EXHIBIT A

# Surveillance of Illnesses Following Immunization
1978-1979

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## 1978-1979

Vaccines are recommended and administered to millions of individuals every year on the presumption that the benefits far outweigh the risks. In the risk-benefit equation, the benefits may be easily defined--vaccinations can and do prevent serious diseases. On the risk side of the equation are the adverse reactions to vaccination. Since some adverse effects may occur very rarely, it is often difficult to recognize their relationship to vaccination and to estimate the rate at which they occur. Additionally, many events reported to occur following receipt of vaccine may not be related directly to the vaccine. Continuing evaluation of the balance of risks and benefits requires the surveillance of reactions following vaccination.

A formal monitoring system has been developed by the Immunization Division, Bureau of State Services, Center for Disease Control. This system collects information from vaccinees who report any illness requiring medical attention during the 30-day period following receipt of vaccine. Reports are made to local and State health departments and are then forwarded to CDC for collation. The system was instituted on a pilot basis in several States early in 1978 and formalized nationwide in October 1978. While reporting of illness following vaccination is now mandatory from all Federally funded Immunization Projects, it is still voluntary from the private sector. Figure 1 is a copy of the form presently used, entitled “Report of Illness Following Vaccination.” This form is triplicate, but the top sheet (shown in Figure 1) is the only copy which contains patient identifying information. This copy is retained locally. This form requests specific information on the individual who experienced an illness following receipt of vaccine. Additional information that will be requested on future forms is the patient’s immunization history prior to the dose in question. The diagnoses and symptomatology described in the section “Brief description of

illness" are coded in accordance with the International Classification of Disease, ninth revision, Clinical Modification (lCD 9-CM).

As of December 31, 1979, a total of 1,440 adverse events following vaccination have been reported. Table 1 shows the number of reports received by CDC, comparing the calendar year 1978 with 1979. Both the absolute number of reports received, and the number of areas reporting increased in 1979, reflecting the gradual implementation of the surveillance system. In 1979, 11.1 percent of reports came from vaccine administered in the private sector, as compared with 9.5 percent in 1978. Fourteen reports concern vaccine administered-by military providers. Table 2 shows the number of reports of adverse events following vaccination by antigen administered, comparing 1978 with 1979. The vaccine most frequently reported to be associated temporally with adverse events was DTP, followed by OPV and MMR. This parallels vaccine practices, with DTP being administered most frequently, followed by OPV.

Table 3 shows the breakdown of reports received by vaccine combinations administered in 1978 and 1979. Of the 514 reports of illnesses following receipt of OPV, only 26 followed the administration of OPV alone. Three hundred thirty-two individuals received DTP simultaneously with OPV, 31 received Td with OPV, 50 received DTP and MMR with OPV, and 14 received Td and MMR with OPV. This simultaneous administration of multiple antigens makes it difficult to assess the role of individual antigens in the etiology of adverse events following immunization.

Table 4 shows the breakdown of reports received, by clinical illness and vaccine type, for the combined period 1978 and 1979. It should be noted that an event following the simultaneous administration of two vaccines is shown in both vaccine columns. Thus, all 193 local reactions reported following receipt of OPV represent individuals receiving OPV simultaneously with a parenterally administered vaccine--i.e, DTP, Td, and/or MMR. Additionally, an individual

having a local reaction at the site of injection could also have had a convulsive episode and thus would be shown in both rows in the table. The clinical illness titles represent composites of symptoms based on the ICD9-CM coding system. The bottom line of the table, labeled “Total Number of Individuals Involved” represents the number of individuals reported to have had adverse events following the receipt of each type of vaccine.

For all vaccine types except MMR, the most frequently reported adverse events are local reactions. These represent approximately 40 percent of the reports received overall, decreasing from 45 percent of reports in 1978 to 38 percent in 1979. This decrease may reflect improved functioning of the system, since the guidelines for implementation of the surveillance system discourage the reporting of local reactions except when there is an increased frequency noted.

The next most frequently reported adverse events were, fever--unaccompanied by other systemic or localizing signs--and rash. In the cumulative file, these two symptoms account for 32 percent of all reports received. If local reactions, fever-only, and rash are considered minor symptoms, then 72 percent of all adverse events reported were minor.

Arthritis and/or arthralgia accounted for 52 percent of all reports of illnesses following receipt of rubella vaccine. All 24 reports involved individuals over age 20 years--a finding consistent with the increased frequency in adults reported in the literature.

Tables 5-9 are estimates of age specific rates of illnesses reported following receipt of vaccine in the public sector in 1979. They are expressed as the number of reports per million doses of vaccine administered. Tables 7-9 include reports relating to all vaccines containing the specific antigen mentioned. The bottom line of each table gives the overall rate of reporting individuals experiencing any adverse event following the receipt of the specific

vaccine.

In Table 5 we see the age-specific rates of illnesses following receipt of DTP. Local reactions were most frequently reported, with an increasing rate with increasing age. Febrile convulsions were most frequent in the 1- to 4-year-old age group.

Table 6 shows the age-specific rates of illnesses following receipt of adult Td vaccine. There is a trend of increasing rates with increasing age. Local reactions in the greater than 20-year-old age group were reported at a rate 10-fold greater than that reported in the 5- to 9-year-old age group. This trend is consistent with reports in the literature of an increased incidence of local reactions following Td correlated with previous immune status.

Table 7 shows age-specific illness rates following receipt of mumps antigen containing vaccines. All reports of encephalopathy were following receipt of MMR.

Table 8 shows age-specific rates of illness following receipt of measles antigen containing vaccines. There is a decreasing rate of febrile illnesses with increasing age.

Table 9 shows the age-specific illness rates following receipt of rubella antigen containing vaccines. The rates of illnesses seen in the greater than 20-year-old age group are much higher than those seen in the younger age groups.

In March of 1979, the Tennessee Department of Health reported that four infants died suddenly in the 24-hour period following receipt of DTP vaccine. An extensive investigation neither established nor refuted a causal relationship A review of the surveillance file for 1978 and 1979 revealed that 43 reports of sudden deaths in infancy in the 30 days following receipt of DTP vaccine had been received. Figure 2 shows the number of cases of sudden death following receipt

of DTP by month of occurrence for the period May 1978 through December 1979. Twenty-five of the 43 deaths (58 percent) had autopsy findings consistent with sudden infant death syndrome (SIDS). Ten (or 23 percent) of the deaths occurred in March. This coincides both with the investigation of the cluster in Tennessee and with the usual seasonal incidence of SIDS.

The age range of the cases was 6 weeks to 13 months, with a mean of 304 months and a median of 2 months. The male to female ratio was 1.6 to 1.

Following receipt of DTP; the range was from several hours to 28 days, with a mean of 5.4 days and a median of 1.5 days.

Of the 43 deaths reported, 28 different lots of vaccine from four different manufacturers were involved. Only one lot was reported to have more than two deaths; this was the lot involved in the Tennessee cluster. Thirty-six (84 percent) had received OPV simultaneously with DTP. Of the 30 infants where the immunization history was known, 73 percent had received their first dose, 20 percent their second dose, and 7 percent their third dose.

The 43 sudden deaths following receipt of DTP have similar age, sex, and seasonal characteristics as reported for SIDS. The usual age at vaccination with DTP coincides with the peak incidence of SIDS. The high proportion of reported deaths that occurred within 24 hours of receipt of vaccine may reflect recall bias, as people are more likely to attribute causality to events occurring shortly before an unexpected and unexplained death.

The maintenance of a surveillance system to monitor adverse events following receipt of vaccines has three main roles. The first and most important role of the system is to learn about previously unrecognized vaccine reactions of low incidence that might surface after wide-scale vaccine use, e.g., Guillaip-Barre syndrome following swine influenza vaccine program.

A second role of the system is to maintain a vigilance for clustering of vaccine reactions following the administration of a specific lot of vaccine. For example, the clustering of sterile abscesses following two lots of Sclavo DTP which resulted in the recall of the lot.

A third role is to refine estimates of the occurrence of known vaccine reactions. In the past, there had been problems in the ascertainment of both the frequency of reactions following vaccination and the number of doses of vaccine actually administered. Until recently, determination of the frequency of reactions was dependent upon vaccine field trials and sporadic reports to the Bureau of Biologics (BOB) at FDA, the vaccine manufacturers, and public health centers. The present surveillance system permits continuing estimation of this frequency--albeit an underestimate due to the relative passive nature of the system. The data reported do not establish causality or lack of causality between an adverse event and the immunization received. The system does highlight areas in which there is a need for special studies to determine causality.

FIGURE 1

Form AvProveC
OMB No. 68-R 1661

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CENTER FOR DISEASE CONTROL
ATLANTA, GEORGIA 30333

## REPORT OF ILLNESS FOLLOWING VACCINATION

**PATIENT**

Patient Name:

IPhona: 1 1 - — a.c. exe. num.

Patient Addr-

Date Of Birth: m cm m Mo. Oay Yr. | ‘ex’ ❑M❑ ’ | “ate: m | ‘:::,” Uln

County of Restdence:

Dateof Report: ~] IT] ~[ Mo Day Vr.

**REPORTING SOURCES**

Patient's Physician:

Phone: 1 1 1 1 1 1 1 1 1 1 1 1 1 1 a.c. exe. num.

Physician's Address:

Parwn Making Report:

Phone: 1 1 1 1 1 1 1 1 1 1 1 1 1 1 . . exe. num.

**VACCINES**

--at e: m m m Mo, Day Yr.

Provider: O Public ❑ ;ivate ~M!litary ~ Other

Name of Provider:

lelow, enter all vaccines given on the above date.

| Vaccine: | ●1 | ●2 | #3 | *4 |
|---|---|---|---|---|
| Type | | | | |
| Manufacturer | | | | |
| Lot Number | | | | |
| Roum | | | | |
| Method | | | | |
| Site | | | | |

**ILLNESS**

Date of Illness: m m m Mo, Oay Yr.

Brief Description of Illness:

“=’itdiz’’’’n yes EINO ❑ ’nk ‘fy6Name0fHmpita ”

Laboratory Results:

**PREVIOUS HISTORY**

Previous Illness or Reactlon to Vaccination: ❑ yes clNO ❑ lunk

History of Convulsions in Patient: cl” clNO ❑ un’

History of Convulsions in Family: ❑ lyes clNO ❑ NO clunk ❑ u”k

Descrtba:

**7-DAY FOLLOW-UP**

Date m m m Mo. Day Vr. ❑ Recovered ❑ partalRecoverYn lllDDeath

Comments

Record additional comments on a separate page and attach to this form,

This report is authorized by law (42 (JSC 247b; 42 c F R 51 b). Its subm Ission Is needed to monitor possible rea CtlOn S to VaCCInat iOn and iS voluntary except w hen required as a :ondtt 10 n of immu nlzat Ion grant awards.

CDC 10.365-79

REPORTING AGENCY COPY

**Figure 2**
**Number of SIDS Temporally Associated with Receipt of DTP by Month of Occurrence**
**May 1978 – December 1979**

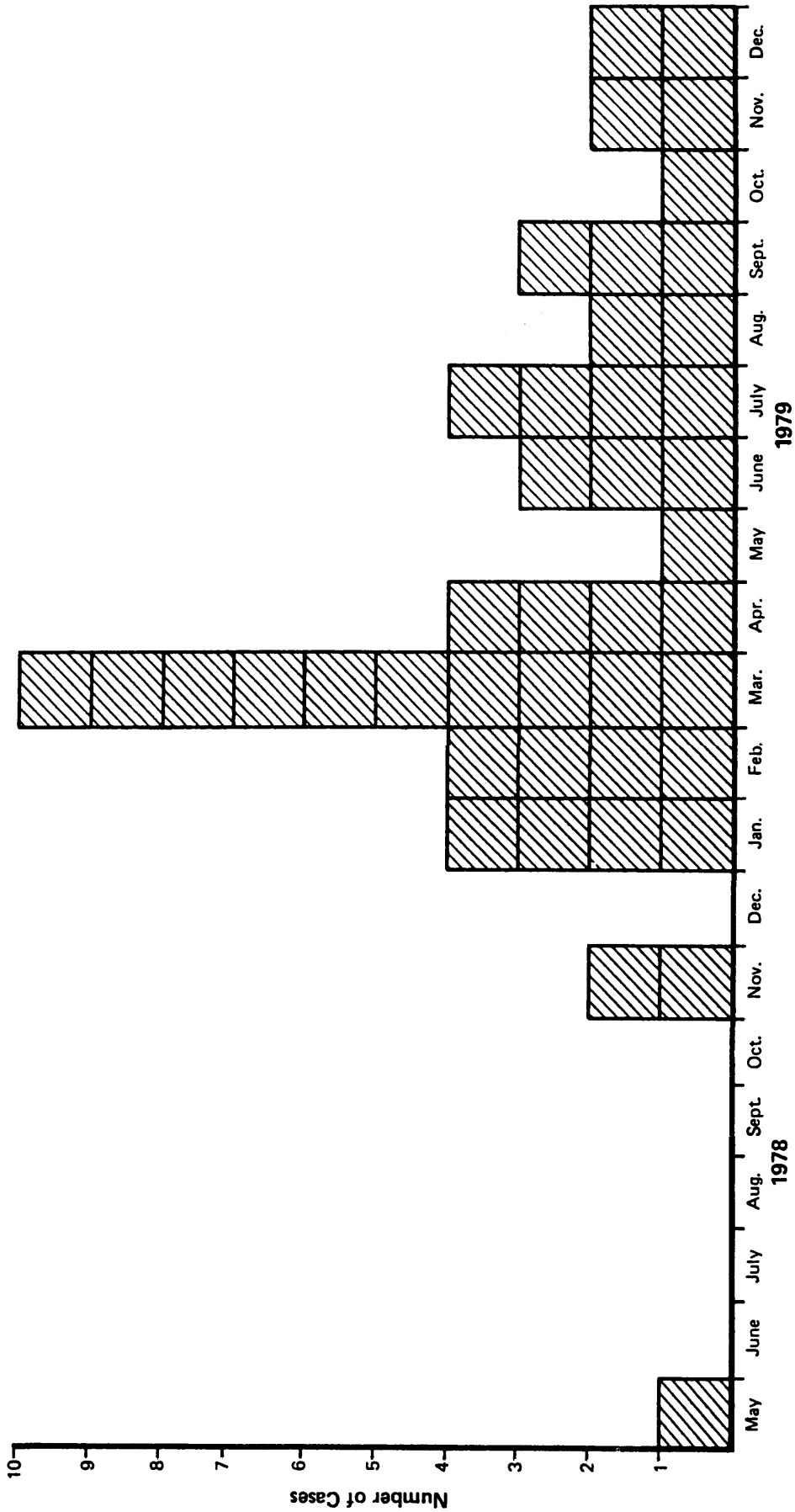

Table 1

Number of Reports Received
1978 and 1979*

| | 1978 | 1979 | Total |
|---|---|---|---|
| Number of Reports | 486 | 954 | 1,400 |
| Number of Areas Reporting | 33 | 48 | 48 |
| Number received vaccine from: | | | |
| Public Provider | 320 | 747 | 1,067 |
| Private Provider | 46 | 106 | 152 |
| Military Provider | 3 | 11 | 14 |

*As of February 15, 1980

Table 2

Number of Reports Received by Antigen
Administered in Decreasing Order
1978 and 1979*

| | 1978 | 1979 | Total |
|---|---|---|---|
| DTP | 230 | 462 | 692 |
| TOPV | 141 | 373 | 514 |
| MMR | 80 | 144 | 224 |
| Td - Adult | 42 | 123 | 165 |
| Influenza | 69 | 97 | 166 |
| Mumps | 9 | 43 | 52 |
| Rubella | 14 | 32 | 46 |
| Tetanus toxoid | 4 | 31 | 35 |
| M-R | 18 | 28 | 46 |
| Measles | 40 | 25 | 65 |
| Smallpox | 3 | 16 | 19 |
| Typhoid | 2 | 9 | 11 |
| DT - Pediatric | 8 | 8 | 16 |
| Cholera | 0 | 6 | 6 |
| Yellow Fever | 0 | 5 | 5 |
| Pneumovax | 2 | 3 | 5 |
| Rabies - DEV | 0 | 1 | 1 |
| Rabies - HRIG | 0 | 1 | 1 |
| Tuberculosis | 0 | 1 | 1 |
| IPV | 0 | 0 | 0 |

*Reports received as of February 15, 1980

Table 3

Immunizations Received by Individuals
Reported to Have Illnesses in the 30 days
Following Receipt of Vaccine - 1978 and 1979*

| Single Antigen Only | 1978 | 1979 | Total |
|---|---|---|---|
| DTP | 130 | 143 | 293 |
| MMR | 59 | 92 | 151 |
| Influenza | 66 | 96 | 162 |
| Td | 11 | 79 | 90 |
| Rubella | 8 | 30 | 38 |
| Mumps | 5 | 17 | 22 |
| Measles | 30 | 19 | 49 |
| TOPV | 10 | 16 | 26 |
| MR | 6 | 9 | 15 |
| **Two Antigens** | | | |
| DTP & OPV | 76 | 256 | 332 |
| Td & TOPV | 9 | 22 | 31 |
| DTP & MMR | 4 | 5 | 9 |
| OPV & MMR | 2 | 6 | 8 |
| MR & Mumps | | 5 | 5 |
| Td & Mumps | 3 | | 3 |
| OPV & Mumps | 1 | 2 | 3 |
| Td & MR | 1 | 2 | 3 |
| Measles & Rubella | | 2 | 2 |
| Td & Measles | 2 | | 2 |
| Td & MMlt | | 1 | 1 |
| DTP & Mumps | | 1 | 1 |
| DTP & MR | 1 | | 1 |
| OPV & Measles | 1 | | 1 |
| OPV & MR | 1 | | 1 |
| OPV & Rubella | 1 | | 1 |

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Table 3 Continued

| Three Antigens | 1978 | 1979 | Total |
|---|---|---|---|
| OPV & DTP & MMR | 13 | 37 | 50 |
| Td&OPV&MR | 7 | 7 | 14 |
| OPV & DTP & Mumps | 1 | 10 | 11 |
| Td & OPV & Measles | 4 | 2 | 6 |
| Td&OPV&MMR | 2 | 3 | 5 |
| OPV & DTP & MR | 2 | 3 | 5 |
| Td & OPV & Mumps | 1 | 1 | 2 |
| DTP & OPV & Measles | 2 | | 2 |
| Td & OPV & Rubella | 2 | | 2 |
| DTP & Mumps & MR | | 1 | 1 |
| OPV & Measles & Mumps | | 1 | 1 |

*For those reports where full immunization histories are knon.

Table 4

Clinical Illnesses Reported to Have Occurred in the 30-day Period Following Immunization by Vaccine Received
1978 & 1979

| Clinical Illness | Vaccine Type | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | DTP | OPV | MMR | Td | Flu | Mumps | Rubella | MR | Measles |
| Local Reactions | 346 | 193 | 35 | 106 | 55 | 15 | 13 | 7 | 22 |
| Fever-- only | 88 | 73 | 29 | 12 | 33 | 12 | 3 | 5 | 7 |
| Rash | 90 | 82 | 105 | 20 | 8 | 11 | 14 | 13 | 22 |
| Allergic Reactions | 29 | 30 | 9 | 5 | 5 | 3 | 4 | 3 | 3 |
| Anaphylaxis | | | | | 1 | | | | 2 |
| Arthritis and/or Arthralgia | 13 | 19 | 7 | 8 | 9 | 2 | 24 | 2 | 2 |
| Convulsions-Febrile | 52 | 41 | 33 | 1 | | 1 | | 1 | 4 |
| Convulsions--Non-febrile | 18 | 15 | 8 | 6 | | 1 | 1 | 4 | 2 |
| Encephalopathy | 11 | 9 | 8 | 1 | | 3 | | 1 | 3 |
| Guillain Barre Syndrome (GBS) | 3 | 6 | 4 | 3 | 4 | | 1 | | 1 |
| Reye's Syndrome | | | | | | | | | |
| Paralysis--non GBS | 5 | 6 | 2 | 1 | 7 | 1 | | | 1 |
| Other necrologic Symptoms | 44 | 41 | 33 | 6 | 17 | 5 | 3 | 6 | 7 |
| Sudden Infant Death Syndrome (SIDS) | 28 | 25 | | | | 1 | | 1 | |
| Deaths from All Causes | 44 | 34 | 2 | | 7 | 1 | | 1 | 2 |
| Total number of Individuals Involved | 692 | 513 | 224 | 162 | 159 | 52 | 46 | 45 | 65 |

Table 5

Age Specific Reports of Illness in the 30 Days
Following Receipt of DTP Administered in the Public Sector
Expressed as Cases Per Million Doses Administered-1979

| | Age (in years) | | | |
|---|---|---|---|---|
| Clinical Illness | <1 | 1-4 | 5-9 | All Ages |
| Local Reactions | 20.4 | 24.4 | 3003 | 25.0 |
| Fever--Only | 9.1 | 9.2 | 12.7 | 10.8 |
| Rash | 11.5 | 9.6 | 8.4 | 10.5 |
| Allergic Reactions | 1.6 | 3.2 | 4.2 | 2.8 |
| Convulsions--Febrile | 400 | 12.3 | | 6.7 |
| Convulsions--non-Febrile | 2.4 | 2.3 | | 2.1 |
| Encephalopathy | 0.8 | 0.9 | | 0.7 |
| Other Necrologic symptoms | 2.4 | 4.6 | 3.2 | 3.7 |
| SIDS | 6.3 | 0.5 | | 300 |
| Deaths | 9.1 | 0.5 | | 4.2 |
| Any reaction | 58.8 | 62.5 | 58.8 | 62.5 |

Table 6

Age Specific Reports of Illness in the 30 Days
Following Receipt of Td Administered in the Public Sector
Expressed as Cases Per Million Doses Administered-1979

| | Age (in years) | | | | |
|---|---|---|---|---|---|
| Clinical Illness | 5-9 | 10-14 | 15-19 | >20 | All Ages |
| Local Reactions | 12.7 | 1106 | 18.9 | 166.7 | 27.8 |
| Fever--Only | 2.1 | 1.9 | 2.5 | 409 | 2.7 |
| Rash | | 3.9 | 1.3 | 14.7 | 4.3 |
| Convulsions-Febrile | | | 103 | | 003 |
| Convulsions --non-febrile | | 1.9 | 2.5 | 409 | 1.7 |
| Encephalopathy | | 1.0 | | | 0.3 |
| Other Necrologic symptoms | | | 1.3 | 4.9 | 0.7 |
| Any reaction | 17.8 | 20.4 | 27.8 | 200.0 | 38.5 |

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Table 7

Age Specific Rates of Reported Illnesses in the 30 Days
Following Receipt of Mumps* Administered in the Public Sector
1979 Expressed as Cases Per Million Doses Administered

| | Age (in years) | | | | | |
|---|---|---|---|---|---|---|
| Reactions | 1-4 | 5-9 | 10-14 | 15-19 | >20 | All Ages |
| Local Reactions | c 1 | 6.0 | 16.9 | 8.0 | | 1003 |
| Fever--Only | 13.1 | 9.6 | 1001 | | | 11.4 |
| Rash | 28.4 | 6.0 | 3.4 | | 121.6 | 20.5 |
| Allergic Reactions | 3.5 | | 3.4 | | | 2.2 |
| Convulsions-Febrile | 1.4 | | | | | 0.7 |
| Convulsions-Non-feb. | 3.5 | | | | | 1.8 |
| Encephalopathy | 007 | | | 8.0 | | 0.7 |
| Other Necrologic Symptoms | 7.6 | 2.4 | 10.1 | | | 6.2 |
| Any reaction | 21.4 | 14.4 | 23.6 | 8.0 | 121.6 | 19.8 |

*For all mumps containing vaccines (mUmPS + MMR)

Table 8

Age Specific Rates of Reported Illnesses in the 30 Days Following Receipt of Measles* Administered in the Public Sector 1979 Expressed as Cases Per Million Doses Administered

| | Age (in years) | | | | | |
|---|---|---|---|---|---|---|
| Reaction | 1-4 | 5-9 | 10-14 | 15-19 | >20 | All Ages |
| Local Reactions | 10.0 | 8.9 | 10.0 | 8.9 | | 10.4 |
| Fever-- only | 10.7 | 7.4 | 2.9 | | | 7.3 |
| Rash | 30.7 | 3.0 | 10.0 | | 41.7 | 18.9 |
| Allergic Reactions | 2.9 | 1.5 | 2.9 | | | 2.1 |
| Anaphylaxis | | | 1.4 | | | 0.3 |
| Convulsions--Febrile | 10.7 | | 1.4 | 2.2 | | 5.2 |
| Convulsions--Non-Feb. | 3.6 | | 2.9 | 4.5 | | 2.8 |
| Encephalopathy | 0.7 | | 1.4 | 2.2 | | 0.9 |
| Other Necrologic Symptoms | 7.9 | 1.5 | 7.5 | | | 5.5 |
| Any reaction | 65.7 | 22.2 | 31.4 | 29.0 | 125.0 | 48.6 |

*For all measles containing vaccines (measles + MR + MMR)

Table 9

Age Specific Rates of Reported Illnesses in the 30 Days Following Receipt of Rubella* Administered in the Public Sector 1979 Expressed as Cases Per Million Doses Administered

| Reaction | Age (in years) 1-4 | 5-9 | 10-14 | 15-19 | >20 | All Ages |
|---|---|---|---|---|---|---|
| Local Reactions | 9.3 | 8.4 | 11.9 | 10.9 | 158.6 | 12.2 |
| Fever--only | 12.2 | 8.4 | 2.4 | | | 9.1 |
| Rash | 29.5 | 3.4 | 7.1 | | 238.0 | 23.2 |
| Allergic Reactions | 2.9 | 1.7 | 2.4 | | 39.7 | 3.0 |
| Arthritis and/or Arthralgia | 0.7 | 1.7 | | | 515.6 | **6.5** |
| Convulsions--Febrile | 10.8 | | 2.4 | | | **6.1** |
| Convulsions--Non-feb. | 3.6 | | 2.4 | 10.9 | | 3.0 |
| Encephalopathy | 0.7 | | | 5.5 | | 0.8 |
| Other necrologic symptoms | 7.2 | 1.7 | 9.5 | | | 6.1 |
| Any reaction | 65.4 | 23.6 | 30.9 | 43.8 | 793.2 | 51.7 |

*For all rubella containing vaccines (rubella + MR + MMR)