaneous adsorbents	20	19
Chlorpheniramine meleate	18	20

* For cases, includes period from onset of antecedent illness until hospitalization for RS

† During the second study period, 12 (19%) of 64 cases received phenothiazines, but only 8% did so before onset of RS (severe vomiting)

RS Symptoms Ohio, December 1978 to March 1980

- Match-pair multiple logistic model

Variable	Of	<u>Unadjusted</u>		<u>Adjusted</u>	
		X ²	P	X ²	P
Headache	1	0.08	NS	0.52	NS
Sore throat	1	1.62	NS	1.48	NS
Fever	1	8.60	<.01	5.44	<.06
Aspirin	1	30.18	<.001	27.00	<.001
Full model	4			37.20	<.001

Aspirin	Lower Bounds	Estimate of Relative Risk	Upper Bounds
Unadjusted	2.87	11.69	47.01
Adjusted	2.73	11.50	68.48

RS: Aspirin Use by Highest Level of Fever

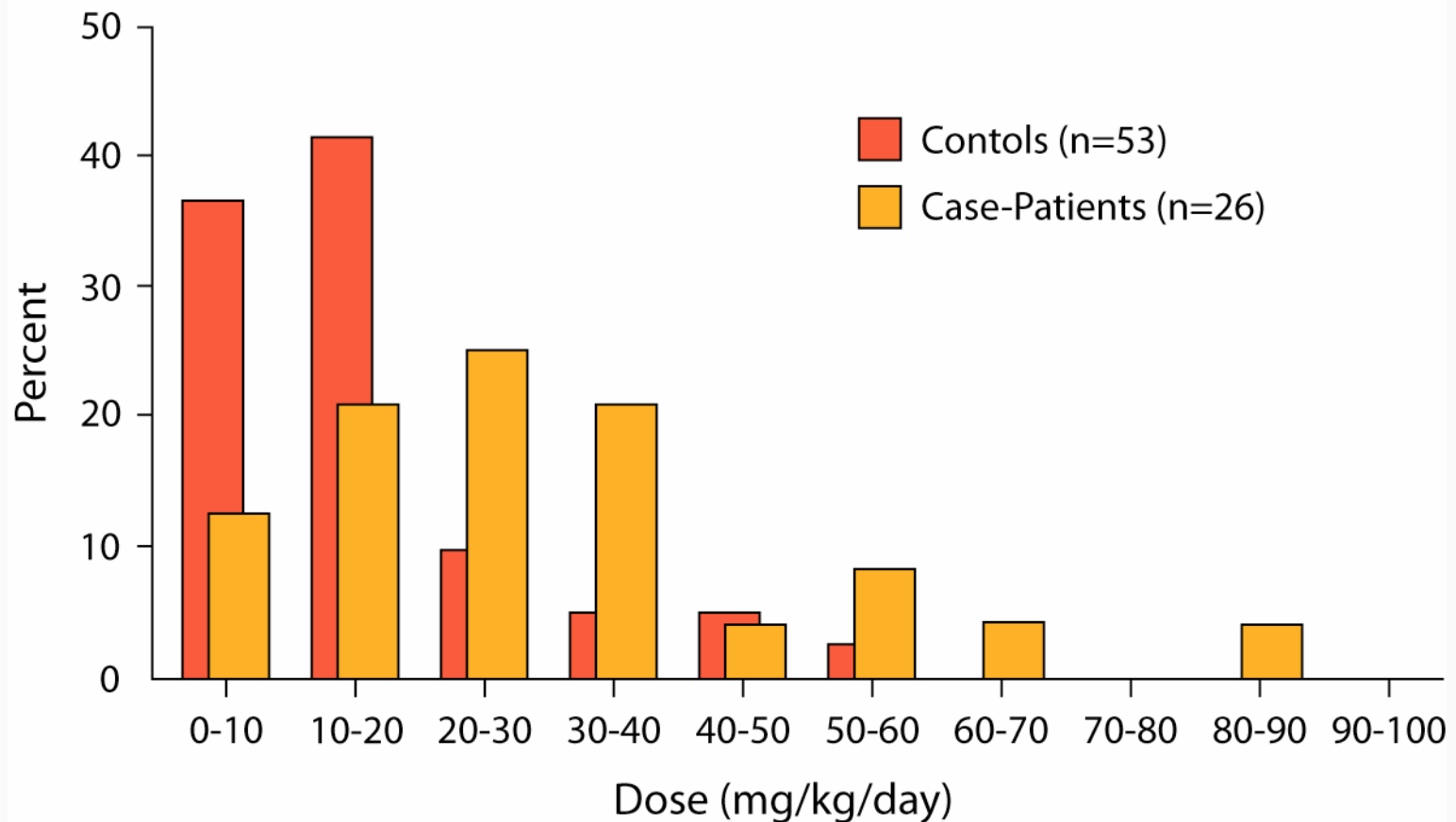
■ Reported 1978–1980, Ohio

Highest Temp °C (°F)	<u>Cases</u>	<u>Controls</u>
None	21/23 (91%)	39/61 (64%)
Unknown temp	10/11 (91%)	13/19 (68%)
37.1 – 37.7–99.9	4/4 (100%)	4/6 (67%)
37.8 – 38.8 (100.0-101.9)	18/18 (100%)	21/28 (75%)
>38.9 (\geq 102.0)	41/41 (100%)	33/44 (75%)
Total	94/97 (97%)	110/156 (71%)

Michigan Study, 1979–80, 1980–81

- In 1979–80, 25 cases of RS were matched with 46 controls by age (+/- 1 yr.), race, school, and presence of similar viral illness
 - Aspirin = cases, 24/25 (95%)
 - ▶ Controls, 30/48 (65%) $p < .005$
 - Acetaminophen = cases 1/24 (4%)
 - ▶ Controls 16/46 (34%) $p < .005$
- In 1980–81, 12 cases of RS were matched to 29 controls for ages, nature of antecedent viral illness, school, and maximum temperature elevation
 - Aspirin = cases, 12/12 (100%)
 - ▶ Controls 13/29 (45%)
 - Acetaminophen = cases 0/12 (0%)
 - ▶ Controls 16/29 (55%)

Doses of Salicylates Administered to Case-Patients and Controls



Aspirin and Acetaminophen Use and RS (Matched)

Aspirin and Acetaminophen Use by RS Cases and Matched Controls, Michigan, 1980 and 1980-81				
	Cases, No. (%)	Controls, No. (%)	χ^2^*	P†
As antipyretic				
Aspirin, all subjects, 1980	24/25 (96)	30/46 (85%)	10.24	<.002
Aspirin, controls matched to cases ± 0.6 °C, 1980	14/14 (100)	12/19 (63)	6.25	<.02
Acetaminophen, all subjects, 1980	0/25 (4)	16/46 (34)	8.41	<.006
Acetaminophen, controls matched to cases, ± 0.6 °C, 1980	0/14 (0)	3/19 (15)	2.89	>.06
For any purpose				
Aspirin, all subjects, 1980	24/25 (96)	34/46 (73)	6.76	<.01
Aspirin, controls matched to cases, ± 0.6 °C, 1980	14/14 (100)	14/19 (73)	4.41	<.06
Aspirin, all subjects, 1980-81	12/12 (100)	13/29 (45)	9.89	<.002
Acetaminophen, all subjects, 1980	4/25 (16)	19/46 (41)	4.0	<.06
Acetaminophen, controls matched to cases, ± 0.6 °C, 1980	1/14 (7)	6/19 (31)	2.25	>.06
Acetaminophen, all subjects, 1980-81	0/12 (0)	16/29 (55)	9.0	<.006

* χ^2 indicates Mantel-Haenszel χ^2 method

†Mantel-Haenszel χ^2

Aspirin and Acetaminophen Use and RS (Unmatched)

Unmatched Characteristics, RS Cases and Controls, Michigan, 1980 and 1980–81

	1980		1980–1981	
	Cases (n = 25)	Controls (n = 46)	Cases (n = 12)	Controls (n = 28)
Mean duration, days of viral illness (range)	5.7 (3-11)	5.8 (2-15)	4.8 (37)	5.3 (2-10)
Mean age of parents, yr (range)	35.5 (24-?)	35.6 (24-56)	37.4 (29-47)	35.8 (23-50)
Mean No. of medications received during viral illness	4.0 (109)	3.7 (0-13)	3.8 (3.6)	4.0 (0-9)
Mean peak reported temperature, °C (range)	(37.0-40.6)	(37.0-40.0)	(37.0-38.9)	(37.0-39.2)

Antecedent Respiratory Illnesses Table

Symptoms and Associated Actions Reported During Antecedent Respiratory Illnesses for 25 Case-Patients and 135 Matched Controls

Symptom or Action	Case-Patients (n = 25)	Controls				Total (n = 135)
		Emergency Room (n=29)	Inpatient (n = 22)	School (n = 41)	Community (n = 43)	
Duration (mean days)	4.9	10.2	10.7	8.9	9.4	9.6
Overall severity score (mean)*	1.5	1.6	1.8	1.7	1.6	1.7
Fever score (mean)*	1.8	1.9	2.1	1.9	1.9	1.9
Mean peak temperature, °C†	36.2	38.4	38.7	36.4	38.4	38.4
Fever‡	64 (2.5)	79 (3.70)	68 (3.20)	88 (3.97)	72 (3.29)	78 (3.59)
Cough ‡	7 (4.16)	97 (6.71)	82 (6.72)	93 (6.66)	91 (6.92)	91 (6.77)
Headache ‡	56 (2.79)	48 (3.36)	55 (3.06)	83 (3.62)	74 (3.31)	68 (3.41)
Muscle aches ‡	24 (3.17)	31 (4.00)	41 (4.89)	37 (3.20)	42 (3.67)	38 (3.79)
Sore throat ‡	64 (2.88)	62 (6.39)	59 (3.54)	76 (4.55)	72 (3.74)	69 (4.49)
Absent from school/in bed	80 (3.35)	93 (3.69)	82 (3.50)	95 (3.97)	77 (4.18)	87 (3.94)
Consulted/saw health care provider ‡	44	66	55	49	40	50

*Based on main care provider's report of none (=0), mild (=1), moderate (=2), or severe (=3); † Included only if fever was indicated and measured (13 case-patients, 18 emergency room controls, 13 inpatient controls, 29 school controls, and 22 community controls; ‡ Values are percentages of patients: mean number of days of duration among patients reported to have these symptoms or actions are shown in parentheses

Antecedent Respiratory or Chickenpox Table

Generic Components of Medications Administered to 20% or More of Study Subjects During Antecedent Respiratory or Chickenpox Illnesses

Generic Component	Case-Patients (n = 27)	Controls Exposed, %					Total (n = 140)
		Emergency Room (n=30)	Inpatient (n = 22)	School (n = 45)	Community (n = 43)		
Acetaminophen	29.6	90.0	77.3	91.1	81.4	85.7	
Alcohol	44.4	53.3	50.0	46.7	72.1	56.4	
Amoxicillin	7.4	20.0	0.0	4.4	11.6	9.3	
Caffeine	22.2	6.7	4.5	2.2	14.0	7.1	
Camphor	14.8	10.0	9.1	13.3	20.9	14.3	
Chlorpheniramine maleate	22.2	23.3	22.7	20.0	37.2	26.4	
Dextromethorphan hydrobromide	29.6	36.7	22.7	33.3	60.5	40.7	
Eucalyptus oil	29.6	13.3	13.6	28.9	27.9	22.9	
Guaifenesin	22.2	43.3	36.4	31.1	34.9	35.7	
Menthol	40.7	26.7	13.6	33.3	39.5	30.7	
Phenol	11.1	16.7	4.5	8.9	20.9	13.6	
Phenylephrine hydrochloride	14.8	6.7	22.7	20.0	20.9	17.9	
Phenylpropanolamine hydrochloride	18.5	40.0	36.4	33.3	44.2	38.6	
Pseudoephedrine hydrochloride	29.6	16.7	31.8	26.7	48.8	32.1	
Salicylates*	96.3	40.0	27.3	44.4	34.9	37.9	

*Salicylates include biemuth subsalicylate, magnesium salicylate, and acetylsalicylates; the only salicylate exposure for one case and 11 controls was to biemuth subsalicylate, and for two additional controls the only exposure was to magnesium salicylate.

Salicylates and Acetaminophen Table

Odds Ratios for Exposure to Salicylates and Acetaminophen of 27 Case-Patients vs. 140 Controls*

		Controls			
	Emergency Room	Inpatient	School	Community	Total
Salicylates	(4.9)† 39	(7.8) 66	(4.4) 33	(5.9) 44	(5.8) 40
Acetaminophen	0.04 (0.18)‡	0.13 (0.51)	0.04 (0.16)	0.06 (0.30)	0.06 (0.18)

*Odds ratios are based on matched set analyses and are not adjusted for differences in the severity of the antecedent illness.

† Lower 95% confidence limit

‡ Upper 95% confidence limit

1. Arizona, 1978, Influenza A outbreak
 - 7.7 RS cases and 8/16 ill controls used salicylates (p<.05)
2. Michigan, 1979-80, Influenza B outbreak
 - 83 cases of RS
 - 24/25 cases and 30/46 controls used salicylates (p < .05)
3. Michigan, 1980-81, Influenza A outbreak
 - 18 cases of RS
 - 12/12 RS cases and 12/29 controls used salicylates (p <.05)

4. Ohio, 1978–80, Influenza outbreaks
 - 97 cases of RS
 - 97% of cases and 71% of controls used salicylates (p < .01)
5. CDC Nationwide Study, January 1985–May 1986
 - 27 cases of RS, matched for age, race, and type and timing of antecedent illness
 - 97% of cases and 35% of controls had used salicylates (odds ratio = 40, lower 95% CI = 5.8)

Influenza and RS Table

Predominant influenza strains, reported cases of RS and varicella-associated RS, RS incidence, and RS fatality rate—U.S., 1974 and 1977-88*

RS Cases

Year†	Predominant influenza strains Jan-May	Total	Varicella-associated	Incidence of RS§	Case-fatality rate (%)
1974	B	379	--	0/6	41
1977	B	454	73	0.7	42
1978	A(H3N2)	236	69	0/4	29
1979	A(J1N1)	389	113	0.6	32
1980	B	555	103	0.9	23
1981	A(H3N2)	297	77	0.5	30
1982	B	213	45	0.5	35
1983	A(H3N2)	198	28	0.3	31
1984	A(H1N1)+B	204	26	0.3	26
1985	A(H3N2)	93	15	0.2	31
1986	B	101	5	0.2	27
1987	A(H1N1)	36	7	0.1	29
1988	A(H3N2)	20	4	0.0	30

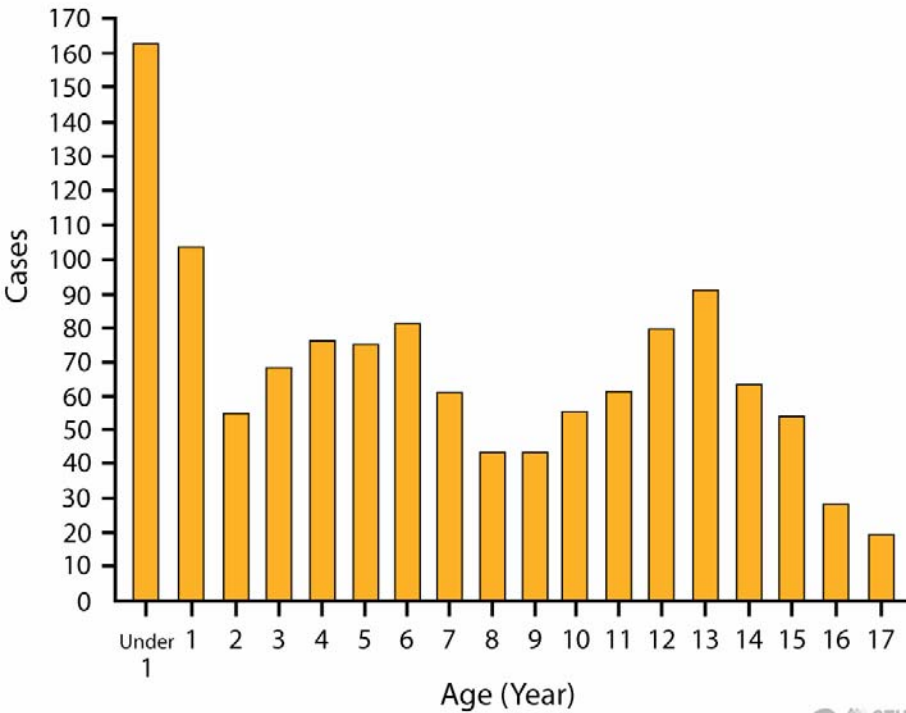
*Continuous RS surveillance began in December 1976. Data for 1988 are provisional.

† RS reporting year begins December 1 of previous year

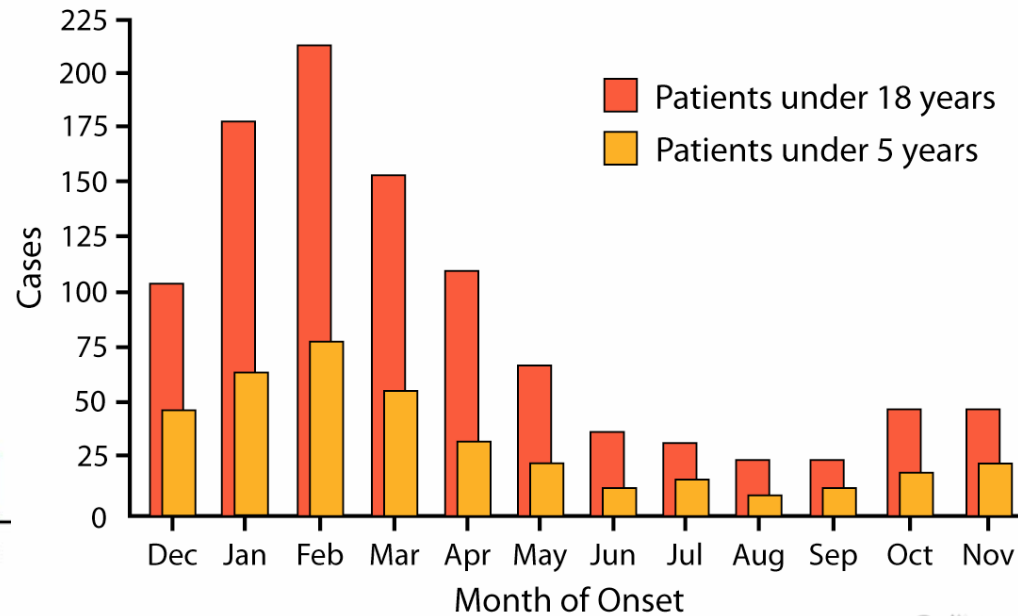
§ Per 100,000 U.S. population <18 years of age (U.S. Bureau of the Census data)

By Age at Onset and by Season

Number of Reported Cases of Reye's Syndrome According to Age at Onset, December 1981– November 1997



Seasonal Variation in Reported Cases of Reye's Syndrome December 1980 – November 1997



Reye's Syndrome in the United States from 1981 through 1997

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Background: Reye's syndrome is characterized by encephalopathy and fatty degeneration of the liver, usually after influenza or varicella. Beginning in 1980, warnings were issued about the use of salicylates in children with those viral infections because of the risk of Reye's syndrome.

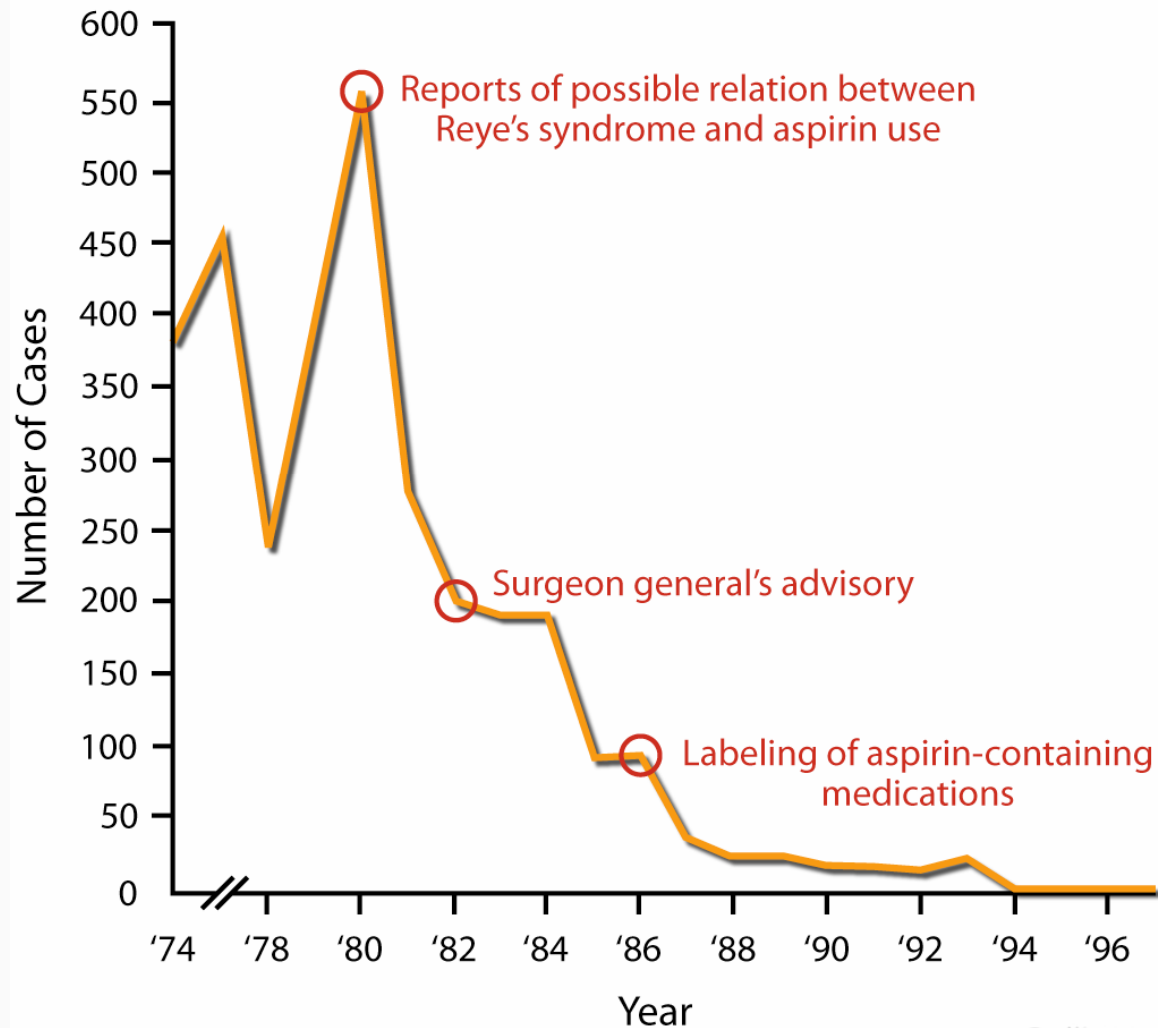
Methods: To describe the pattern of Reye's syndrome in the United States, characteristics of the patients, and risk factors for poor outcomes, we analyzed national surveillance data collected from December 1980 through November 1997. The surveillance system is based on voluntary reporting with the use of a standard case-report form.

Results: From December 1980 through November 1997 (surveillance years 1981 through 1997), 1207 cases of Reye's syndrome were reported in patients less than 18 years of age. Among those for whom data on race and sex were available, 93 percent were white and 52 percent were girls. The number of reported cases of Reye's syndrome declined sharply after the association of Reye's syndrome with aspirin was reported. After a peak of 555 cases in children reported in 1980, there have been no more than 36 cases per year since 1987. Antecedent illnesses were reported in 93 percent of the children, and detectable blood salicylate levels in 82 percent. The overall case fatality rate was 31 percent. The case fatality rate was highest in children under five years of age (relative risk, 1.8; 95 percent confidence interval, 1.5 to 2.1) and in those with a serum ammonia level above 45 μg per deciliter (26 μmol per liter) (relative risk, 3.4; 95 percent confidence interval, 1.9 to 6.2).

Conclusions: Since 1980, when the association between Reye's syndrome and the use of aspirin during varicella or influenza-like illness was first reported, there has been a sharp decline in the number of infants and children reported to have Reye's syndrome. Because Reye's syndrome is now very rare, any infant or child suspected of having this disorder should undergo extensive investigation to rule out the treatable inborn metabolic disorders that can mimic Reye's syndrome. NEJM 1999;340:1377-1382

Reye's Syndrome in the U.S. from 1981–1997

Reye's Syndrome in the United States from 1981–1997



Evidence of Causal Association

	Tampons/TS	Salicylates/Reyes
1. Strength of association	4+	3+
2. Consistency	4+	4+
3. Specificity	2–3+	1+ – 0 (?)
4. Temporality	4+	2+ (?)
5. Biological-gradient	4+	3+
6. Plausibility	4+	0 (?)
7. Coherence	4+	0 (?)
8. Experiment (removal of exposure)	4+	4+
9. Analogy	N/A	N/A