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# PREVENTION OF INFLUENZA AND OTHER RESPIRATORY DISEASES (U)

ANNUAL PROGRESS REPORT

BY

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)
1) An explosive epidemic of H1N1 influenza occurred at Lowry AFB during February 1978. No H1N1 vaccine had been available and personnel under 25 were almost uniformly seronegative.
2) Influenza (febrile) attack rates were estimated to be about 30% in students, who ranged in age from 17 to 23. An additional 20% were probably infected during the epidemic.
3) The permanent party, most of which is over 25 years of age had far lower attack rates than the students.

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4) A small number of cases of H3N2 influenza occurred between 30 November 1977 and 30 January 1978, but the spread of this disease was very limited in this vaccinated population.
5) The H1N1 virus strains differed from H3N2 strains in many ways. Isolation and identification were more difficult and lack of avidity of the prototype A/USSR/90/77 strain created difficulty in serodiagnosis. The most useful antigen for HI tests was an ether-split vaccine concentrate (PD) prepared from A/USSR/92/78
6) Surveys of HI atnibody levels of military and civilian populations between 17 and 24 years of age indicated that approximately one half had been infected during or following the February 1978 epidemic.
7) Studies of experimental H1N1 vaccines of 60 µg and 20 µg potencies showed that the former, whether split or whole virus, produced seroconversion in a very high proportion of persons. The 20 µg vaccine was less effective. A second injection of vaccine produced a good booster effect.
8) Evaluation in volunteers in November 1978 of the standard military vaccine (Connaught 20 µg, whole virus) showed a very satisfactory response to seronegative persons and a striking booster response in persons with antibody. The response was comparable to the 60 µg vaccines in the earlier studies.
9) A second H1N1 occurred in January 1979 after all base personnel had received H1N1 vaccine. In contrast to the first epidemic, it ran a slow smouldering course and febrile URI rates never reached high levels in the student population. During the peak week of the 1978 epidemic there were 119.0/1000/wk; in 1978 the rate during the peak week was 11.4/1000/wk.
10) While the 1979 H1N1 strains showed some antigenic drift the relevance of this to vaccine effectiveness remains difficult to determine because of the lack of avidity of most recently isolated H1N1 strains.
11) Antibody levels for A/Texas/77 and B/Hong Kong/72 were extremely high as a result of double immunization with vaccines. No cases of either disease were detected during the 1978-79 winter.
12) Only a single case of adenovirus disease was detected. Rubella, in contrast to previous years, has become very rare since the immunization program was instituted at Lackland AFB. Streptococcal pharyngitis occurred throughout the season, but at a relatively low level.

CONTENTS

I. Febrile Upper Respiratory Infections (URI) at Lowry Air Force Base from 1 November 1977 to 30 January 1978

A. Overall rate

The incidence of febrile URI infections remained very low from 1 November 1977 to 30 January 1978 and at no time exceeded 5.9/1000/week in the student population.

B. Influenza

Cases of influenza A occurred throughout this period, with the earliest case documented on 2 November 1977. Some were caused by A/Victoria strains and others by A/Texas strains. A total of 21 cases were confirmed by laboratory studies. Fourteen were in permanent party personnel and 7 in students. Six of the 21 had not received vaccine in 1977.

Both A/Victoria and A/Texas strains were prevalent in the Denver area during this period. The situation was similar to that observed during the 1976-77 season, when these strains caused an appreciable amount of illness in the civilian population and were repeatedly introduced into the Lowry population but failed to cause an epidemic. Antibody levels in the Lowry personnel are almost uniformly high as a result of vaccination with the A/Victoria/75 strain. The failure of the influenza A strains to spread and to cause illness is best explained on the basis of a favorable response to vaccination.

No influenza B was detected during this period.

C. Other febrile URI

Four cases of parainfluenza-2 were identified prior to the Christmas break. No adenovirus illness was found.

Rubella incidence appeared to have dropped sharply since rubella vaccination was started at Lackland, but precise figures are not available.

II. The February, 1978 H1N1 Epidemic - 30 January to 1 March 1978

A. Serologic screening

With the receipt of information that epidemics caused by an H1N1 virus were occurring in the USSR and in Hong Kong the sera of patients collected between 1 November 1977 and early January 1978 were screened for antibody against H1N1 virus strains A/FM1/47, A/AA/57, and A/USSR/90/77. Students under 20 years of age had no H1 antibody. On the other hand, permanent party over 23 years of age frequently had antibody against A/FM1/47 and, at lower levels against A/USSR/90/77. It was shown that persons in the age group 23 to 32 who had received A/New Jersey/76 vaccine a year ago had a reasonably good response to H1N1 strains. Younger persons responded poorly or not at all and older persons showed only a modest response. These data were presented in last year's annual report.

B. The epidemic

The first confirmed cases of H1N1 influenza were seen on 30 January and thereafter there was an increasing flood of patients with typical clinical influenza. The epidemic peaked 8 days later. The number of cases then fell off rapidly and reached the pre-epidemic level in 3 weeks (Figure 1).

It was immediately apparent that the student population was being affected far more than the permanent party. While it is likely that the permanent party when ill with influenza used the dispensary less frequently than the students, the differences in rates are far too great to be explained by this difference. In Figure 2 an estimate of febrile URI rates in students is shown. The very sharp rise observed in the students was only faintly reflected in the permanent party. During the first 2 weeks of the epidemic the difference in rates was approximately 10 to 1.

C. Estimates of attack rate of A/USSR/77

An estimate of the number of cases of illness caused by the A/USSR/77 virus is presented in Tables 1 and 2. Several assumptions have been made and the final figures should be regarded as approximations. The main assumption is that all illness occurring during the epidemic in excess of that seen during the pre-epidemic period was due to influenza. The second is that excess night or weekend visits during the epidemic were made by students rather than by permanent party. This interpretation was based on general observations by dispensary personnel rather than on actual count and may be subject to some error.

In the student population 30.4% came to the dispensary with febrile URI or made night or weekend visits. An additional 25.1% came to the dispensary with URI but without fever at the time of their visit. Some may have been revisits. The total excess number of visits, during the 3 week period of the epidemic was 1732 of 3209 students, or 55.5% (Table 1).

In the permanent party rates were strikingly lower. Only 138 of 4824 or 2.8% reported with febrile illness (Table 2). It is worth pointing out that twice as many permanent party as students reported with A/Victoria/75 influenza this season. The difference may not be as large as these figures suggest, but it is obvious that A/USSR/77 caused relatively little illness among the permanent party.

D. Laboratory observations

Results came slowly because the virus strains behaved in many ways differently from H3N2 strains. About 25 strains were promptly isolated in Rhesus monkey kidney tissue culture (RMKTC) and identified as being of A/USSR/77 type. Among the first 50 serum pairs collected during the epidemic 36 showed antibody increases of 4-fold or more in homologous HI tests, CF tests or both. This was considered a poor yield and work continued. Further laboratory investigations are described in a following section.

The following points should be made:

1) These strains grew more slowly in RMKTC than recent H3N2 strains as measured by the time of appearance of hemadsorption.

2) Even when 4+ hemadsorption and CPE were observed, most tissue culture fluids did not agglutinate chicken red blood cells. They, however, agglutinated guinea pig red blood cells or human O cells. HI tests with guinea pig cells were best read after 1.5 or 2 hours. Tests with O cells were hard to read and results were inconsistent.

3) The virus eluted rapidly from chicken red blood cells.

4) Many persons failed to show 4-fold rises in titer in convalescent sera, and very few show high rises, suggesting either that the strain A/USSR/77 was non-avid or that antibody took more than 3 weeks to rise. The latter possibility was investigated and disproved.

5) Complement-fixation tests were less useful than usual because most persons had influenza A antibody as a result of vaccination.

E. Comment

Not since 1957, when the Asian (H2N2) epidemic occurred has Lowry AFB experienced an influenza outbreak as sharp as this. The situation recalled that which existed before vaccination was given to all personnel. During that period it was repeatedly observed that unvaccinated recruits or recently inducted military personnel were particularly vulnerable to influenza. During the years since vaccination of all personnel has been carried out, the impact of influenza has been blunted, even when the disease was widespread in the surrounding civilian community. Only in 2 years, namely 1968 and 1972, when sharp antigenic change reduced vaccine effectiveness, have there been epidemics with high incidence. While serious illness or complications requiring hospitalization were not observed during this epidemic, a very large proportion was rendered ineffective within a very short period of time. For those who might have thought that influenza vaccination was not needed, the experience of this epidemic should provide a convincing evidence of the value of an effective vaccine.

This outbreak has been described in a manuscript entitled "An Epidemic Caused by H1N1 Virus" by Gordon Meiklejohn, M.D., Theodore C. Eickhoff, M.D., Patricia Graves and Josephine I which has been accepted for publication in MILITARY MEDICINE. A copy of this manuscript is enclosed.

III. Surveys for H1N1 Antibody

Tests conducted last year in permanent party personnel at Lowry and in adult and elderly civilians had shown that a large proportion had HI antibody for H1N1 strains, presumably as a result of infection during the decade 1947-57. This was a surprising finding, since there was no evidence in tests with sera from persons with H3N2 influenza infections of a boosting of H1N1 antibody levels. It appeared that H1N1 antibody and protection against illness had persisted for more than 20 years. This suggests that the so called "short lived immunity" against influenza was the result, primarily, of continuing antigenic drift or shift rather than antibody decay.

A. HI antibody levels in Lowry students after February, 1978 epidemic

The results of HI tests to determine antibody levels in the student population between 1 January and 30 June, 1978 are shown in Table 3. In these tests the antigen used was the Parke-Davis ether split antigen prepared from strain A/USSR/92/77. This antigen had been shown to be far more sensitive in detecting antibody than whole virus preparations of the prototype strain A/USSR/90/77. It was, perhaps, too sensitive, since, as noted in Table 3, 7% of young (under 23 years old) persons had titers of 8. None were higher than that.

With this antigen the great majority of patients with influenza had been shown to have titers in their convalescent sera of 16 or higher. Most were between 32 and 128. Only 10% were 256 or higher.

Following the epidemic sera were screened in two population groups in order to find out the extent to which influenza had infected the students. This might have occurred either at Lowry or during their earlier period of training at Lackland. First, among 62 persons reporting with febrile URI after the epidemic was over 47% were found to have titers of 8 or less, but 53% had titers of 16 or more, suggesting that they had been recently infected. A similar pattern was found when 103 sera from students were tested prior to a vaccine trial in June 1, 1977. At that time 51% had HI titers of 8 or less and 49% had titers of 16 or more, again suggesting that approximately one half of these young adults were infected during the late winter or spring of 1977.

B. Young civilians in Denver in the fall of 1978

At the time of the Lowry H1N1 epidemic there was evidence of influenza in the civilian community. This was particularly noticeable on college or university campuses. Scattered outbreaks occurred in schools, but there was no widespread epidemic. Adults over 25 rarely became ill with influenza and no excess of pneumonia cases or of deaths was observed.

In order to determine how widely H1N1 had actually spread, sera from 128 young (under 25 years) civilians were obtained through the courtesy of the Colorado State Health Department and examined by HI test for antibodies to A/USSR/92/77, A/Texas/77 and B/Hong Kong/72. Results are shown in Tables 4 and 5. If one assumes that titers of 16 or more are evidence of previous infection, it appears that 88% of this group have been infected by H3N2 viruses and 43% by H1N1 viruses. The latter figure is higher than one would have estimated on the basis of clinical and epidemiological observations. Antibody for influenza B at this level was found in only 27% of persons. This situation has existed now for several years, but no extensive influenza B epidemic has occurred.

C. Antibody levels in prevaccination sera in November, 1978.

Sera from 67 students were collected before vaccine was given during the first week of November, 1978 (Table 6). Forty-eight percent had titers of less than 8, 8 had titers of 8 and 44% had titers of 16 or more. These persons came from all parts of the country and had passed through

basic training at Lackland AFB. They had not received H1N1 vaccines. It appeared that this group resembled the civilian group from Colorado and that the first wave of H1N1 had infected approximately half of young adults, leaving the remaining half susceptible to infection.

## IV. Evaluation of H1N1 Vaccines

### A. Participation in National Program in summer of 1978

The program for evaluation of newly prepared H1N1 vaccines (A/USSR/70/77) was integrated with the National Program which was designed to determine the optimum type of vaccine and amount of antigen for various segments of the population. Variables included (1) type of virus, whether whole virus or split; (2) the amount of viral antigen as determined by measurement of micrograms of hemagglutinin; (3) the number of doses needed (1 or 2); (4) the frequency and severity of systemic and local reactions. Volunteering students from Lowry AFB constituted a major segment of the age group 18 to 23 which was selected for study.

#### 1. Results with first dose with differing amounts of antigen

Split virus vaccines prepared by Wyeth containing 60 g or 20 g of HA and whle virus vaccines prepared by Merck, Sharp and Dohme containing 60 and 20 µg of HA were tested. Another MSD vaccine containing 20 µg HA each of A/USSR/90/77, A/Texas/77 and B/Hong Kong/72 was given as a second dose to persons who had received vaccine or placebo injection. A Connaught Laboratories whole virus vaccine containing 20 µg of A/USSR/90/77 and 7 µg HA each of A/Texas/77 and B/Hong Kong/72 was used in the fall for immunization of military personnel and results are included for comparison with the others. All personnel were bled before and 3 to 4 weeks after vaccination.

Results following the first injection in all volunteers are presented in Tables 6 & 7. The numbers lost much of their significance when it was found that 51 of the 94 volunteers (54%) already had titers of 16 or higher. Those individuals whose titers were 16, 32, or 64 uniformly showed sharp boosts in titer to higher ranges with all vaccines. Persons with titers of 128 or higher showed little change. Useful comparisons were limited to seronegative persons, and these were few in number (Table 8).

In seronegative persons both the Wyeth 60 µg and MSD 60 µg vaccines provided sharp rises in titer levels. With the former 92% and with the latter 88% of persons showed 4-fold or greater increases in titer. The response was less satisfactory with the Wyeth 20 µg and MSD 20 µg vaccines, with 60% and 69% of persons showing 4-fold or greater increases in titer. The second MSD vaccine, with a 20-20-20 µg formula, produced a better response, 89% of persons showing 4-fold increase in titer. A similar result was seen with the standard military vaccine used in November, 1978.

The numbers of persons in all but one of these vaccine groups are too small to permit definite comparisons. Certain observations

seem warranted. First, with the experimental vaccines the 60 µg vaccines were more effective than the 20 µg vaccines. Second, the split virus vaccines were as effective as the whole virus vaccines. Third, the two whole virus vaccines administered after the trial containing 20 µg HA performed as well as the earlier 60 µg vaccines. This raises questions about the reliability of the HA tests used to standardize these vaccines in predicting antibody response in man. This is an important question. It appears that it is still essential to obtain this information by testing vaccines in sero-negative humans.

2. Results with second dose

Persons in the 4 experimental vaccine groups received a second injection of MSD whole virus vaccine containing 20 µg of A/USSR/77 4 weeks later and were bled 2 weeks after this. Results are shown in Table 9. In each vaccine group some individuals with low titers showed small increases in titer, but increases in titer of 4-fold or more were few in number; thus the second injection appeared to be of more value in the recipients of the 20 µg than of the 60 µg vaccines. The effect, however, was to reduce the number of persons with titers of 8 or less (most susceptible) to a very small percentage or to nil. This might cause a significant increase in protective efficacy especially if there was appreciable antigenic drift in the following season.

3. Coordination with the Center for Disease Control

The sera collected in the experimental vaccine study were tested both at the University of Colorado Medical Center and at the Center for Disease Control. Initially the paired sera collected before and after the first injection of vaccine and subsequently these sera, along with a third collected after the second injection of vaccine were tested again. Results are shown in Tables 10 and 11.

There is good concordance between the results obtained in the 2 laboratories. The chief difference was that the baseline in sero-negative persons where A/USSR/92/77 split-virus antigen was used was higher in the CDC tests. Results in both laboratories show the relatively insensitivity of A/USSR/90/77 in detecting HI antibody.

4. Results with A/Texas/77 and B/Hong Kong/72

Serum pairs from 95 persons who received 2 injections of the experimental vaccines were also tested for HI antibody against A/Texas/77 and B/Hong Kong/72 (Table 10). These persons had previously received vaccine at Lackland AFB containing 200 CCA units each of A/Texas/77 and B/Hong Kong/72. Consequently titers for both viruses were high before they received their second injection. Ninety-three percent of persons had titers of 16 or higher for both viruses. A slight booster effect was noted with the A/Texas/77 component, but almost no change was observed with B/Hong Kong/72. This was consistent with previous observations that a second injection of vaccine has little boosting effect on persons who already have antibody at high levels.

Comment:

Data on reactions are incorporated in the CDC report. Despite the large amount of antigen included in the 2 vaccines, reactions were infrequent and generally mild. No late reactions were observed. Copies of the consent forms are attached to the report. The length and detail of the form were a strong deterrent to the recruitment of volunteers.

B. Evaluation of military vaccine

1. Formula

The vaccine was whole virus Connaught Laboratories product (Lot #2166HK) which was labeled as containing 21 μg of A/USSR/90/77 and 7 μg of A/Texas/77 and of B/Hong Kong/72. Administration to recruits was begun at Lackland AFB about 10 September 1978. Personnel already transferred to Lowry AFB received vaccine during the second week of November. The volunteers whose sera were tested had received bivalent vaccine containing A/Texas/77 and B/Hong Kong/72 while at Lackland but had not received A/USSR/90/77 vaccine.

2. Results with A/USSR/92/77 antigen

The whole group of 67 persons responded well to vaccination. Ninety-five percent of the post-vaccination sera had titers of 16 or more and 72% had titers of 128 or more (Table 13).

However, 44% of this group had titers of 16 or higher before vaccination and it seemed likely that many of these markedly elevated titers might have been due to the fact that these persons had been primed as a result of infection earlier in the year and were showing the expected booster response. For this reason, the group was divided into two parts. The first consisted of 32 persons with titers less than 8, who presumably had not had H1N1 infections. The second consisted of 30 persons with titers of 16 or more who had probably been infected. Five persons with titers of 8 were not included because one could not be certain whether they had or had not been infected.

This division brought out the difference between the satisfactory but relatively modest primary response or seronegative persons and the booster response in persons infected several months (8 or 9) earlier. The former responded well. Ninety-four percent had titers of 16 or more. Most had titers between 32 and 128. The seropositive group showed a much greater response. Ninety-seven percent had titers of 128 or higher.

3. Response to A/Texas/77 and B/Hong Kong/72

The volunteers in this study, as in the earlier program to evaluate the experimental vaccines, had received bivalent vaccine containing 200 CCA units each of A/Texas/77 and B/Hong Kong/72 while at Lackland AFB. Consequently the HI titers of most persons were already high at the time when vaccine was given. There was a slight upward shift in the distribution of titers, more for A/Texas/77 than for B/Hong Kong/72.

With the former 98% of persons had titers of 64 or more, well above the "protective" level.

4. Comment

The titers for H1N1 following administration of this 20 µg vaccine were higher than those of persons who received either of the 2 experimental 20 µg vaccines (Table 8) and were almost as high as those seen in persons who received 60 µg vaccines. This raises questions about current determinations of vaccine potency.

The vaccine response of persons infected several months earlier was greater than those who received a second injection 1 month after the first. Whether this difference is to the better priming by infection or is due to the longer interval between priming and vaccination cannot be determined by these findings.

The response to A/Texas/77 and B/Hong Kong/72 following a second vaccination is consistent with many earlier observations. Persons who have had moderate or marked response to the first injection usually show little or no change in titer following the second. Only those persons who continue to have low titers after the first injection respond with 4-fold or greater rises in titer. The titers of these persons are usually raised to "protective" levels.

V. Comparison of Serologic Methods for Diagnosis

In the past either the HI test using a strain from the current epidemic or a complement fixation test using infected allantoic fluid has provided a highly sensitive diagnostic method in unvaccinated persons. In vaccinated persons the complement fixation test loses sensitivity because acute phase sera have antibody in titer sufficiently high that a 4-fold increase in titer cannot be shown in the convalescent sera. Because the HI test appeared to be relatively insensitive with A/Vict/75 strains, A/Victoria/75 and A/USSR/90/77 antigens were compared in CF tests.

Among 55 serum pairs collected between 26 January and 24 February the diagnosis of A/USSR influenza was confirmed in 46. Three others had 2-fold increases in titer in 1 or both tests and 2 had confirmed A/Victoria influenza. One of the 46 had A/USSR isolated from throat washings but failed to show a significant antibody rise.

Of the 45 confirmed H1N1 cases 39 (87%) showed a 4-fold or greater increase in HI antibody titer using A/USSR/92/77 (PD) antigen. Only 29 of 45 (64%) showed a significant rise in titer in CF tests with A/Victoria/75 antigen. However, 39 of 45 (87%) showed a significant rise in CF antibody titer when A/USSR/77 antigen was used. This difference in yield was due mainly to the lower titer in the acute phase serum. Convalescent titers differed little with the 2 antigens, but the lower initial titer with A/USSR/77 converted many equivocal (2-fold) or negative results into diagnostic increases in titer.

Serologic procedures remain important in vaccine studies if all cases are to be identified, particularly in vaccinated persons. During the past year, when virus

strains often were not isolated from confirmed cases and the conventional HI test with whole virus was insensitive, complement fixation tests with a H1N1 antigen were particularly useful.

## VI. Problems with Laboratory Procedures

In February 1978 attempts to isolate influenza strains from influenza patients were far less successful than in recent years, when either A/Victoria/75 or A/Texas/77 strains were recovered from approximately 90% of cases. Most isolation attempts were made in Rhesus monkey kidney tissue culture and the success rate was about 50%. The strains grew more slowly than H3N2 strains and rarely caused either hemadsorption or CPE in less than 5 days. A limited number of isolation attempts in chick embryos were no more successful.

Once isolated in RMKTC the strains presented problems in identification. They could readily be typed as influenza A strains by CF tests, but the tissue culture fluids failed to agglutinate chicken cells. It was found, however, that they did agglutinate guinea pig or human "O" cells and the former provided a satisfactory method for strain typing. Agglutination patterns were less definite than those seen with chicken cells and tests were best read after 90 to 120 minutes. Rapid elution of virus from cells was observed. Virus strains isolated in chick embryos or passed through chick embryos usually agglutinated chicken cells and were readily typed by conventional methods.

A further vexing problem was that the prototype strain A/USSR/90/77 behaved like a non-avid strain. Tests on sera collected during the upslope of the epidemic ultimately showed that more than 91% had had influenza. However, when these serum pairs were tested against A/USSR/90/77 only half showed significant rises in HI antibody titers (Table 15). Strain A/FM1/47 produced a better yield (78%), but the best results were obtained with an ether-split vaccine concentrate kindly provided by Dr. F. Brandon of Parke-Davis Co. This antigen has since been used for routine diagnosis. It did not provide as clean a baseline as most whole virus antigens, and titers of 8 or occasionally 16 were found in persons who are presumably seronegative. Nevertheless, it has been useful and satisfactory. Its sensitivity has raised questions about what should be considered a "protective" level i.e. would a titer of 16, usually accepted in this laboratory as providing a high degree of protection, have the same significance, or should the level be set at 32 or even higher? Test of prevaccination sera in June 1978 with A/USSR/90/77 indicated that only 24% had titers of 16 or more. With the A/USSR/92/77 (PD) antigen the comparable figure was 49%. The latter figure is presumably correct (Table 16).

This problem of avidity first received attention early in the H1 period, when many strains were isolated which reacted very poorly with human antisera. Others, such as A/FM1/47 are extremely avid. This problem arose again with influenza B strains in 1972, when early egg passage B/Hong Kong/72 like strains failed to behave satisfactorily in HI tests. Only after 15 or 20 chick embryo passages did they become avid. Problems of avidity confuse the issue of how significant antigenic change in H1N1 strains appearing later in 1978 may be.

## VII. Severity of Illness With H1N1 Influenza

The fact that H1N1 influenza virus has infected approximately half of the young adults without causing community-wide epidemics has raised the question whether this virus is less virulent and causes milder illness than H3N2 strains. It has been noted earlier that a large number of clinic visits (about 20%) were made during the epidemic by students who did not have fever at the time when they were seen.

For this reason the oral temperatures of students reporting with fever (>99°F) and confirmed H1N1 influenza were examined (Table 17). Unfortunately, the number of students reporting was so large that it is probable that this group is biased in favor of those who were more ill only 24% of the group had temperatures of 102°F or higher. This is smaller than the figure reported last year (39%) in a small group of 23 unvaccinated persons with H3N2 influenza and higher than that observed in a group of vaccinated persons with influenza (16%). The data are inadequate to permit conclusions.

## VIII. Comparison of the H1N1 Outbreaks of 1978 and 1979

The 1978 outbreak was an explosive epidemic with the characteristics of a new influenza strain in a totally susceptible population (Figure 3).* Only 8 days passed between the first detected case and the epidemic peak. The epidemic ran its course within 3 weeks, with only a few scattered cases over the following month. A minimum of 30% of the student population was ill with febrile URI during the 3 weeks of the epidemic and there was suggestive evidence, derived from excess clinic visits, that approximately 50% were infected with 20% having only minor or nonfebrile illness. The permanent party, representing an older segment of the population had far less influenza than the students.

In late 1978 and early 1979, when H1N1 influenza reappeared the pattern was very different. The student population at this time differed in 2 important respects. First, approximately one-half had acquired H1N1 antibody as a result of infection prior to arriving at Lowry and were presumably immune. Second, all students received vaccine early in November containing 20 micrograms of H1N1 hemagglutinin, to which they had shown a good antibody response.

The best comparison of attack rates in the two epidemics and of the effectiveness of vaccine in the second (1979) epidemic is obtained from the daily visits for febrile URI from the student population. These are presented in Table 18.

In 1978 rates were very low (4.9 to 5.9) before influenza appeared at the end of January and rose rapidly to an explosive peak of 119/1000/week during the week starting 30 January. Thereafter rates fell off rapidly, with the last case detected during the week of 13 March.

In 1979 the first cases occurred during the second week of November. Six cases were detected before the Christmas break, but there was no rise in febrile URI rates. All personnel had been vaccinated during the second week of November and vaccine effectiveness presumably was reached about 2 weeks later. This, together with the fact that half of this group had already been immunized by infection may have limited spread.

*Figure 3 will follow.

After the Christmas break, when students returned from their homes in all parts of the country and when H1N1 influenza was widespread in the Denver area, cases began to occur in vaccinated students and permanent party. A peak rate of 11.4/1000/week was reached during the week starting 8 January and rates then declined. During the week of 22 January the rate fell to 4.7%.

It is dangerous to compare what happens in one epidemic with another which occurs a year later. The fact that about one half of the students were already immune has already been noted. Nevertheless, based on past experience, a sharp epidemic with high attack rates would have been expected with half the population susceptible. This can be interpreted, therefore, as a challenge to a vaccinated population into which influenza was repeatedly introduced over a period of 10 weeks. No epidemic resulted.

## IX. Observations on the Antigenicity of 1979 H1N1 Strains

Epidemics caused by H1N1 strains were not detected in the northern hemisphere between the late spring and early fall, but were reported from a number of countries in the southern hemisphere. There was evidence that the virus responsible for these epidemics had undergone some antigenic drift. Investigators at the CDC, using cross HI tests with ferret antisera, noted a considerable difference between strains A/Brazil/78 and A/USSR/90. A strain isolated in California late in 1978, A/Calif/1/78, behaved in much the same manner as A/Brazil/78, and the CDC has recently reported that most strains isolated from outbreaks in the USA this winter have been of the A/Brazil/78 type.

Because significant antigenic drift might affect vaccine efficacy and make it advisable to change vaccine composition, sera from last year's A/USSR/90 cases and from persons vaccinated with A/USSR/90 vaccine were tested against the old and several new strains. In the first test the antigens used were A/USSR/92/77 (PD), A/Calif/1/78 and A/Brazil/78. With sera from cases (Table 19) higher and more frequent titer rises were noted with A/USSR/92/77. A/Calif/1/78 was next and A/Brazil/78 was a poor third. Since the latter 2 presumably are antigenically similar it appeared that this difference was due to the low avidity of the A/Brazil/78 strain provided by the CDC. For comparison results of tests of the same sera run against A/USSR/90, which is clearly a strain with low avidity, are included. Results resemble those obtained with A/Calif/1/78, but are different from those obtained with A/Brazil/78.

The same pattern was seen with serum pairs from 31 seronegative persons who had received whole virus 20 µg A/USSR/90/78 vaccine (Table 20). The highest titers and percent seroconversion were observed in tests with the A/USSR/92/78 antigen, with A/Calif/1/78 next and A/Brazil/78 a poor third. It is worthwhile to note that with all 3 antigens the antibody response following vaccination was greater than that following infection.

A comparison was then made of results with A/USSR/90/78 and A/Den/9284/78, a strain isolated in December, 1978. Sera from the same 25 cases which occurred during the February 1978 epidemic were tested and from a different group of persons who were vaccinated in November, 1978, some of whom were seronegative and some seropositive.

In tests with sera from the cases, results with A/USSR/90/77 (Table 21) differed slightly from those seen in an earlier test (Table 18). Twenty-four percent of convalescent sera had convalescent titers of <8 and another 24% had titers of only 8. Thus only 52% of persons with proven influenza had 4-fold increases in titer. With A/Den/9284/78 there again were 24% of persons with titers of <8 in their convalescent sera and 4% with titers of 8, but 72% had significant rises in antibody titer with sera from vaccinated persons (Table 22) the distribution of titers in the prevaccination sera was similar, but the proportion of persons showing 4-fold or greater rise in titer was slightly higher (72%) with A/Den/9284/78 than with A/USSR/90/77 (64%).

These results do not resolve the question of whether the observed differences are due to antigenic drift or to differences in avidity in tests with human sera. This question will not be fully answered until an H1N1 strain is found which will react with convalescent sera from all, or almost all influenza patients. This is not the case with any of the strains so far tested against patients with influenza in December 1, 1978 or January 1, 1979 (Table 23). The ether-split antigen prepared from A/USSR/92/78 continues to provide a far more effective means for demonstrating increases in HI antibody than any of the newer strains. Much work remains to be done.

A decision on next year's vaccine composition must be made while the significance of antigenic drift remains unclear. The data obtained here suggests that the lower titers to the new strains in cases and vaccinees may be due as much to lack of avidity as to antigenic change. The fact that a vaccinated population experienced little illness in the face of long and repeated challenge is a strong argument against the need for changes in vaccine composition.

## X. Summary

1) An explosive epidemic of H1N1 influenza occurred at Lowry AFB during February 1978. No H1N1 vaccine had been available and personnel under 25 were almost uniformly seronegative.

2) Influenza (febrile) attack rates were estimated to be about 30% in students, who ranged in age from 17 to 23. An additional 20% were probably infected during the epidemic.

3) The permanent party, most of which is over 25 years of age had far lower attack rates than the students.

4) A small number of cases of H3N2 influenza occurred between 30 November 1977 and 30 January 1978, but the spread of this disease was very limited in this vaccinated population.

5) The H1N1 virus strains differed from H3N2 strains in many ways. Isolation and identification were more difficult and lack of avidity of the prototype A/USSR/90/77 strain created difficulty in serodiagnosis. The most useful antigen for HI tests was an ether-split vaccine concentrate (PD) prepared from A/USSR/92/78.

6) Surveys of HI antibody levels of military and civilian populations between 17 and 24 years of age indicated that approximately one half had been infected during or following the February 1978 epidemic.

7) Studies of experimental H1N1 vaccines of 60 μg and 20 μg potencies showed that the former, whether split or whole virus, produced seroconversion in a very high proportion of persons. The 20 μg vaccine was less effective. A second injection of vaccine produced a good booster effect.

8) Evaluation in volunteers in November 1978 of the standard military vaccine (Connaught 20 μg, whole virus) showed a very satisfactory response to seronegative persons and a striking booster response in persons with antibody. The response was comparable to the 60 μg vaccines in the earlier studies.

9) A second H1N1 occurred in January 1979 after all base personnel had received H1N1 vaccine. In contrast to the first epidemic, it ran a slow smouldering course and febrile URI rates never reached high levels in the student population. During the peak week of the 1978 epidemic there were 119.0/1000/week; in 1978 the rate during the peak week was 11.4/1000/week.

10) While the 1979 H1N1 strains showed some antigenic drift the relevance of this to vaccine effectiveness remains difficult to determine because of the lack of avidity of most recently isolated H1N1 strains.

11) Antibody levels for A/Texas/77 and B/Hong Kong/72 were extremely high as a result of double immunization with vaccines. No cases of either disease were detected during the 1978-79 winter.

12) Only a single case of adenovirus disease was detected. Rubella, in contrast to previous years, has become very rare since the immunization program was instituted at Lackland AFB. Streptococcal pharyngitis occurred throughout the season, but at a relatively low level.

Recent Publications:

Meiklejohn, G., Eickhoff, T.C., and Graves, P.: Antibody Response of Young Adults to Experimental Influenza A/NJ/76 Vaccines. J. Infect. Dis. 136(Suppl): S456-S459, 1977.

Meiklejohn, G., Eickhoff, T.C., Graves, P., and I, J.: Antigenic Drift and Influenza Vaccine Effectiveness, 1976-77. J. Infect. Dis. 138:618-624, 1978.

Meiklejohn, G., Eickhoff, T.C., Graves, P. and I, J.: An Influenza A Epidemic Caused by H1N1 Virus. Military Medicine (in press).

Fishaut, M., McIntosh, K., and Meiklejohn, G.: Rapid Subtyping of Influenza A Virus Isolates by Membrane Fluorescence. J. Clin. Microbiol. (In press, February, 1979).

| Week | Students: Day visit with fever | Students: Night* visits | Students: Day visits without fever | Permanent party with febrile URI |
|---|---|---|---|---|
| 9-15 January | 16 | 54 | 345 | 11 |
| 16-22 January | 16 | 34 | 407 | 21 |
| 22-29 January | 19 | 44 | 377 | 27 |
| Average for 3 weeks | 17 | 44 | 376 | 20 |
| 30 Jan - 5 Feb | 139 (122) | 209 (165) | 578 (199) | 45 (20) |
| 6-12 February | 382 (365) | 240 (196) | 831 (455) | 101 (81) |
| 13-19 February | 133 (116) | 55 (11) | 529 (153) | 49 (29) |
| Total excess | (603) | (372) | (807) | (135) |

( ) Indicates excess over average of 3 preceding weeks

* Excess patients considered to be URI with fever.

Table 1. Number of clinic visits for upper respiratory infection before and during H1N1 influenza epidemic from student population.

| | Students | | Permanent Party | |
|---|---|---|---|---|
| | No. | Rate* | No. | Rate |
| Excess febrile URI | 603 | 18.8 | 135 | 2.8 |
| Excess night visits | 372 | 11.6 | | |
| Excess URI without fever | 807** | 25.2 | | |

*No./1000/week Student population 3209
Permanent party 4824

**May include revisits

Table 2. Estimates of illness rates in students and permanent party during H1N1 influenza epidemic.

| Classification | Percent of persons with HI titer of | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | <8 | 8 | 16 | 32 | 64 | 128 | 256 | 512 | 1024 |
| Pre-epidemic URI (46) | 93 | 7 | - | - | - | - | - | - | - |
| Cases of Influenza (116) | | | | | | | | | |
| Acute | 77 | 19 | 3 | - | 1 | - | - | - | - |
| Conv. | 1 | 3 | 14 | 24 | 27 | 22 | 7 | 3 | - |
| Post-epidemic URI (62) | 39 | 8 | 10 | 15 | 18 | 8 | 3 | - | - |
| Pre-vaccination SERA (103) | 43 | 9 | 25 | 10 | 9 | 5 | - | - | - |

Table 3. Comparison of distribution of HI antibody titers in different population groups (P.D. vaccine antigen)

| Group | Age | Year Bled | Percent of persons with titer of 8 or less | 16 | >32 |
|---|---|---|---|---|---|
| Military | 17-24 | 1977 | 93 | 7 | 0 |
| Civilian | <25 | 1978 | 63 | 12 | 25 |

Table 4. Comparison of HI antibody titers for A/USSR/92/77 of military personnel bled in 1977 with Denver area civilians of same age bled fall of 1978. Data suggest that at least 30% have been infected with A/USSR/77 virus.

| Test Strain | Percent of persons with titer of | | | | | | | | | Percent |
|---|---|---|---|---|---|---|---|---|---|---|
| | <8 | 8 | 16 | 32 | 64 | 128 | 256 | 512 | 1024 | ≥16 |
| A/Texas/77 | 8 | 4 | 8 | 19 | 26 | 24 | 7 | 4 | 0 | 88 |
| A/USSR/92/77 | 37 | 20 | 15 | 12 | 10 | 4 | 1 | 1 | 1 | 43 |
| B/Hong Kong/72 | 63 | 10 | 11 | 7 | 5 | 3 | 0 | 1 | 0 | 27 |

Table 5. HI antibody titers of 128 civilians from Denver area less than 25 years old in tests with A/Texas/76, A/USSR/92/77, and B/Hong Kong/72 in November 1978.

| | Serum | Number of persons with HI titer of <8 | 8 | 16 | 32 | 64 | 128 | 256 | 512 | 1024 | % with ≥4 x rise |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Wyeth 60 | Pre- | 7 | 5 | 6 | 2 | - | - | - | - | - | |
| (20) | Post- | 1 | - | - | 3 | 1 | 2 | 5 | 3 | 5 | 95 |
| M.S.D. 60 | Pre- | 8 | - | 8 | 1 | 3 | 1 | | | | |
| (21) | Post- | - | - | 3 | 2 | 2 | 4 | 4 | 6 | - | 88 |
| Wyeth 20 | Pre- | 7 | 2 | 6 | 1 | 4 | 2 | - | - | - | |
| (22) | Post- | 1 | 2 | 1 | 2 | 2 | 3 | 2 | 4 | 5 | 73 |
| M.S.D. 20 | Pre- | 13 | 1 | 4 | 5 | 2 | 2 | - | - | - | |
| (27) | Post- | 5 | - | 3 | 4 | 4 | 6 | 2 | 1 | 2 | 63 |
| Placebo | Pre- | 10 | 1 | 3 | 1 | - | - | - | - | - | |
| (15) | Post- | 9 | 2 | 3 | 1 | - | - | - | - | - | 0 |

Table 6. Distribution of pre- and post-vaccination HI antibody titers in sera from persons in the 4 experimental groups (tested with A/USSR/92/78 PD antigen).

| | | Cumulative % with HI titer of more than | | | | | | | | % with |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 8 | 16 | 32 | 64 | 128 | 256 | 512 | 1024 | ≥4 x rise |
| Wyeth 60 (20) | Pre- | 67 | 39 | 11 | - | - | - | - | - | |
| | Post- | 95 | 95 | 95 | 80 | 70 | 65 | 40 | 25 | 95 |
| M.S.D. 60 (21) | Pre- | 68 | 60 | 20 | 16 | 5 | - | - | - | |
| | Post- | 100 | 100 | 86 | 76 | 67 | 47 | 29 | - | 88 |
| Wyeth 20 (22) | Pre- | 68 | 59 | 32 | 27 | 9 | - | - | - | |
| | Post- | 95 | 86 | 82 | 73 | 64 | 50 | 41 | 23 | 73 |
| M.S.D. 20 (27) | Pre- | 52 | 48 | 33 | 15 | 7 | - | - | - | |
| | Post- | 81 | 81 | 70 | 55 | 41 | 19 | 11 | 7 | 63 |

Table 7. Comparison of HI antibody response of all volunteers to the 4 experimental vaccines (tested with Parke-Davis ether-split antigen from strain A/USSR/92/77).

| Vaccine | Serum | Cumulative percent with HI titer more than 8 | 16 | 32 | 64 | 128 | 256 | 512 | 1024 | % with 4x rise |
|---|---|---|---|---|---|---|---|---|---|---|
| Wy 60 (12) | Pre- | -- | -- | -- | -- | -- | -- | -- | -- | |
| | Post- | 100 | 92 | 92 | 75 | 61 | 58 | 17 | 17 | 92 |
| MSD 60 (8) | Pre- | -- | -- | -- | -- | -- | -- | -- | -- | |
| | Post- | 88 | 88 | 88 | 88 | 62 | 25 | -- | -- | 88 |
| Wy 20 (10) | Pre- | 10 | -- | -- | -- | -- | -- | -- | -- | |
| | Post- | 80 | 60 | 60 | 50 | 30 | 30 | 20 | 10 | 60 |
| MSD 20 (13) | Pre- | -- | -- | -- | -- | -- | -- | -- | -- | |
| | Post- | 69 | 69 | 62 | 31 | 15 | 15 | 8 | 8 | 69 |
| MSD (20-20-20) (9) | Pre- | -- | -- | -- | -- | -- | -- | -- | -- | |
| | Post- | 89 | 89 | 89 | 56 | 33 | 22 | -- | -- | 89 |
| CL 21-7-7* (31) | Pre- | 3 | -- | -- | -- | -- | -- | -- | -- | |
| | Post- | 100 | 90 | 77 | 58 | 35 | 19 | 6 | -- | 90 |

*Standard military vaccine in November, 1978 (Lot #2166HK)

Table 8. Comparison of results of HI tests in seronegative persons after first injection of 6 different H1N1 vaccines.

| Vaccine | | Serum | Cumulative percent with HI titers more than 8 | 16 | 32 | 64 | 128 | 256 | 512 | 1024 | % with 4x rise | % with titer >16 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Wy 60 | (14) | 2 | 93 | 86 | 86 | 71 | 64 | 57 | 14 | 14 | | 86 |
| | (12) | 3 | 100 | 100 | 100 | 83 | 67 | 58 | 17 | 17 | 8 | 100 |
| MSD 60 | (9) | 2 | 78 | 78 | 78 | 78 | 56 | 22 | 22 | 22 | | 78 |
| | (8) | 3 | 88 | 88 | 88 | 88 | 88 | 38 | 13 | 13 | 13 | 88 |
| Wy 20 | (11) | 2 | 73 | 56 | 56 | 45 | 27 | 27 | 18 | 9 | | 56 |
| | (10) | 3 | 100 | 100 | 90 | 50 | 50 | 30 | 20 | 20 | 10 | 100 |
| MSD 20 | (13) | 2 | 77 | 69 | 62 | 38 | 15 | 15 | 8 | 8 | | 69 |
| | (12) | 3 | 85 | 85 | 70 | 62 | 24 | 16 | 8 | 8 | 8 | 85 |

Table 9. Comparison of HI antibody levels of seronegative persons in sera collected after first (2) and second* injections of experimental vaccines.

*MSD 20-20-20

| Test Antigen | Place Tested | Serum | Cumulative percent with HI titer more than <8 | 8 | 16 | 32 | 64 | 128 | 256 | 512 | 1024 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| A/USSR/92/77 | UCMC | Pre- | 44 | 57 | 49 | 22 | 14 | 7 | 0 | 0 | 0 |
| | | Post- | 19 | 82 | 79 | 69 | 56 | 50 | 35 | 22 | 9 |
| A/USSR/90/77 | UCMC | Pre- | 58 | 43 | 24 | 9 | 7 | 4 | 2 | 0 | 0 |
| | | Post- | 26 | 74 | 60 | 56 | 52 | 42 | 34 | 19 | 14 |

| Test Antigen | Place Tested | Serum | Cumulative percent with HI titer more than <8 | 10 | 20 | 40 | 80 | 160 | 320 | 640 | 1280 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| A/USSR/92/77 | CDC | Pre- | 24 | 76 | 55 | 39 | 16 | 7 | 3 | 0 | 0 |
| | | Post- | 7 | 94 | 84 | 76 | 58 | 51 | 39 | 23 | 9 |
| A/USSR/90/77 | CDC | Pre- | 56 | 45 | 31 | 11 | 5 | 2 | 0 | 0 | 0 |
| | | Post- | 20 | 80 | 71 | 64 | 51 | 38 | 24 | 14 | 8 |

Table 10. Comparison of results of HI tests done at University of Colorado Medical Center and at the Center for Disease Control with paired sera from 102 persons bled before and after first injection of experimental vaccines.

| Test Antigen | Place Tested | Serum | Cumulative percent with HI titer more than <8 | 8 | 16 | 32 | 64 | 128 | 256 | 512 | 1024 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| A/USSR/92/77 | UCMC | Pre- | 51 | 49 | 46 | 34 | 19 | 7 | 5 | 0 | 0 |
| | | 2 | 15 | 87 | 83 | 80 | 70 | 57 | 42 | 28 | 14 |
| | | 3 | 4 | 95 | 95 | 92 | 84 | 70 | 52 | 31 | 18 |
| A/USSR/90/77 | UCMC | Pre- | 78 | 21 | 14 | 7 | 7 | 3 | 1 | 0 | 0 |
| | | 2 | 35 | 66 | 60 | 54 | 48 | 39 | 30 | 18 | 9 |
| | | 3 | 22 | 78 | 75 | 63 | 54 | 41 | 28 | 16 | 11 |

| Test Antigen | Place Tested | Serum | Cumulative percent with HI titer more than 10 | 10 | 20 | 40 | 80 | 160 | 320 | 640 | 1280 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| A/USSR/92/77 | CDC | Pre- | 20 | 80 | 59 | 42 | 18 | 7 | 3 | 0 | 0 |
| | | 2 | 5 | 95 | 87 | 79 | 65 | 53 | 41 | 23 | 8 |
| | | 3 | 0 | 99 | 99 | 95 | 79 | 61 | 46 | 20 | 3 |
| A/USSR/90/77 | CDC | Pre- | 49 | 50 | 33 | 11 | 6 | 4 | 1 | 0 | 0 |
| | | 2 | 18 | 83 | 71 | 59 | 51 | 42 | 30 | 10 | 2 |
| | | 3 | 3 | 96 | 85 | 74 | 58 | 44 | 26 | 8 | 0 |

Table 11. Comparison of results of HI tests with A/USSR/92/77 and A/USSR/92/77 in University of Colorado Medical Center and the Center for Disease Control Laboratories with 3 sera from 92 persons who received 2 injections of experimental vaccines. (The pre- and second blood are a repeat of test shown in Table ).

| Serum | No. of persons | Percent with A/Texas/77 HI titer more than 8 | 16 | 32 | 64 | 128 | 256 | 512 | 1024 | % with ≥2x rise | % with ≥4x rise |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Pre- | 95 | 93 | 93 | 80 | 66 | 45 | 30 | 18 | 11 | | |
| Post- | 95 | 97 | 97 | 91 | 83 | 73 | 49 | 31 | 16 | 36 | 27 |
| | | Percent with B/HK/72 HI titer more than | | | | | | | | | |
| Pre- | 95 | 94 | 93 | 86 | 73 | 41 | 30 | 20 | 11 | | |
| Post- | 95 | 94 | 94 | 89 | 80 | 59 | 33 | 25 | 17 | 8 | 4 |

Table 12. HI antibody response to A/Texas/77 and B/HK/72 of persons who received trivalent MSD 20-20-20 vaccine. All persons had previously received bivalent PD ether split vaccine containing 200 CCA units of A/Victoria/75 and of B/HK/72.

| | | Percent of persons with titers of | | | | | | | | | % with titer ≥128 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | <8 | 8 | 16 | 32 | 64 | 128 | 256 | 512 | 1024 | |
| All Persons (67) | Pre-vacc. | 48 | 8 | 11 | 22 | 8 | 3 | 2 | 2 | 0 | |
| | Post-vacc. | 0 | 5 | 3 | 14 | 8 | 24 | 17 | 16 | 15 | 72 |
| Persons with titer <8* (32) | Pre-vacc. | 100 | -- | -- | -- | -- | -- | -- | -- | -- | |
| | Post-vacc. | 0 | 6 | 6 | 25 | 16 | 25 | 3 | 13 | 6 | 47 |
| Persons with titer ≥16 (30) | Pre-vacc. | 0 | 0 | 23 | 47 | 17 | 7 | 3 | 3 | 0 | |
| | Post-vacc. | 0 | 0 | 0 | 3 | 0 | 24 | 24 | 24 | 28 | 97 |

Table 13: Distribution of HI antibody titers for A/USSR/92/77 (PD antigen) of 67 students at Lowry AFB before and 3 weeks after receiving trivalent influenza vaccine containing 20 µg each of A/USSR/92/77, A/Texas/77 and B/Hong Kong/72. All had previously received bivalent vaccine containing A/Texas/77 and B/Hong Kong/72.

*Five persons with titers of 8 are not included because it is uncertain whether "antibody" at this level is due to infection during 1978 or is non-specific.

( ) indicates number in group.

| Test Strain | Serum | Percent of persons with HI titers of | | | | | | | | | % with 4x rise |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | <8 | 8 | 16 | 32 | 64 | 128 | 256 | 512 | 1024 | |
| A/Texas/77 | Pre-vacc. | 1 | 1 | 3 | 6 | 15 | 27 | 21 | 16 | 9 | |
| | Post-vacc. | 0 | 0 | 1 | 1 | 12 | 21 | 37 | 19 | 7 | 15 |
| B/Hong Kong/72 | Pre-vacc. | 1 | 4 | 16 | 15 | 16 | 18 | 13 | 4 | 10 | |
| | Post-vacc. | 0 | 0 | 12 | 16 | 25 | 15 | 19 | 6 | 6 | 9 |

Table 14: Distribution of HI antibody titers of 67 students before and 3 weeks after receiving trivalent vaccine containing 20 mg each of A/Texas/77, B/Hong Kong/72 and A/USSR/92/77. All had previously received bivalent vaccine containing A/Texas/77 and B/Hong Kong/72.

| Antigen (No. of Persons) | Serum Specimens | Percent of persons with HI titer of | | | | | | | | Percent with 4X rise |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 8 | 8 | 16 | 32 | 64 | 128 | 256 | 512 | 1024 | |
| A/USSR/77 (116) | Acute | 100 | -- | -- | -- | -- | -- | -- | -- | -- | |
| | Conv. | 23 | 25 | 26 | 16 | 5 | 3 | -- | 1 | -- | 51 |
| A/FM1/47 (80) | Acute | 76 | 15 | 6 | 3 | -- | -- | -- | -- | -- | |
| | Conv. | 10 | 5 | 22 | 42 | 8 | 11 | -- | 1 | -- | 78 |
| P.D. Vaccine* (116) | Acute | 77 | 19 | 3 | -- | 1 | -- | -- | -- | -- | |
| | Conv. | 1 | 3 | 14 | 24 | 27 | 22 | 7 | 3 | -- | 91 |

*Ether-split Parke-Davis A/USSR/77 vaccine concentrate.

Table 15. Results of HI tests with sera from patients with influenza during H1N1 outbreak at Lowry AFB, February 1 to February 14, 1978.

| | Percent of persons with titer of | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Antigen | <8 | 8 | 16 | 32 | 64 | 128 | 256 | 512 | 1024 | % ≥16 |
| P.D. vaccine | 43 | 9 | 25 | 10 | 9 | 5 | - | - | - | 49 |
| A/USSR/77 | 60 | 17 | 17 | 2 | 2 | 2 | 1 | - | - | 24 |

Table 16. Comparison of HI antibody titer distribution of pre-vaccination sera using P.D. vaccine and A/USSR/77 virus antigen.

| Temperature (F) | No. of Persons | % of Persons |
|---|---|---|
| <100 | 6 | 4.3 |
| 100-100$^9$ | 46 | 32.8 |
| 101-101$^9$ | 54 | 38.6 |
| 102-102$^9$ | 28 | 20.0 |
| 103-103$^9$ | 5 | 3.6 |
| >104 | 1 | 0.7 |

Table 17. Clinic oral temperature of 140 cases of A/USSR/78

| 1977-1978 | | | 1978-1979 | | |
|---|---|---|---|---|---|
| Week Starting | No. Febrile URI Clinic Visits | No./1000/week | Week Starting | No. Febrile URI Clinic Visits | No./1000/week |
| 9 Jan | 16 | 4.9 | 29 Oct | 2 | |
| 16 Jan | 16 | 4.9 | 6 Nov | 11 | 4.6 |
| 23 Jan | 19 | 5.9 | 13 Nov | 15 | 6.3* |
| 30 Jan | 139 | 43.3* | 20 Nov | 16 | 6.7* |
| 6 Feb | 382 | 119.0* | 27 Nov | 8 | 3.4 |
| 13 Feb | 78 | 24.3* | 4 Dec | 10 | 4.2 |
| 20 Feb | 23 | 7.2* | 11 Dec | 8 | 3.4* |
| 27 Feb | 26 | 8.1* | 18 Dec | 7 | 2.9* |
| 6 Mar | 21 | 6.5* | Christmas break | | |
| 13 Mar | 17 | 5.3* | 2 Jan | 10 | 4.2* |
| 20 Mar | 22 | 6.8 | 8 Jan | 27 | 11.4* |
| | | | 15 Jan | 16 | 6.7* |
| | | | 22 Jan | 11 | 4.7* |

*Influenza cases detected

Table 18. Comparison of febrile URI rates in student population in the 2 H1N1 outbreaks (based on daytime clinic visits).

| Test Strain | Serum | Percent with titer of <8 | 8 | 16 | 32 | 64 | 128 | 256 | 512 | 1024 | % with 4x rise |
|---|---|---|---|---|---|---|---|---|---|---|---|
| A/USSR/92/77 | Acute | 88 | 12 | -- | -- | -- | -- | -- | -- | -- | |
| (P.D.) | Conv. | -- | 16 | 24 | 24 | 24 | 12 | -- | -- | -- | 88 |
| A/Calif/1/78 | Acute | 100 | -- | -- | -- | -- | -- | -- | -- | -- | |
| E2 | Conv. | 12 | 32 | 24 | 24 | 8 | -- | -- | -- | -- | 56 |
| A/Brazil/78 | Acute | 100 | -- | -- | -- | -- | -- | -- | -- | -- | |
| E8 | Conv. | 56 | 32 | 8 | 4 | -- | -- | -- | -- | -- | 12 |
| A/USSR/90/77* | Acute | 100 | -- | -- | -- | -- | -- | -- | -- | -- | |
| E8 | Conv. | 24 | 16 | 16 | 32 | 4 | 4 | -- | 4 | -- | 60 |

*Run in different test

Table 19. Comparison of results of HI tests using 4 H1N1 strains with serum pairs from 25 cases occurring in February, 1978.

| Test Strain | Serum | Percent with titer of | | | | | | | | | % with 4x rise |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | <8 | 8 | 16 | 32 | 64 | 128 | 256 | 512 | 1024 | |
| A/USSR/92/77 (P.D.) | Pre- | 97 | 3 | -- | -- | -- | -- | -- | -- | -- | |
| | Post- | -- | 10 | 13 | 19 | 23 | 16 | 13 | 6 | -- | 90 |
| A/Calif/1/78 E2 | Pre- | 97 | 3 | -- | -- | -- | -- | -- | -- | -- | |
| | Post- | 19 | 23 | 32 | 3 | 10 | 13 | -- | -- | -- | 58 |
| A/Brazil/78 E8 | Pre- | 100 | -- | -- | -- | -- | -- | -- | -- | -- | |
| | Post- | 45 | 23 | 13 | 6 | 13 | -- | -- | -- | -- | 32 |

Table 20. Comparison of results of HI tests with 3 H1N1 strains with serum pairs from 31 seronegative persons who received H1N1 vaccine

| Test Strains | Serum | Percent with titer of <8 | 8 | 16 | 32 | 64 | 128 | 256 | 512 | 1024 | % with 4x rise |
|---|---|---|---|---|---|---|---|---|---|---|---|
| A/USSR/90/77 | Acute | 100 | -- | -- | -- | -- | -- | -- | -- | -- | |
| E10 | Conv. | 24 | 24 | 24 | 16 | 8 | -- | 4 | -- | -- | 52 |
| A/Den/9284/79 | Acute | 96 | 4 | -- | -- | -- | -- | -- | -- | -- | |
| E3 | Conv. | 24 | 4 | 20 | 32 | 8 | 12 | -- | -- | -- | 72 |

Table 21. Comparison of results of HI tests using A/USSR/90/77 and A/Den/9284/79 with serum pairs from 25 cases occurring in February, 1978.

| Test Strain | Serum | Percent with titer of <8 | 8 | 16 | 32 | 64 | 128 | 256 | 512 | 1024 | % with 4x rise |
|---|---|---|---|---|---|---|---|---|---|---|---|
| A/USSR/90/77 E10 | Pre- | 60 | 8 | 20 | -- | -- | 4 | 4 | -- | 4 | |
| | Post- | 12 | 12 | 4 | 16 | 4 | 8 | 4 | 24 | 16 | 64 |
| A/Den/9284/79 E3 | Pre- | 52 | 12 | 20 | -- | 8 | 4 | 4 | -- | -- | |
| | Post- | 16 | -- | -- | 20 | 12 | 16 | 20 | 4 | 12 | 72 |

Table 22. Comparisons of results of HI tests with A/USSR/90/77 and A/Den/9284/79 with serum pairs from 25 seronegative persons who received H1N1 vaccine

| Patient No. | Onset Date | HI titer with test antigen A/USSR/92/78 | A/Calif/1/78 | A/Brazil/78 | A/Den/9284/78 | CF Test | Virus Isolated |
|---|---|---|---|---|---|---|---|
| 1 | 12/13 | <8/64 | <8/16 | <8/<8 | <8/16 | 16/16 | 0 |
| 2 | 12/21 | <8/16 | <8/<8 | <8/<8 | <8/8 | <8/<8 | + |
| 3 | 1/2 | 8/64 | <8/16 | <8/8 | <8/16 | <8/64 | + |
| 4 | 1/2 | 8/128 | <8/128 | <8/64 | <8/64 | <8/64 | + |
| 5 | 1/2 | <8/16 | <8/<8 | <8/<8 | <8/<8 | <8/64 | + |
| 6 | 1/2 | 8/64 | 8/32 | <8/16 | 32/128 | 16/64 | + |
| 7 | 1/4 | <8/16 | <8/8 | <8/<8 | <8/<8 | 8/16 | + |
| 8 | 1/4 | <8/64 | <8/16 | <8/<8 | <8/<8 | 16/32 | 0 |
| 9 | 1/4 | 16/64 | <8/32 | <8/16 | <8/32 | <8/64 | + |
| 10 | 1/5 | 32/128 | <8/32 | <8/16 | <8/16 | <8/32 | + |
| TOTAL | | 10/10 | 7/10 | 4/10 | 6/10 | 6/10 | 8/10 |

Table 23. Comparison of result of HI tests with 4 different H1N1 antigen on paired sera from 10 patients with influenza in December 1978 or January 1979.

## VOLUNTEER AGREEMENT

Lowry Air Force Base and the University of Colorado Medical Center have jointly studied the effectiveness of "flu" vaccines for many years. This year the occurrence of "Russian" influenza at Lowry and other military bases has made it necessary to prepare new vaccines and it is essential to determine whether one or two injections of vaccine are needed. We are asking you to help us in this study to make a contribution to both military and civilian populations in the development of better vaccines to protect persons from the "flu". You are asked, as a volunteer, to donate a tube of blood (10.0 ml or 2 1/2 teaspoons) from your arm before you receive your shot and 2-3 weeks after your vaccination to determine how much protection from the "flu" was provided by the vaccination.

I, _____, having full capacity to consent, do hereby volunteer to participate in this study.

_____
Signature Date

_____
Witness Date

## VOLUNTEER CONSENT AGREEMENT

I, _____, having attained my eighteenth (18th) birthday, and otherwise having the full capacity to consent, do hereby volunteer to allow throat washings to be taken from me and/or blood to be drawn from me now and again 3 weeks later for the purpose of determining the cause of my upper respiratory tract illness.

Ms. Viola DeTuerk has explained to me the nature of these studies, and that these studies are an important part of the studies of upper respiratory tract infection and the effectiveness of influenza vaccines being carried out at Lowry Air Force Base by Drs. Gordon Meiklejohn and Theodore Eickhoff of the University of Colorado Medical Center.

_____

Signature Date

I was present during the explanation referred to above, as well as the volunteer's opportunity for questions, and hereby witness his signature.

_____

Witness' Signature Date

FIGURE 1

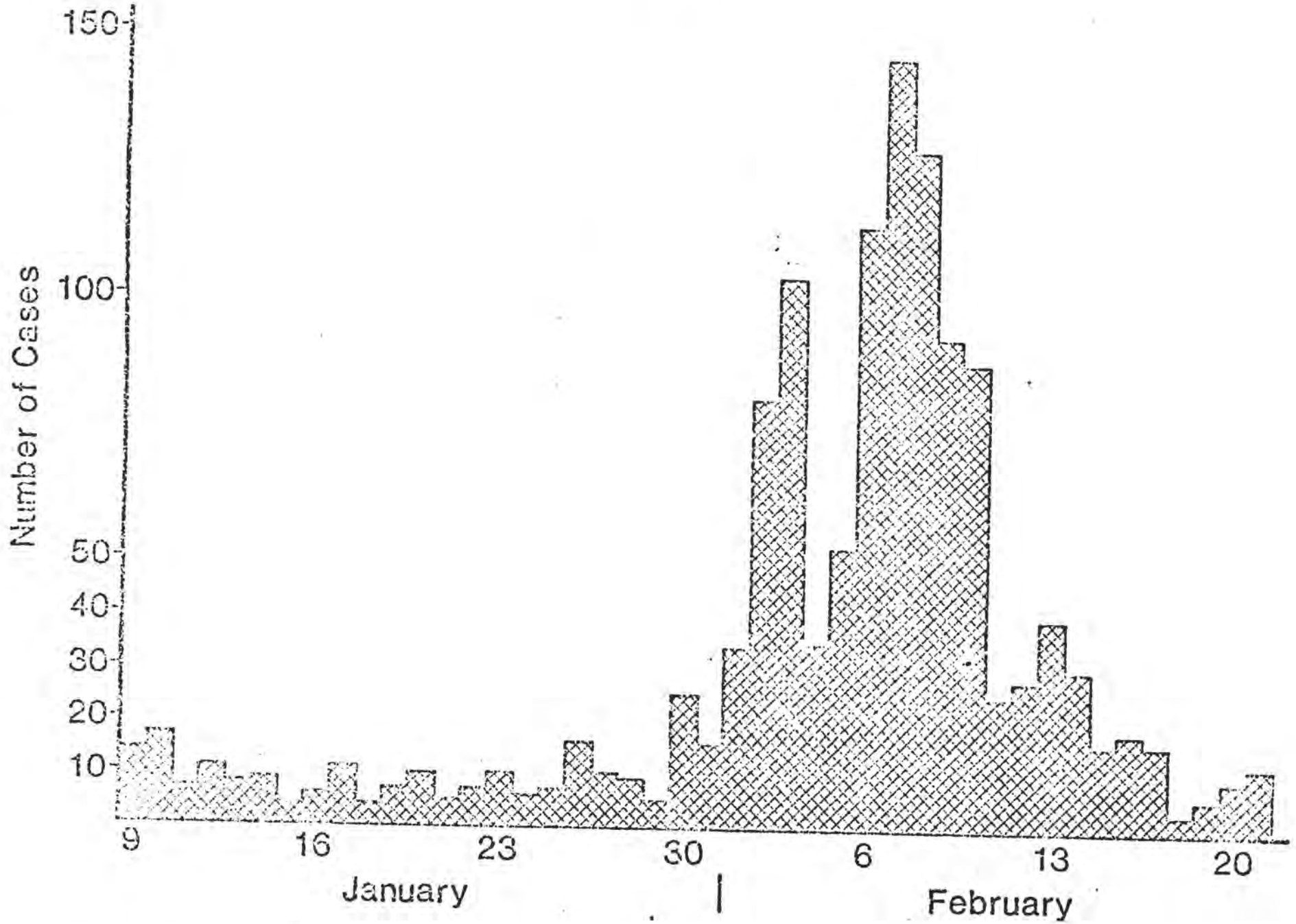
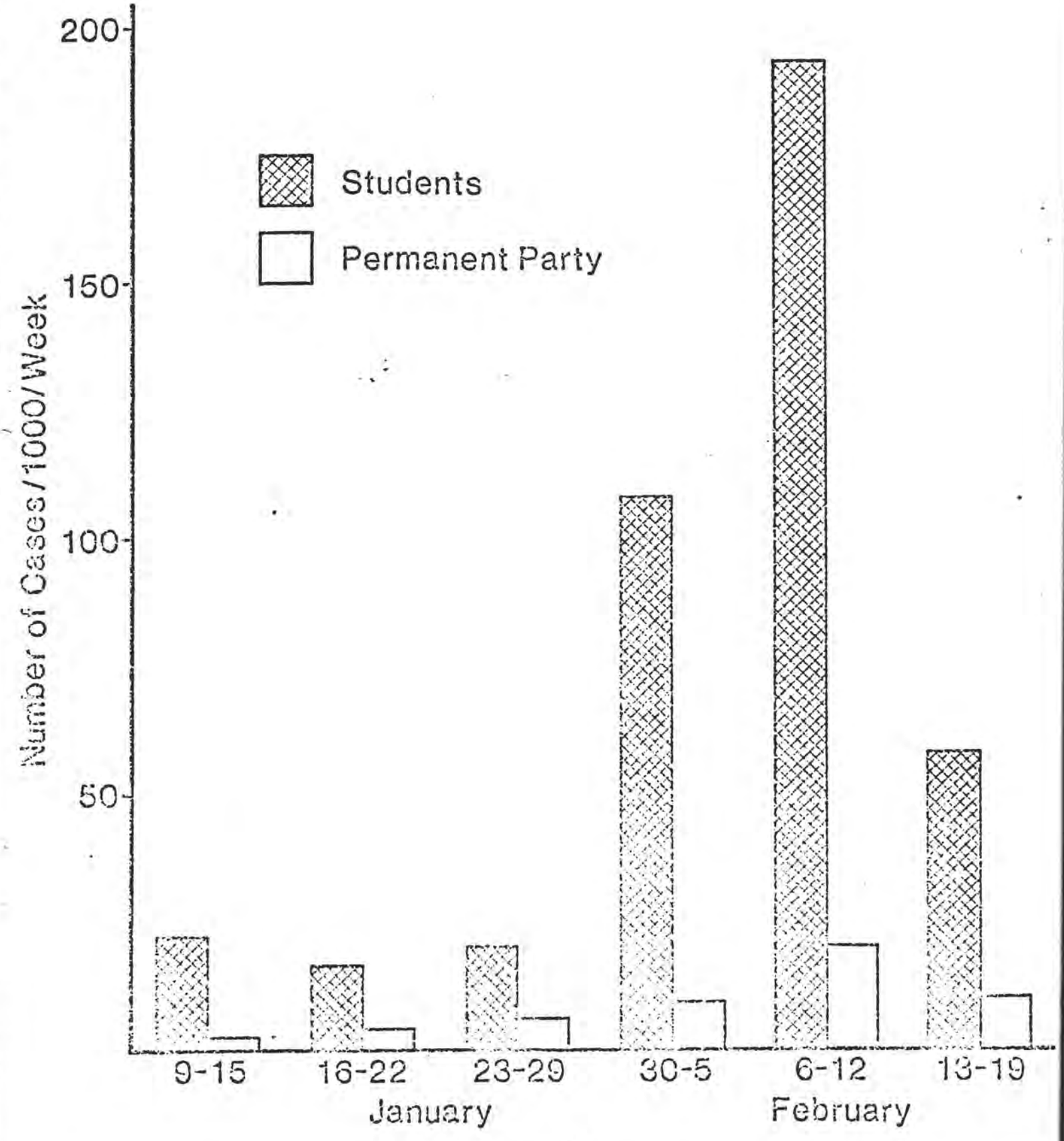

150
100
50
40
30
20
10
Number of Cases
9
16
23
30
6
13
20
January
February

FIGURE 2


200
150
100
50
Number of Cases/1000/Week
Students
Permanent Party
9-15
16-22
23-29
30-5
6-12
13-19
January
February

# SUPPLEMENTARY

# INFORMATION

DEPARTMENT OF THE ARMY
U S ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
FORT DETRICK, FREDERICK, MD 21702-5012

MCMR-RMI-S (70-1y)

ERRATA
AD-B081473

19 JUL 1996

MEMORANDUM FOR Administrator, Defense Technical Information Center, ATTN: DTIC-OCP, Fort Belvoir, VA 22060-6218

SUBJECT: Request Change in Distribution Statements

1. The U.S. Army Medical Research and Materiel Command, has reexamined the need for the limited distribution statement on technical reports. Request the limited distribution statement for the following accession numbers be changed to "Approved for public release; distribution unlimited," and that copies of these reports be released to the National Technical Information Service.

| | | | |
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| ADB087493 | ADB068920 | ADB108614 | ADB092559 |
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| ADB096009 | ADB091643 | ADB091748 | ADB113188 |
| ADB097567 | ADB097568 | ADB081493 | |

2. The point of contact for this request is Ms. Virginia Miller, DSN 343-7327.

FOR THE COMMANDER:

(23)

CORNELIUS R. FAY III
Lieutenant Colonel, MS
Deputy Chief of Staff for
Information Management