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EPIDEMIOLOGICAL SURVEILLANCE OF INFLUENCE AND OTHER RESPIRATORY DISEASES IN MILITARY PERSONNEL

Annual Report

Gordon Meiklejohn, M.D.
Theodore C. Eickhoff, M.D.

February 1984
(For the period 1 June 1983 to 31 January 1984)

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Summary

1. Despite the presence of H3N2 and H1N1 influenza A and influenza B on the Base during the 1982-83 season, febrile respiratory disease rates remained at unprecedentedly low levels.

2. In the student population no cases of influenza B were detected; only a single case of H3N2 influenza and only 14 cases of H1N1 influenza were detected. The combined attack rates of all three viruses in students and permanent party was less than 0.5%.

3. In order to determine whether the antigenic drift in the new H3N2 strain A/Philippines/2/83 would significantly reduce the effectiveness of A/Bangkok/79 vaccine, sera from Air Force recruits were tested and showed good A/Philippines/82 response to A/Bangkok vaccine. In order to further clarify this issue, sera from Naval recruits in San Diego who had received either A/Bangkok or A/Philippines as the H3N2 component were tested in parallel. Recipients of the A/Bangkok vaccine showed a highly satisfactory response to the A/Philippines vaccine. These results suggested that it would be justifiable to use up the remaining stocks of 1982-83 vaccine before shifting over to the newer formulations containing the A/Philippines/2/82 strain. This resulted in sizable savings in vaccine cost.

4. The vaccine response to 1983-84 vaccine of both recruits and permanent party at Lackland Air Force Base was tested in December 1983. Again, there was excellent response to the H3N2 and influenza B components. Furthermore, the H1N1 component appeared to provide not only an excellent response to the A/Brazil/79 strain but also to three of the newer H1N1 strains which have been isolated in the southern hemisphere.

5. While the response of permanent party was slightly lower than that of the recruits, it appeared that the 1983-84 formulations would provide a high degree of protection. The incorporation of a new strain into the vaccine for the 1984-85 year might be helpful in other segments of the population and would be acceptable for the military population.

6. When serum pairs from recruits vaccinated in 1982-83 were tested against older H3N2 strains, it was shown, in accordance with the doctrine of original antigenic sin, that current vaccines would provide a high degree of protection against any of the earlier H3N2 strains.

7. Considerable effort was made to assess the usefulness of various procedures in determining need for antigenic strain composition of the vaccine. It was concluded that the testing of human antibody response continues to be an essential guide and provides data far more pertinent than the titers of ferret antisera. Considerable emphasis has been placed in recent years on the latter by the C.D.C. for the civilian population.

8. When the oral temperatures of confirmed cases of H1N1 and H3N2 influenza A were compared, essentially no difference was found. Patients with influenza B tended to have considerably lower temperatures than those with influenza A viruses.

Summary (continued)

9. The relationship between the oral temperature and the success in isolating virus in influenza patients was compared. With H3N2 influenza, virus recovery rates were higher in patients with higher fever. There was not, however, a similar relationship with either H1N1 influenza or influenza B.

10. Complement fixation tests using RSV antigen of 140 serum pairs collected last spring showed fourfold increases in titer in 3 individuals and twofold increases in titer in an additional 11 persons. Preliminary results with ELISA technique suggest that this may prove to be more sensitive in detecting antibody and plans are being made for testing larger numbers of serum in order to delineate better the role of this agent as a cause of febrile URI.

11. Other viral diseases play an insignificant role in the disease picture during the 1982-83 season. Only four cases of adenovirus disease and no rubella or rubeola were detected.

I. Introduction

During the past year the principal investigator had the opportunity to review and summarize the 30 annual reports submitted on this contract since its inception in 1952 (Meiklejohn G. Viral respiratory disease at Lowry Air Force Base in Denver, 1952-1982. J Infec Dis 1983;148(5):775-84.) The story which unfolds is a most encouraging one. At the time when the studies began, Lowry Air Force Base was plagued by febrile respiratory diseases. The Base had a 400-bed hospital and a medical complement of 25-30 medical offices. Streptococcal disease was rampant and acute rheumatic fever was occurring at a rate of more than 100 cases per annum. Influenza epidemics occurred at frequent intervals, causing high attack rates in unvaccinated troops. The Asian epidemic of 1957 taxed the hospital to its limit. Adenovirus disease caused by types 4 and 7 occurred in annual epidemics which lasted from January to early spring, with febrile URI rates as high as 50/1000/ week.

Since the early 1960s there has been no hospital on the Base. Viral respiratory disease is now readily handled in a dispensary by a staff consisting of three medical officers, two physicians' assistants and two nurse practitioners. The rare case requiring hospitalization is handled at Fitzsimons Army Hospital. Adenovirus disease has been virtually eliminated since the policy of administering oral vaccine to incoming recruits at Lackland Air Force Base was instituted in the early 1970s. No types other than types 4 and 7 have appeared as significant causes of illness. Streptococcal pharyngitis still occurs, causing roughly 10 to 15% of all febrile URI, but there have been no large outbreaks and no acute rheumatic fever. Influenza continues to be the one problem which cannot yet be considered solved.

Even with influenza, however, the situation has changed remarkably for the better. A series of vaccine trials in the 1950s and early 60s established the effectiveness of inactivated aqueous vaccine of sufficient potency and appropriate strain composition. It was also shown that vaccine which raised antibody levels of most recipients to sufficiently high levels effectively prevented illness and disease transmission. For the past 15 years there have been only two outbreaks of any significance: the first in 1972 when the England variant of H3N2 first appeared, and the second in 1977-78 when H1N1 (Russian) influenza A appeared and no vaccine was available. The latter episode provided a vivid reminder of what influenza can do in an unvaccinated population. Approximately 50% of the student population reported ill during a one-month period after introduction of the virus. Since that time H1N1 influenza has reappeared on several occasions, but in vaccinated personnel has caused very little illness. Febrile URI rates remain at record low levels, rarely exceeding 5/1000/week, and have not caused a disruption of training programs.

Other viral diseases such as rubella and rubeola have been eliminated since the policy was adopted at Lackland Air Force Base of screening recruits for antibody to these agents and vaccinating those who were seronegative.

It would appear that the situation is well under control and that little further needs to be done. This may be true of all the viruses except for influenza, which remains an enigma. The unique capacity for antigenic change which characterizes this virus poses a continuing threat. The sophisticated techniques of modern biology are slowly unraveling the explanation for the capacity of this virus to misbehave as it does and provide hope that in the future even better methods for control will be found. Meanwhile, however, constant surveillance

must be maintained and adjustments must be made in vaccine composition as the virus changes. Our laboratory has been involved in two of these discussions during the past year relating to change in composition of both H3N2 and H1N1 constituents of the vaccine. It remains essential to maintain continuing surveillance of these diseases and to utilize an experienced laboratory to monitor antigenic differences and in the future to evaluate new agents which might provide still better control of influenza.

II. Summary of Influenza Occurrence during 1982-83 Season

It has been noted in recent reports that since the winter of 1977-78, the number of cases of influenza of any type has been very small and the rates of febrile upper respiratory disease (URI) have remained at unprecedentedly low levels. Completion of laboratory tests on sera from patients with febrile URI in the 1982-83 winter again shows the same pattern. (Figure 1) Despite the occurrence of influenza B and both H1N1 and H3N2 influenza A, the rates of febrile URI never exceeded 3.8 per 1,000 per week.

Cases of influenza B occurred over a 16-week period but at no time were there more than two cases in any week. Thus, despite the introduction of this virus on at least nine occasions, there was no evidence of spread.

H3N2 influenza also was introduced on at least four occasions, but at no time were there more than five cases in any one week. As with influenza B, with one exception, all cases occurred in members of the permanent party.

H1N1 influenza first appeared during the week of March 21 and, during the following week, 10 cases were detected in students and one in the permanent party. The following week five cases were found. Two additional cases occurred during the early weeks of May. This was the only one of the three viruses which caused a noticeable increase in the rate of febrile URI. H.I. tests on the cases in students showed that the illness was limited to those with extremely low level antibody titers (<8 or 8). The cases were dsitributed among seven student squadrons with no more than three cases in any one squadron. Thus, there was ample opportunity for the virus to take off, but it failed to show the capacity to spread in this well-immunized population.

III. Controversy about Possible Ineffectiveness of Vaccine Containing A/Bangkok/79 in Protection against A/Philippines/2/82 Outbreak

In last year's report it was noted that in tests with sera from Air Force recruits bled in the fall of 1982, the response of those who received the A/Bangkok/79 antigen was highly satisfactory in tests with the more recently isolated A/Philippines/82 strain. These results were in direct conflict with those reported by the CDC which, on the basis of tests with ferret antisera and tests with Air Force recruits, had suggested a far greater antigenic variation than the results reported from this laboratory. It appears in retrospect that the difference is mainly due to the fact that the CDC tests were done with very low passage virus which may have been non-avid, while ours were done with a more avid recombinant (X=79) A/Philippines/82 virus.

It was important to clarify this difference since there was a large stockpile of vaccine on hand containing the A/Bangkok/79 strain and the question was whether to use it until it was exhausted or to discard it and replace it with the newer formulation containing A/Philippines/82. It proved to be impossible to

carry out this study at Lackland Air Force Base. The arrangements were made through the AFEB with the cooperation of the Navy and Bureau of Biologics to test in a side-by-side manner the standard military vaccine containing A/Bangkok/79 and a newly prepared trivalent vaccine containing A/Philippines/82 strain.

The vaccines used were (1) standard military vaccine (1982-83) which contained 15 mcg each of A/Bangkok/79, A/Brazil/78 and B/Singapore/79, and (2) vaccine containing A/Philippines instead of A/Bangkok/79. The latter was prepared during early 1983 and had been checked by the Bureau of Biologics for potency before being shipped to San Diego for trial in Naval recruits. Both vaccines were whole virus preparations made by Connaught. Pre-vaccination sera were taken at the time of induction and post-vaccination sera 18 days later, slightly earlier than is customary.

Frozen sera were received in excellent shape from San Diego from 160 Navy recruits, of whom 81 had received A/Bangkok vaccine and 79 had received the A/Philippines vaccine. The sera were run in three tests. The results checked extremely well from test to test and controls appeared to be as close as possible. After opening the code, it was obvious that there had been roughly equal numbers of recipients of each vaccine in each test, thereby insuring the validity of the comparison.

The response to the A/Bangkok vaccine, when measured with A/Bangkok antigen, was again excellent, as it had been in earlier tests. A/Bangkok response to A/Philippines vaccine was also extraordinarily good, as one would expect when a new variant is used to stimulate antibody against an earlier strain. The A/Philippines response to the two vaccines was slightly lower with the A/Bangkok vaccine than we had observed in our earlier tests. With the homologous vaccine (A/Philippines), 94% of individuals had titers of 32 or higher, while with the A/Bangkok vaccine this percentage was 80. It is noteworthy that, at a level of 1 to 16, the two vaccines appeared to be comparable and the difference was in the height of the titer response rather than in the number of individuals who responded.

In Table 2 data are presented on distribution of antibody titers in the vaccinated students over the period from 1976 to the present. The group is divided into three segments: those with titers of 8 or less being considered highly susceptible; those with titers of 32 or more considered essentially resistant; and those with titers of 1 to 16 being considered intermediate with an expected lowering of incidence by perhaps 50 to 75% over expected rates in unvaccinated persons.

There has been no year in which the attack rate in students exceeded 1%. The data which are most comparable to the present situation are those for 1976-77 and 1977-78, when the distribution of antibody levels was quite similar to that observed with the A/Philippines antibody levels in the present year. In the two earlier years the observed attack rates were 0.8% and 0.1%. While one would prefer to see the distribution of titers like that observed with A/Bangkok vaccine, i.e., 99% with titers of 32 or higher, it is reasonable to assume that A/Philippines vaccine, when given to all personnel, would provide a high level of protection and would almost certainly prevent any sizable epidemic.

In addition, one must take into account that in the outbreaks of H3N2 influenza reported to date from the southern hemisphere, cases have been caused

by a mixture of the two variants, and no massive A/Philippines outbreaks have yet been reported. These data support the use of existing stockpiles of the 1982-83 vaccine until they are exhausted.

IV. Antibody Response to the 1983-84 Vaccine

The standard military vaccine to be used during the 1983-84 season is a trivalent whole virus inactivated vaccine prepared by Connaught which contained 15 mcg each of strains A/Philippines/2/82 (X-79), A/Brazil/11/79 and B/Singapore/222/79. Serum pairs were collected from 113 newly arrived recruits at Lackland Air Force Base under the direction of Lt. Col. David Gremillion and in addition from 37 members of the permanent party. The latter were included because questions have been raised about the efficacy of vaccine in older individuals and because it has been noted in our studies that titers tend to be somewhat lower in vaccinated permanent party.

The antibody responses of recruits to the H3N2 and B components were excellent (Table 3). Prior to vaccination, 25% were seronegative; after vaccination, only 3%. The percentage with post-vaccination titers of 32 or higher rose from 20% to 95%. Permanent party, on the other hand, had a somewhat smaller number of seronegative individuals prior to immunization. After vaccination the percent with titers of 32 or higher was 85%. The percent of individuals with fourfold or greater rise in titers was 21% in the permanent party and 90% in the students.

The B/Singapore response was similarly very satisfactory. Almost none of the students or permanent party were seronegative prior to immunization and, following immunization, 100% had titers of 32 or higher. Again, the percentage with fourfold or greater rises was considerably higher in the student population than in the permanent party. The failure of the permanent party to show further increases in titer recalls observations of earlier years, when it was shown that a second injection of aqueous vaccine rarely produced significant increases in titers. All the permanent party had been vaccinated during the prior season.

V. The Need for Changing the H1N1 Component?

During 1983 antigenic drift was noted in a number of H1N1 virus strains isolated from patients in the Far East and South Pacific. This raised the question of whether A/Brazil/78 component would provide a satisfactory degree of protection. To put the situation in perspective, it is worth recalling (Table 4) that H1N1 virus first appeared during the 1977-78 season and has now been prevalent for more than six years. During this period everyone in the recruit age group has been infected at least once, and, with each passing year, the proportion of individuals with antibodies to H1N1 viruses has increased. The fact that titers have tended to be higher with time suggests a second infection in many of these individuals, since it is unlikely that individuals who had been infected four or five years earlier would have titers as high as many of those shown in Table 4. One would expect that this population would respond extremely well to vaccination.

Antibody response of recruits to A/Brazil was excellent; 95% had titers of 32 or higher following vaccination (Table 5). It is of some interest that even though the number of seronegative individuals was slightly higher when tested with new strains, A/Chile/1/83, A/Dunedin/7/83 and A/New Caledonia/4/83, the antibody response was comparable to that following A/Brazil/79; more than 90% of

individuals had titers of 32 or higher in their post-vaccination sera. These results suggested that in the recruit population it would make little difference whether the vaccine was changed from the A/Brazil/79 component to one of the newer strains.

A slightly different picture was observed in tests with sera from permanent party who also had been vaccinated in 1982 (Table 6). Almost all of these individuals had antibody in their prevaccination sera. Following vaccination the percent with titers of $\geq$32 for A/Brazil/78 was 98%. The number of individuals with titers of $\geq$32 with the new strains is somewhat lower, ranging from 86% of A/Chile/1/83 to 69% of A/Dunedin/7/83. This might cause concern about the effectiveness of the A/Brazil component in this population were it not for the fact that it was very clear in 1977-78, when the H1N1 epidemic occurred in an unvaccinated population, that the permanent party members 23 years old or older were essentially free of illness during the epidemic. Even those with low or absent H.I. antibody titers appeared to be immune to H1N1 influenza. The data in Table 7 illustrate the response to vaccinating of permanent party who had pre-existing antibody.

The percent of persons in student and permanent party groups with titers of 32 or more in pre- and post-vaccination sera are summarized in Table 8. The distribution of antibody titers in students was uniformly very high and was somewhat lower in the members of the permanent party.

VI. Observations on the Doctrine of Original Antigenic Sin

It was noted earlier in the discussion of H1N1 strains that the H1N1 virus had been prevalent now for more than six years. H3N2 strains have been present for 16 years, since 1968, when the A/Hong Kong/68 epidemic occurred. It was, accordingly, of some interest to test the sera of recruits vaccinated in 1982 with vaccine containing A/Bangkok/79 virus not only against A/Bangkok/79 but also a number of the earlier H3N2 strains and against A/Philippines/82. Thirty pairs were tested against these H3N2 viruses and also against the H2N2 virus A/Japan/305/57. Results are shown in Tables 9 and 10.

Examination of the distribution of pre-vaccination titers of 30 recruits who got the 1982 A/Bangkok vaccine shows that all had been infected at some time in the past with H3N2 viruses. It is probable that most were infected in 1968 by the original A/Hong Kong/68 virus and/or that those who were missed at that time were infected primarily or secondarily with A/England/72.

As one follows the pre-vaccination titers over the years, it is obvious that, with strain variation, a larger proportion of individuals is found with titers which leave them in the susceptible range.

If no adjustment had been made in vaccine composition, it is likely that influenza incidence would be quite high.

It is of interest that the great majority of this group of individuals aged from 17 to 21 has antibody for the H2N2 strain of influenza A virus, presumably as a result of infection acquired between 1957 and 1968, i.e., while they were still less than 10 years of age.

The distribution of post-vaccination titers is quite different from that of pre-vaccination titers. Almost all now show titers of 32 or higher against all the members of the H2N2 family which were tested.

The highest titers continue to be against the earlier A/Hong Kong/68 and A/England/72 viruses, demonstrating again the validity of the doctrine of original antigenic sin.

Regardless of what vaccine is used, it is clear that antibody levels are high against the strains by which the individual was originally infected, and there is no need for concern about a reappearance of the earlier viruses.

The increase in the percentage of individuals who had fourfold rises in antibody titer reflects the fact that those individuals with high titers rarely responded sharply to vaccination.

The final titers are as high against the earliest virus strains as against the more recent strains.

VII. Assessment of the Need for Change in Strain Composition of Vaccine

Influenza viruses are unique in their capacity for antigenic change, either major (antigenic shift) or minor (antigenic drift). As a result, in contrast to most vaccine against infectious agents, there must be continuing changes in the strain composition of vaccines. There is no uncertainty when antigenic shift from one influenza A family to another occurs. The need is obvious when major segments of the population are found to be seronegative against the new virus and a new epidemic or pandemic is almost inevitable. The problem at such a time is not one of decision regarding vaccine composition but of speed of production of effective vaccine.

When antigenic drift occurs the decision may be more difficult. Three factors are important in this decision. The first is the demonstration that a sizable proportion of the target population is seronegative against the new strain. The second is the demonstration in the laboratory, presently by the use of ferret antisera, that there is a significant difference between old and new viruses. The third is the demonstration that the new virus has the capacity to spread and cause epidemics. This last point is important because, if one tests large numbers of virus isolates, one almost invariably discovers variants which appear to be very different from the prevalent strains and yet these variants do not appear to have the factors necessary for epidemic spread. Examples of this are the A/Bangkok/2/79 strain of influenza H3N2 and the A/Fukushima/79 strain of H1N1 influenza. Both of these were markedly different from prevalent strains, but did not cause epidemics.

In recent years decisions have been based in large measure on data obtained from immunizing ferrets with virus isolates and comparing the antibody titers of these animals against current and earlier members of the same virus family. Ferrets inoculated with a wild virus develop a highly strain-specific response and are ideal for detecting differences between virus strains. They have, however, limitations in that it may be difficult to produce an antiserum of high titer and newly isolated viruses may also lack avidity and thus give falsely low titers. This appears to have been a factor in data presented on the A/Philippines/82 virus during the past year.

The most definitive data on the need for strain change comes from determining the response of appropriate human populations to vaccine. Fortunately, through

the cooperation of Dr. Gremillion and his associates at Lackland Air Force Base and more recently during the past summer with the Navy, it has been possible to test pre- and post-vaccination sera from newly inducted recruits and to determine antibody response not only to the old but also to the new and potentially epidemic strains. The pre-vaccination sera give a clue as to the need for change. If a large segment of this population is seronegative (titer <8 or 8), an outbreak of considerable size can be anticipated in military units unless vaccination is given. Conversely, if the vaccine produces a sharp elevation in titer against both old and new strains (titers of 32 or higher), the need for change is probably negligible.

We have looked at our data from earlier years in order to obtain better perspective on the relative value of tests with human sera or ferret antisera. Homologous response is shown in Table 11 and heterologous response in Table 12.

The need for vaccination is apparent when one looks (Table 11) at the columns showing pre-vaccination antibody levels. With the exception of three years in the mid 1970s, a relatively large number of individuals fell into the highly susceptible group with titers of 8 or less. On the basis of observations made during the 1950s, one would anticipate attack rates of 5-10% or even higher if this group had been exposed to influenza A viruses if vaccination had not been done.

The number of individuals falling into the highly susceptible range has tended to increase during the last four years and is highest when tested against the A/Philippines/82 strain.

The response to vaccination appears in most years to have been highly satisfactory, particularly in the last five years when in each year the number of individuals with titers of 32 or higher has exceeded 90%. Barring striking strain variation, one would anticipate very little in the way of clinical illness in a population with titers as high as this.

The purpose of Table 12 is to compare the usefulness of tests with specific ferret antiserum in making such a prediction with that of human sera collected before and after vaccination. There have been six years in which there has been a change in vaccine composition when it has been possible to obtain data bearing on the need for change in vaccine composition. Ferrets inoculated with a new virus strain ordinarily develop a high titer of homologous antibody and a lower titer of antibody against a more recent strain. Results are shown in the column under the heading "Ferret Data." Differences in titer between the old and the new vary from 4 to 16-fold.

In the columns headed "Human Data," the pre- and post-vaccination distribution of H.I. antibody titers evoked by the old vaccine against the new strains is shown. These are obviously lower than those observed in the earlier table, in which the homologous antibody response was observed, and in no instance approached the 90% level (until the strain A/Philippines was tested). The lack of correlation between ferret and human data is quite obvious. If one looks at the three years in which the ferret sera showed differences of 8-fold in titer between old and new, one sees a wide variation in the percentage of individuals vaccinated who had titers of 32 or greater. These range from 64% to 90%. When the ferret sera showed a titer difference of 16-fold, the range was from 70-90%.

The striking specificity of sera of ferrets inoculated for the first time with influenza virus was recognized in the 1940s. These obviously provide a lead, but the human response is far more reliable as a guide.

During the coming year the CDC and BOB have indicated they believe it desirable to change the H1N1 component, while leaving the H3N2 and B components the same as last year. The tests which we have conducted with H1N1 viruses, notably A/Brazil and three of the newer isolates from the southern hemisphere, indicate that in a recruit population it is immaterial whether A/Brazil or one of the new strains is used. In permanent party, previously vaccinated, there does appear to be an advantage in favor of using one of the new strains over A/Brazil, and the data from nursing home residents obtained by the Bureau of Biologics also suggest that a new strain would be preferable.

This is a curious decision since the evidence is clear that the population that are now 29 years or older are essentially immune to H1N1 viruses. This was convincingly shown during the 1978 epidemic at Lowry Air Force Base when cases were essentially confined to individuals under 23 years of age at that time. Nonetheless there is no harm in changing since it can be assumed that, if A/Brazil should continue to be the prevalent virus, any one of the new strains would produce a highly effective A/Brazil response in addition to a good homologous response. The choice between the new strains rests on rather tenuous grounds, and at a recent meeting of the Bureau of Biologics the decision was made to defer for a month the decision on which strain to pick pending further observations on the epidemic spread of any of these new viruses.

VIII. Virus Isolation in Relation to Clinical Severity of Influenza

For many years it has been believed that virus is most readily isolated from patients who have high fever than from those who have lower fever. For that reason it has been of some interest to compare the results of virus isolations from patients with different degrees of fever at the time when they report to the dispensary. A single oral temperature is by no means an adequate measure of illness severity, but it is the only one which we have because none of the patients were hospitalized. Results of attempts at virus isolation from patients with influenza by either virus isolation and/or increase in H.I. antibody and/or increase in C.F. antibody are shown in Table 13. The old notion that patients with higher fever are more likely to yield virus is borne out in the results with the H3N2 strains since there is an increase in isolation rate from 67% in patients between 99 and 99.8 and percentage from those with temperatures over 102. There was not, however, the same cleancut relationship with either H1N1 virus and with influenza B.

The actual recovery rates are rather disappointing, with low rates of 61% recovery for H1N1, 75% for H3N2 and 68% for influenza B. They indicate the need for serodiagnosis as well as virus isolation if one is to obtain a complete identification of all cases. It might be noted here that our experience with using Rhesus Monkey Kidney, which is in our hands, obtains higher yields than dog kidney or chick embryos.

IX. Clinical Observations

Table 14 shows the distribution by oral temperature at the time reported at the dispensary observed in patients with H3N2 or H1N1 influenza A or with

influenza B. It has been our impression that patients with influenza B tend to have lower temperatures than those with the influenza A viruses and the data appear to bear this out. Only 7% of them had temperatures over 102 while 43% had temperatures less than 100°F.

There was no significant difference between the temperatures of patients with H3N2 influenza and those with H1N1 influenza. Approximately 40% of each of these had temperatures of more than 101°. In this respect influenza stands out at the present time at Lowry Air Force Base as the disease most likely to cause a temperature of more than 101°. The only other common disease which does so is streptococcal pharyngitis. Thus, a cluster of patients with temperatures over 101° can often serve as a marker for the appearance of influenza.

It is noted that all the patients included in Table 14 had received influenza vaccine. We lack an adequate number of cases of unvaccinated individuals in the same age group to permit an adequate comparison. While temperatures may be slightly lower in the vaccinated than in the unvaccinated, there is a large degree of overlap and it is not uncommon to see patients with high fever who have received vaccine.

X. Role of Respiratory-Syncitial Virus (RSV) as a Cause of Febrile URI

A large proportion of LAFB patients with febrile respiratory disease fall into an unclassified category after tests are completed for influenza and adenovirus diseases. In the past we have looked for other known respiratory agents without much success. Only occasional cases of parainfluenza, conora virus and enterovirus or mycoplasma infections have been documented. During the past year Col. Bancroft suggested that RSV might cause some of these illnesses.

Complement fixation tests have been shown to be relatively insensitive in detecting primary infections of RSV but considerably better in reinfections. In a population aged 17 years or older, complement fixation tests are reasonably sensitive in detecting infection. Recently it has been shown that with ELISA, the yield may be greater, but further data are needed.

We have run complement fixation tests on 140 serum pairs from patients in the unclassified group who were ill between January 4 and May 31, 1983. In this group of 140 serum pairs we found three with fourfold or greater increases in titer and 11 with twofold increases in titer. Six pairs showed a twofold drop in titer. Working with a serum pair from an individual whose titer rose from <8 to 64, we have manipulated the ELISA technique in order to make it more sensitive. By various treatment of the antigen it has been possible to show, with ELISA technique, that the titer increased from <8 to 1024. We plan to test other individuals with fourfold and twofold rises and ultimately to test a large number of individuals who showed no increase in titer in CF tests. If we find the yield no higher than we have observed so far, we will look at pairs of serum from individuals who report with URIs without fever. We use the data obtained from our Pediatric Department virus laboratory to determine the periods of prevalence of RSV.

Figure 1

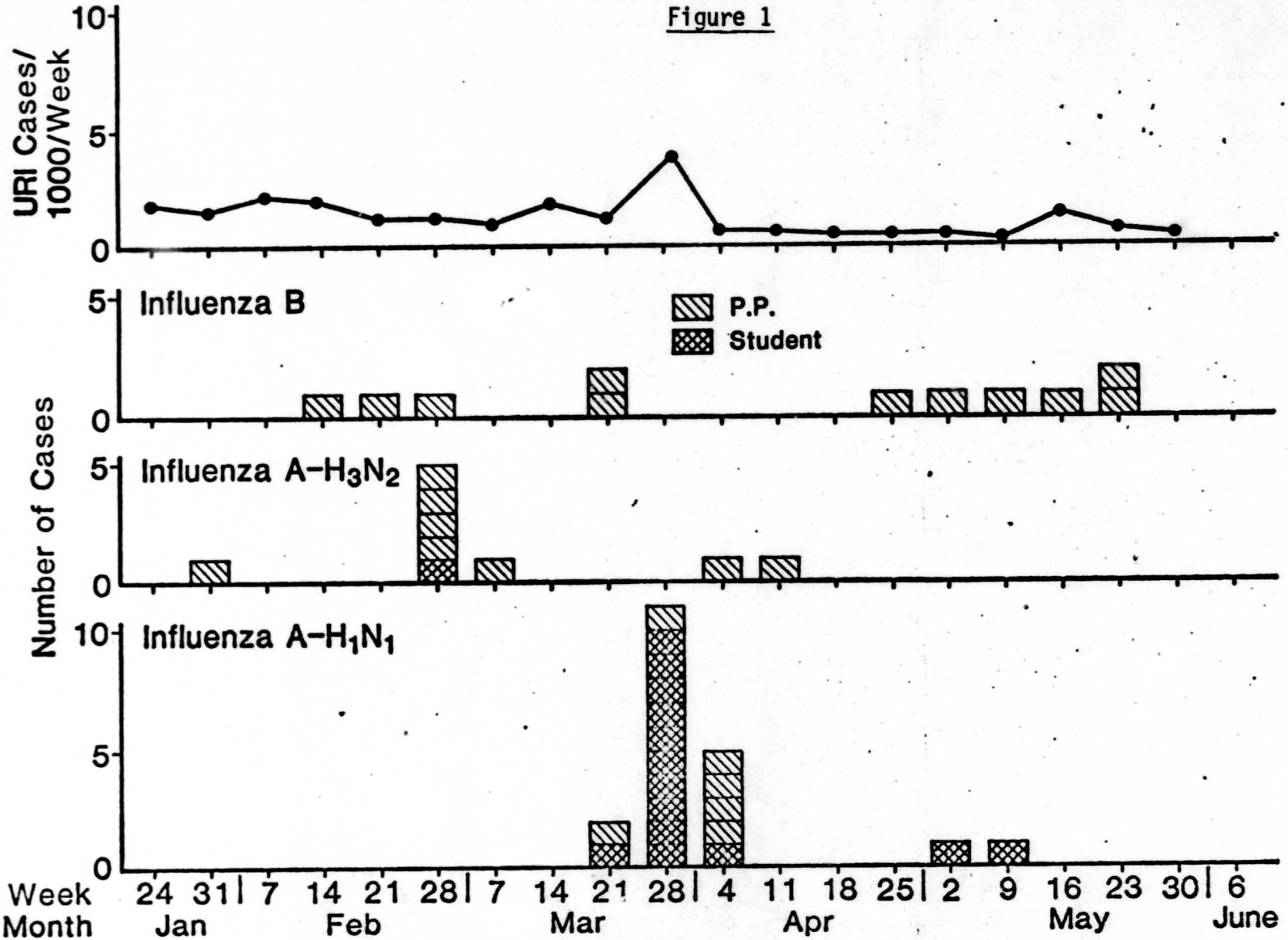

FIG. 1 WEEKLY FEBRILE URI RATES IN STUDENT POPULATION AND THE NUMBER OF CASES OF INFLUENZA H3N2, H1N1, AND B IN STUDENST AND PERMANENT PARTY 1982-1983.

Table 1

Comparison of H.I. antibody response of Naval recruits who received vaccine containing either A/Bangkok/1/79 or A/Philippine/2/82 antigen

A/Bangkok/79 Antibody Response

Vaccine		Cumulative percent of persons with H.I. titer more than:									Percent with ≥ 4x rise
		< 8	8	16	32	64	128	256	512	1024	
A/Bangkok/79	Pre -	27	73	52	30	17	10	1	1	0	
	Post -		100	100	99	92	80	60	43	21	87
A/Phil/82	Pre -	19	81	54	33	10	0	0	0	0	
	Post -	1	99	99	97	93	87	73	55	32	93

A/Philippine/82 Antibody Response

Vaccine		Cumulative percent of persons with H.I. titer more than:									Percent with 4x rise
		< 8	8	16	32	64	128	256	512	1024	
A/Bangkok/79	Pre -	44	56	18	13	6	2	0	0	0	
	Post -	4	96	92	80	73	46	40	17	12	83
A/Phil/82	Pre -	40	59	29	16	6	0	0	0	0	
	Post -	4	96	95	94	86	72	62	36	18	91

Table 2

Post-vaccination titers for challenge strains of H3N2 influenza and attack rates in students from 1976 to present

Year	Vaccine Virus	Challenge Virus	Percent of persons with titers against challenge viruses of: ≤ 8	16	≥ 32	Attack Rate (%) H3N3
1976-7	A/Victoria/75	A/Texas/77	9	16	75	0.8
1977-8	A/Victoria/75	A/Texas/77	4	14	82	0.1
1978-9	A/Texas/77	A/Texas/77	1	5	94	-*
1979-80	A/Texas/77	A/Texas/77	6	1	93	0.9
1980-1	A/Bangkok/79	A/Bangkok/79	5	1	94	-*
1981-2	A/Bangkok/79	A/Bangkok/79	9	1	92	0.02
1982-3	A/Bangkok/79	A/Bangkok/79	1	5	94	0.02
1983-4	A/Bangkok/79	A/Bangkok/79	0	1	99	?
		A/Phil/82	8	12	80	?
	A/Phil/82	A/Bangkok/79	1	2	97	?
		A/Phil/82	5	1	94	?

* No H3N2 present.

Table 3

		Percent with H.I. titers more than									Percent with ≥ 4X rise
A/Phil/2/82 (X-79)											
	Serum	<8	8	16	32	64	128	256	512	1024	
Recruits (113)	Pre-	43	28	17	8	4	0	1	0	0	
	Post-	4	97	96	91	84	70	60	43	32	90
Permanent Party (37)	Pre-	11	90	82	58	31	20	6	3	3	
	Post-	0	100	92	84	57	33	17	6	3	21
B/Singapore/222/79											
Recruits (113)	Pre-	19	81	60	39	27	14	4	0	1	
	Post-	3	97	96	94	84	72	52	32	14	85
Permanent Party (37)	Pre-	0	100	100	93	82	52	33	11	3	
	Post-	0	100	100	100	86	70	38	19	3	13

H.I. antibody response to A/Philippines/2/82 and B/Singapore/222/79 of 113 recruits and 37 permanent party who in November 1983 received whole virus vaccine containing 15 ug of hemagglutinin of A/Bangkok/79, A/Brazil/78 and B/Singapore/79.

All permanent party had been vaccinated one year before.

Table 4

Year	Percent of Persons with H.I. Titer Greater Than								
	<8	8	16	32	64	128	256	512	1024
1978*	100	-	-	-	-	-	-	-	-
1979	69	31	16	6	2	-	-	-	-
1980	44	56	28	8	4	4	4	-	2
1981	43	57	30	13	2	1	-	-	-
1982	20	80	54	35	19	9	5	2	1
1983	17	82	70	50	38	35	27	15	3

*Tested with A/USSR/90/77 whole virus.

Distribution of pre-vaccination H.I. antibody titers for A/Brazil/11/78 in sera of Air Force recruits from 1978 to 1983.

Table 5

RECRUITS

	Percent with H.I. titer greater than									Percent with ≥ 4X rise
	<8	8	16	32	64	128	256	512	1024	
A/Brazil/11/78										
Pre-	25	74	53	28	17	15	11	6	1	
Post-	4	97	96	94	93	90	87	79	67	83
A/Chile/1/83										
Pre-	41	59	27	15	9	5	3	0	1	
Post-	4	97	97	93	89	80	69	62	43	88
A/Dunedin/7/83										
Pre-	50	50	15	11	7	2	1	1	0	
Post-	4	97	95	93	86	73	57	44	38	84
A/New Caledonia/4/83										
Pre-	48	53	17	10	6	2	1	0	0	
Post-	4	95	95	92	88	75	69	50	35	87

H.I. antibody response of 113 Air Force recruits who received trivalent vaccine containing 15 ug of hemagglutinin of A/Brazil/11/78 in tests with four H1N1 strains.

Table 6

PERMANENT PARTY

	Percent with H.I. titer greater than									Percent with ≥ 4X rise
	<8	8	16	32	64	128	256	512	1024	
A/Brazil/11/78										
Pre-	0	100	92	89	73	57	49	35	19	
Post-	0	98	98	98	95	68	57	46	27	18
A/Chile/1/83										
Pre-	3	97	78	59	35	30	16	8	0	
Post-	3	97	97	86	54	46	30	19	3	26
A/Dunedin/7/83										
Pre-	3	98	76	41	27	19	8	3	3	
Post-	3	98	93	69	55	33	25	6	3	24
A/New Caldonia/4/83										
Pre-	0	100	81	49	30	22	11	8	3	
Post-	0	99	99	75	56	48	29	13	5	21

H.I. antibody response of 37 Air Force permanent party who received trivalent vaccine containing 15 ug of hemagglutinin of A/Brazil/11/78 in tests with four H1N1 strains.

Table 7

GROUP	VIRUS STRAIN	PRE-VACC. TITER	NO. OF PERSONS	POST-VACC. RISE IN TITER(%) 0	2x	>4x
Permanent Party (37)	A/Phil/82	<8-8	7	0	43	57
		16-32	19	26	58	16
		≥64	11	64	27	9
	A/Brazil/79	<8-8	3	0	0	100
		16-32	7	14	57	29
		≥64	27	63	30	7
Recruit (40)	A/Phil/82	<8-8	22	5	0	95
		16-32	15	0	7	93
		≥64	3	67	0	33
	A/Brazil/79	<8-8	12	0	8	92
		16-32	13	0	0	100
		≥64	15	27	33	40

Fold increase in H.I. antibody titer following vaccination of persons with different pre-vaccination antibody titers.

Table 8

Percent with post-vaccination H.I. titers $\geq$ 32

	Test Strain	Students		Permanent Party	
		Pre-	Post-	Pre-	Post-
H3N2 --	A/Phil/2/82	20	95	27	84
H1N1 --	A/Brazil/11/78	50	95	89	98
	A/Chile/1/83	25	92	59	86
	A/Dunedin/7/83	23	92	41	69
	A/New Caledonia/ 4/83	26	91	49	75
B --	B/Singapore/ 222/79	77	100	93	100

Summary of pre- and post-vaccination H.I. titers of recruits and permanent party.

Table 9

Test Strain	<8	8	16	32	64	128	256	512	>1024
A/Japan/57	20	10	13	20	23	7	3	3	-
A/Hong Kong/68	0	0	10	13	20	23	23	7	3
A/England/72	0	0	10	10	23	26	17	7	7
A/P.C./73	10	7	23	26	17	7	7	3	0
A/Victoria/75	10	17	17	26	17	3	7	0	3
A/Texas/77	7	10	30	33	13	3	3	0	0
A/Bangkok/79	17	40	26	13	3	-	-	-	-
A/Philippine/82	56	26	13	3	-	-	-	-	-

Distribution of pre-vaccination H.I. antibody titers in tests with A/Japan/57 (H2N2) and seven H3N2 strains.

Table 10

Test Strain	Percent of Persons with Post-Vaccination H.I. Titer of:									% with 4X Rise
	<8	8	16	32	64	128	256	512	>1024	
A/Japan/57	13	7	17	20	20	10	7	7	0	13
A/Hong Kong/68	0	0	3	3	13	17	17	10	36	36
A/England/72	0	0	3	0	10	13	23	13	36	56
A/P.C./73	7	0	0	3	13	17	23	7	30	66
A/Victoria/75	3	0	3	17	13	19	13	17	23	76
A/Texas/77	0	0	3	3	3	20	23	7	40	92
A/Bangkok/79	3	0	3	3	17	26	3	7	36	89
A/Philippine/82	3	0	3	10	30	10	3	13	23	92

Distribution of H.I. antibody titers in post-vaccination sera (A/Bangkok/79 vaccine) in tests with A/Japan/57 (H2N2) and eight H3N2 strains.

Table 11

Season	Vaccine Strain	Vaccine Potency	Percent with H.I. Titer in Pre-Vaccination Sera <8	Pre-Vaccination Sera 16	Pre-Vaccination Sera ≥ 32	Post-Vaccination Sera <8	Post-Vaccination Sera 16	Post-Vaccination Sera ≥32
1972-73	A/HK/68	700 CCA	47	19	34	8	6	86
1973-74	A/England/72	700 CCA	34	19	58	4	0	96
1974-75								
1975-76	A/P.C./73	350 CCA	7	3	90	2	0	98
	A/Scot/73	350 CCA	9	3	88	2	0	98
1976-77	A/Victoria/75	400 CCA	20	12	68	11	7	82
1977-78	A/Victoria/75	400 CCA				4	14	82
1978-79	A/Texas/77	20 ug				1	5	94
1979-80	A/Texas/77	7 ug				6	1	93
1980-81	A/Bangkok/79	7 ug	44	26	30	5	1	94
1981-82	A/Bangkok/79	14 ug	70	17	13	9	1	90
1982-83	A/Bangkok/79	15 ug	66	18	6	1	5	94

Distribution of pre- and post-vaccination H.I. antibody titers in tests with homologous vaccine strain.

Table 12

Season	Vaccine Strain	New Strain	Ferret Data H.I. Titer With Old*	Ferret Data H.I. Titer With New**	Ferret Data △	Human Data H.I. Titer to New Strain*** Pre-Vacc. <8	Pre-Vacc. 16	Pre-Vacc. ≥ 32	Post-Vacc. <8	Post-Vacc. 16	Post-Vacc. ≥32
1972-73	A/HK/68	A/Eng/72	2560	640	4X	36	20	50	22	8	69
1973-74	A/Eng/72	A/P.C./73	640	40	16X	57	16	27	0	7	93
1974-75	A/P.C./73	A/Vic/75	1280	80	16X	20	13	68	11	16	73
1976-77	A/Vic/75	A/Tex/77	640	80	8X		N.A.		9	16	75
1978-79	A/Tex/77	A/Bang/79	2560	320	8X	98	0	2	20	16	64
1981-82	A/Bang/79	A/Phil/82	960	120	8X	82	18	10	6	4	90

* Vaccine strain
** Prevalent epidemic strain
*** Percent with titer of

Distribution of pre- and post-vaccination H.I. antibody titers in tests with new variant strain in year when vaccine composition was changed. Data from ferret sera (CDC) are included for comparison.

Table 13

Percent of Persons with Confirmed Influenza

Virus	H3N2	H1N1	B
No. of Persons	119	138	67
Temperature			
99-99.8	22	28	43
100-101.8	32	32	36
101-101.8	29	22	13
≥102	17	17	7

Distribution of Dispensary Oral temperatures of serologically confirmed patients with H3N2, H1N1 or B influenza. All had received vaccine.

Table 14

Percent of Persons from whom Virus was Isolated

Virus	H3N2	H1N1	B
No. Tested	102	138	65
Temperature			
99-99.8	67	55	79
100-100.8	71	55	53
101-101.8	77	80	80
≥102	92	61	40
Total	75	61	68

Relationship between oral temperature and virus isolation from patients with serologically confirmed H3N2, H1N1 or B influenza. All had received vaccine.

AN INFLUENZA A EPIDEMIC CAUSED BY H1N1 VIRUS

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Running Head: Epidemic of H1N1 Influenza

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An Influenza A Epidemic Caused by H1N1 Virus

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Josephine I****

If influenza experts had been asked a year ago which influenza family would replace the current H3N2 strains, the least likely candidate would have been the H1N1 family. However, extensive outbreaks caused by H1N1 strains were reported from the U.S.S.R. and Hong Kong in November and December of 1977 (4), and it was later learned that the Peoples Republic of China had experienced similar epidemics between May and November (5). The first otubreaks in the U.S.A. were detected in the Rocky Mountain region in a high school in Cheyenne, Wyoming (6), in mid-January and soon afterward at the Air Force Academy in Colorado Springs and Lowry Air Force Base in Denver (7).

Lowry AFB has two populations. The student population, aged 17 to 23, resides on the base in large, modern barracks. The somewhat larger permanent party, or cadre, is older, has close contact with the student population and, for the most part, resides off-base in the Denver metropolitan area. The epidemic struck the student group during the first two weeks of February, causing higher illness rates than any observed since the 1957 H2N2 epidemic. The permanent party had very little illness, and the surrounding civilian community experienced little more than a scattering of local outbreaks, mainly in schools or colleges. Meanwhile a smouldering outbreak of H3N2 influenza, caused by both A/Victoria/75 and A/Texas/77 strains continued in the civilian community from November 1977 to March 1978 but scarcely involved the military population at Lowry AFB which had received A/Victoria/75 vaccine.

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Materials and Methods

Records were kept throughout the winter on the number of persons reporting to the base dispensary with either febrile or non-febrile respiratory disease. Each week throat washings and paired blood specimens were collected from 10 to 20 persons. The throat washings were collected in veal infusion broth and immediately placed in the freezing compartment of a standard refrigerator. Following transport to the virus laboratory they were either tested at once or stored at -70°C. All were inoculated into Rhesus monkey tissue culture (RMTC). Smaller numbers were tested in chick embryos, inoculated by the amniotic route, or in cynomolgous monkey or dog kidney tissue culture. Tissue cultures were checked at frequent intervals for hemadsorption with guinea pig cells and evidence of cytopathic effect. Complement fixation tests using H3N2 and H1N1 allantoic fluid antigens were done using standard procedures (1). All sera were tested by hemagglutination inhibition tests using A/USSR/90/77 and an ether-split vaccine concentrate prepared from the same strain (kindly provided by Dr. Frank Brandon of Parke Davis Co.) as antigens. Many were also tested with A/FM1/47, A/FW/50 and with 2nd passage RMTC fluid infected with a strain isolated during the epidemic (A/Den/8011/78).

Results

Febrile respiratory diseases had been occurring at a very low rate during the first 3 weeks of January. The first case of H1N1 influenza was detected on 26 January. On 30 January illness rates began to rise, climbed very sharply to a peak on 7 February and then rapidly declined (Fig. 1). The last confirmed case occurred on 15 March.

Illness rates in students were very high, rising from a level of 20/1000/week in January to 186/1000/week during the week of 6-12 February. This rise was only faintly reflected in the permanent party, most of whom were 25 years old or older. Illness rates rose only from 5/1000/week to 20/1000/week (Fig. 2). Only 3 cases of influenza H1N1 were confirmed in persons more than 26 years of age.

The attack rate of febrile influenza in students was estimated to be 30%. An additional 20% of the students, in excess of expected dispensary visits, reported with illness without fever during the three weeks of the epidemic, suggesting that the actual number of persons infected was substantially higher. No complications such as pneumonia were seen. The severity of illness was certainly no greater than in recent H3N2 outbreaks and may have been less.

Attempts to recover viruses from throat washings of serologically confirmed cases in RMTC were successful in only 32 of 64 attempts (50%). Isolation attempts in chick embryos were no more successful. Tissue culture fluids from cultures which showed 4+ hemadsorption rarely agglutinated chicken cells, but viruses were readily identified in tests with guinea pig cells. Strains isolated in chick embryos, on the other hand, did agglutinate chicken cells.

Serodiagnosis was difficult with both complement fixation and hemagglutination inhibition tests. Almost all personnel had received whole virus vaccine containing 200 CCA units of A/Victoria/75 and many had C.F. antibody titers of 8 or 16. In tests with A/Victoria/75 antigen persons with titers ≤ 8 than this usually showed significant increases in antibody titer, but those with titers of 16 or more, for the most part showed

only 2-fold titer increases or no increase. However, when A/USSR/77 allantoic fluid antigen was used, titers were low in the acute phase sera and 36% of cases showed significant increases in titer.

In HI tests with 8th egg passage A/USSR/77 approximately half of the cases failed to show ≥4 fold titer rises and the level of convalescent antibody titers was low. When A/FM/47 was used as antigen the proportion of individuals with ≥4 fold titer rises was 78%. When ether-split A/USSR/77 vaccine concentrate was used as antigen the percent with significant increases in antibody titer rose to 91% (Table 1).

Discussion

The epidemic was the most explosive observed at this base since 1957 and serves as a reminder of the speed and extent with which influenza can spread in a population which has had no previous exposure to the epidemic strain. The high attack rate was confined to persons under 25 years of age. Persons over 25 years old had almost no illness in spite of close, daily exposure. The immunity of many older persons, born during the H1N1 decade (1947-57) could in most instances (84%) be explained by the presence of H1 antibody, perhaps enhanced by immunization with HswN1 vaccine the year before. Neuramindase antibody also may have contributed to prevention of illness.

The behavior of the H1N1 strains in the laboratory caused much vexation. Virus strains were less readily isolated than recent H3N3 strains. When isolated in RMTC they usually failed to agglutinate chicken cells and could only be identified in HI tests using guinea pig cells. Like the prototype strain A/USSR/90/77 they were non-avid. HI tests using A/USSR/77 allantoic fluid antigens showed significant

antibody titer rises in only half of the cases. When an ether-split vaccine, prepared from the same strain, was used as antigen over 90% of the same patients showed significant antibody increases.

In epidemiologic terms the H1N1 virus was a surprise. Its source remains obscure, and only its origin in the Far East conforms with other recent epidemics.

Why this virus, which repeatedly demonstrated its capacity to produce illness in young adults in military or college settings, failed to spread more visibly in the civilian population between 1 and 24 years of age, a segment without prior exposure and without antibody, remains unclear.

When H1N1 strains first appeared in the USA in 1947 sharp outbreaks occurred in military installations even though this age cohort would have been expected to have relatively high levels of immunity as a result of exposure to HoN1 strains. Incidence dropped to low levels during the summer, but outbreaks with fairly high attack rates in young segments of the population occurred in the fall and in succeeding years (3). The H1 family remained dominant for a decade, showing continuing antigenic drift until replaced by H2N2 strains in 1957. Little excess mortality was associated with these outbreaks in the USA but in Great Britain in 1951 an H1N1 epidemic was associated with considerable excess mortality (2). How the current H1N1 strains will behave in the coming years is a matter for conjecture.

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ACKNOWLEDGEMENTS

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TABLE I

Antigen (No. of persons)	Serum Specimens	Percent of Persons with HI Titer of <8	8	16	32	64	128	256	512	1024	Percent with ≥4 x rise
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.

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

Figure 1. Number of daily visits to the dispensary by persons with febrile respiratory disease.

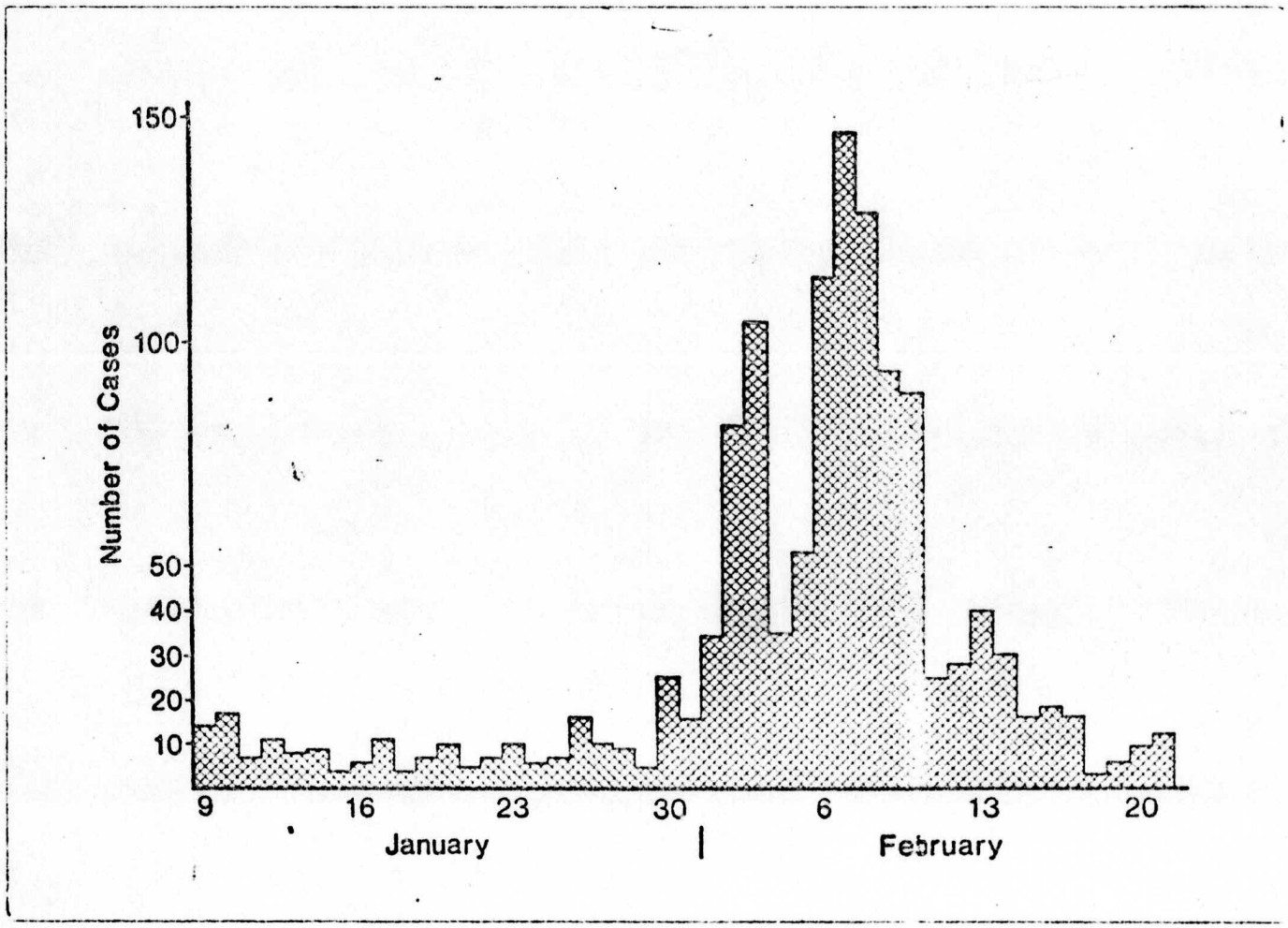
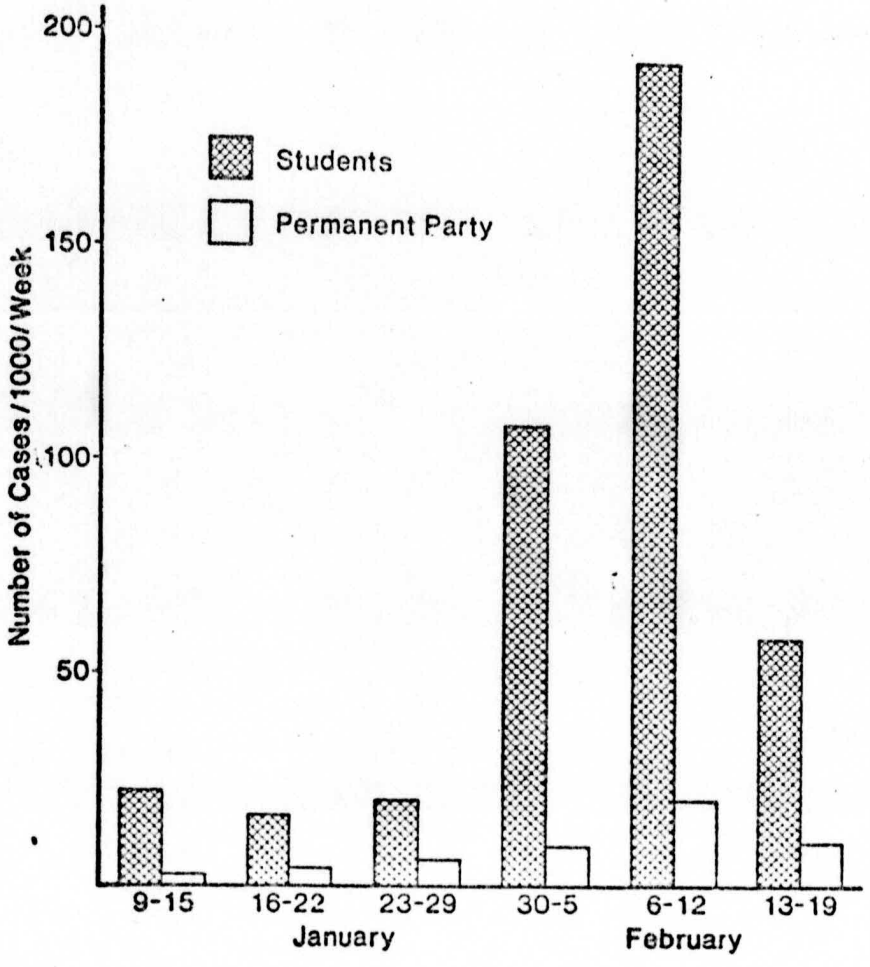

150
100
50
40
30
20
10
Number of Cases
9
16
23
30
6
13
20
January
February

Figure 2. Comparison of attack rates of febrile respiratory disease in student and permanent party populations.


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