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PREVENTION OF INFLUENZA AND OTHER RESPIRATORY DISEASES - LABORATORY STUDIES

AND

EPIDEMOLOGICAL SURVEILLANCE OF INFLUENZA AND OTHER RESPIRATORY DISEASE IN MILITARY PERSONNEL

ANNUAL PROGRESS REPORT

BY

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)
1. H.I. antibody response to a single injection of the 1981 influenza vaccine, which had been increased in potency from 7 to 15 µg of hemagglutinin of each component, was measured in 81 recruits. The response to the H3N2 and H1N1 components was excellent. Response to the influenza B component was mediocre when measured with whole virus B/Singapore/79 antigen, but excellent when tested with ether-split antigen.

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2. The incidence of febrile U.R.I. remained extremely low, despite outbreaks of both H1N1 and B influenza. At no time did the number of cases/1000/week exceed 4.5. This was in sharp contrast to the 1977-78 season when H1N1 influenza struck an unvaccinated student population and produced illness rates of more than 120/1000/week.

3. H1N1 influenza cases first occurred during the week of 11 January, and the outbreak continued for 9 weeks. Only 19 cases were detected in students, a rate of only 0.37%. Twenty-seven cases were detected in the permanent party.

4. Influenza B was also first detected during the week of 11 January, and cases continued to occur over the following 15 weeks, without any sharp peek. Only 5 cases were detected in students, a rate of 0.1%. More cases occurred in the permanent party (33 cases at the time of preparing the report).

5. The "protective" H.I. antibody titer for H1N1 influenza appeared to be 64. For influenza B this titer appeared to be 16 when measured with whole B/Singapore virus antigen and 128 when ether-split antigen was used.

6. Based on the oral temperature of persons reporting to the dispensary, influenza B appeared to be a slightly milder disease than the H1N1 influenza.

7. Other viral diseases presented no problems. Only 7 cases of adenovirus disease were confirmed. Two echo and one Coxsackie virus were isolated. Rubella and Rubeola were not identified. Group A streptococci were isolated for 11% of cases of febrile U.R.I.

8. For confirmation of the diagnosis of influenza B, virus isolation (86%) and complement-fixation tests (77%) were the most sensitive procedures. For H1N1 H.I. tests (93%) and C.F. tests (78%) were considerably more sensitive than virus isolation (59%).

9. When sera from vaccinated recruits were tested against H3N2 strain A/Shanghai/80, which had been considered as a candidate vaccine strain, post-vaccination titers were somewhat lower than the A/Bangkok/79 titers. Nevertheless, almost all persons had titers in the "protective" range.

Cont'd

This report discusses

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1. Introduction

The 1981-82 season proved to be a most unusual and interesting one. Much valuable information was obtained. A large number of recruits had been bled before and after vaccination almost immediately after arrival at Lackland Air Force Base. Consequently the antibody status of the students who arrived at Lowry was well documented. This population was then exposed over a period of many weeks to outbreaks of both H1N1 influenza and influenza B. The epidemic viruses showed little if any drift from those in the vaccine. There was consequently a unique opportunity to evaluate the import of both types of influenza on a totally vaccinated population which had received vaccine of adequate potency which was homologous to the infecting strain.

2. Antibody Response to Vaccination

Hemagglutination inhibiting antibody response

Antibody data on 200 men who had received double injections of 7 µg vaccine (total of 14 µg of each component) at Lackland Air Force Base in May of 1981 were presented in last year's report. In the fall of 1981, paired sera were again obtained from 81 newly arrived recruits who had received the standard military vaccine which contained 15 µg of each of the 3 components, A/Bangkok/1/79, A/Brazil/11/78 and B/Singapore/222/79. This was a whole virus vaccine prepared by Connaught.

In tests with A/Brazil/78 (Table 1), 43% of the individuals tested were seronegative in their pre-vaccination sera. Following vaccination, only 5% remained seronegative. Ninety percent had titers of 32 or more.

In tests with A/Bangkok/79, 57% were seronegative in pre-vaccination sera. Only one remained seronegative following vaccination. Furthermore, 95% of individuals had titers of 32 or higher.

In tests with B/Singapore, 59% were seronegative in the pre-vaccination sera and only 6% were seronegative following vaccination. However, antibody rises were considerably lower than with the influenza A strains. Eighty-three percent had titers of 16 or higher but only 45% had titers of 32 or more.

Because H.I. tests with recent influenza B strains have been capricious and difficult to interpret, this matter was investigated further. With antigen kindly provided by Dr. Gary Noble of CDC, a sample of these sera (25) were tested with ether-split B/Singapore antigen. Table 2 presents results of a test in which titers obtained with virus antigens of B/Singapore and B/HongKong and split B/Singapore antigen were compared. A striking difference is seen with the ether-split antigen. In contrast to the titers obtained with whole B/Singapore virus, when 68% of persons were seronegative, with ether-split antigen only 16% were seronegative. Other individuals spread over the whole range from <8 to 256 in their pre-vaccination sera. Following vaccination, all individuals had titers of 128 or more. These results point up the difficulty of interpreting of H.I. tests with conventional whole virus antigens and suggest that their antibody status may be far more favorable than results obtained in a conventional test would suggest.

Complement fixation tests

The complement fixing antibody response to vaccination in the past has been extremely variable - sometimes being negligible, sometimes quite striking. This has been the result, in part, of vaccine potency and, in part, of methods of vaccine preparation. In this group of recipients of whole virus vaccine, the response to the influenza B component was relatively good and the response to the influenza A component (A/Brazil) was somewhat lower. The results are shown in Table 3.

In tests for influenza B antibody titers were relatively evenly distributed over the range from <8 to 32 and only a single person had a titer of >564. There was a sharp increase in antibody levels following vaccination and only two individuals continued to have titers of 8 or less. Forty-four percent of persons had four-fold increases in titers, 28% had two-fold increases and 28% had no change in titer. There were only four individuals among 80 who had titers of 128 or higher and only a single individual had a titer of 512. This cut-off suggests that individuals with titers of 256 or more could almost certainly represent people who had recently been infected and that from the practical standpoint a strong presumption of recent infection could be made when the convalescent titer exceeded 256.

3. Surveillance

From 15 October 1981 to 1 May 1982, students or permanent party who reported to the base dispensary with febrile (≥99° F) upper respiratory infection were directed to the surveillance office. Throat washings were collected for virus isolation attempts, along with acute phase sera specimens. Convalescent sera were collected 3 weeks later. All sera pairs were tested by complement fixation tests for influenza A (A/Brazil) and B (B/Singapore) and by hemagglutinin-inhibitor tests with appropriate antigens. Diagnosis of influenza was based on one or more of the following: (1) isolation of virus, (2) demonstration of a four-fold or greater rise in titer in complement-fixation and/or hemagglutinin inhibition test.

Incidence rates were calculated only for the student population, which is homogeneous with respect to age (17-23), residence on the base and immunization history. The permanent party which is approximately equal in number, is heterogenous with respect to age, place of residence and immunization history and it was considered impossible to construct a meaningful denominator on which to base an incidence rate. For a variety of reasons there was a decrease in the population of students from whom specimens were obtained. For the period from January to March the percentage was 71%.

4. Incidence of Febrile Respiratory Disease

Records of clinic visits were inspected each day in order to determine the number of students reporting with febrile respiratory disease. Rates continued as in the past two years at extremely low levels. The highest levels were reached during the first two weeks during February with rates of 4.5/1000/week. At this time, there were simultaneous outbreaks of influenza A and B (Table 4).

During the period before the Christmas break, there were six cases of adenovirus infection, four of which occurred in members of the student army detachment and two in members of the Air Force permanent party. Virus strains have been sent to WRAIR for typing. A single case of adenovirus disease was detected following the Christmas break.

Influenza A was first detected during the week of January 11 and cases continued to occur either in students or permanent party through the week of March 8.

Influenza B was first detected during the week of January 11 when an airman recently arrived from Holland, became ill two days later and influenza B virus was isolated from his throat-washing. Parenthetically, it might be noted that influenza B was also present in the civilian population in Colorado at that time. Other cases began to appear in the Base population during the week of February 1 and continued through the week of April 5, a total of 13 weeks.

5. Comparison of Febrile U.R.I. Incidence in Recent and Earlier Years

A series of five charts are presented in order to put the present situation into perspective. The first four show the incidence expressed in numbers of cases/1000/week of febrile upper respiratory infection in the years 1969-70, 1970-71, 1971-72, and 1972-73. The fifth figure shows the incidence of febrile U.R.I. during the five years from 1978 to 1982. In Figure 5, incidence is shown only for the period of 12 weeks following the Christmas break.

Figure 1 1969-70, shows a protracted late winter epidemic which was largely accounted for by adenovirus disease. This pattern had been observed through most of the 1960's. For 12 weeks, rates exceeded 30/1000/week. The peak incidence approached 55/1000/week.

Figure 2 (1970-71) shows a slightly lower incidence with peaks around 30/1000/week. During this year, live oral adenovirus vaccine began to be used, though not on an extensive scale, and much of the disease present was due to adenoviruses.

Figure 3 (1971-72) shows a low incidence throughout the winter without late springtime peak observed in the earlier years. Type 4 and type 7 adenovirus vaccine of sufficient potency was being administered to virtually all recruits at the time of their arrival at Lackland Air Force Base. Rates through most of the winter rarely exceed 10/1000/week.

Figure 4 (1972-73) shows an early peak due to influenza A during which incidence rose rapidly to approximately 60/1000/week. Thereafter, the rate fell and had reached very low levels by the month of March. The influenza epidemic was caused by the England strain of H3N2, which showed a marked antigenic drift from the earlier H3N2 strain, A/HongKong/68, from which the vaccine had been prepared. While there was evidence of moderate protection with this vaccine, most of the Base personnel had not received vaccine before the epidemic struck and a sharp outbreak resulted.

Figure 5 is presented for several reasons. The first year, namely 1978, was the year in which Russian influenza (H1N1) suddenly appeared immediately after the Christmas break. No vaccine was available and all recruits were seronegative. The incidence rose sharply to almost 120/1000/week and thereafter, again fell sharply. During this brief period, it was estimated that approximately half of the student population were ill with influenza. The volume of work overwhelmed the laboratory. Of the individuals from whom specimens were collected during this period, more than 90% had influenza A and it seems fair to assume that this was the agent responsible for virtually all the illness. This outbreak serves as a vivid reminder of what influenza A can do in an unvaccinated and totally susceptible population.

A small outbreak of H3N2 of the A/Texas/78 appeared but had essentially no impact on the student population which had received H3N2 vaccine of the A/Victoria type.

During the following years, all recruits received H1N1 vaccine soon after arrival at Lackland Air Force Base and though H1N1 virus has reappeared on the Base in 1979, 1981 and 1982, the over-all incidence of febrile respiratory disease has at no time exceeded 10/1000/week. During most weeks, it has been far below that level. Only 31 cases were identified in 1979, 55 in 1981 and 19 in 1982. Younger members of the permanent party have been infected also during this period but again at low rates.

It is also noteworthy that influenza B has appeared in 1980 and 1982 and again has had essentially no impact on this totally vaccinated population. Five cases were identified in students in 1980 and again five cases in 1982. Influenza B has caused more illness in permanent party than in students in both years. H3N2 influenza of the A/Bangkok type appeared in 1981 but again had virtually no impact on the students. Only three cases were identified.

6. Outbreak of H1N1 Influenza A

Cases of influenza A, caused by a virus closely related to A/Brazil/78, were first detected during the week of 11 January and continued to occur during the following eight weeks. In the student population, no more than four cases occurred in any week (Table 4) and, as noted earlier, the over-all febrile U.R.I. rate never rose above 4.5/1000/week. For the whole period of the outbreak the incidence of influenza was 0.37%. A slightly larger number of cases occurred in the younger segment of the permanent party, i.e. those under 25 years of age. A moderate outbreak occurred in the civilian community.

The Base population was for a period of nine weeks exposed to a challenge by a virus which, in 1978, had demonstrated the capacity to cause an explosive epidemic in a non-immune population. In 1982, with all students having received a vaccine of appropriate composition and potency, the incidence of disease was negligible. The protection of this population was due, in part, to immunity acquired by previous infection and, in part, to vaccination. The extent to which vaccine contributed cannot be determined. However, it should be noted that prior to vaccination in the fall of 1981, 43% of the students had had titers of <8, and a much higher incidence would have been expected if vaccine had not been given.

7. Outbreak of Influenza B

The first case of influenza B also occurred during the week of 11 January in an airman who had just returned from Holland. It was at first thought that the virus had been introduced by this importation, but it was later learned that influenza B had been occurring in the Colorado Springs area at that time. Two weeks passed before further cases were detected (Table 4). Cases then occurred over the following 9 weeks. As with H1N1 there was no sharp increase at the same time the over-all febrile U.R.I. rate reached only 4.5/1000/week.

The student population was almost completely spared. Only five cases were detected and in no week was there more than one case. The attack rate was less than 0.1%. The permanent party did not fare so well, but, even here, the number of cases was only 25. Surprisingly, these cases were more numerous in the older rather than the younger segment of the permanent party. One-third of the cases were in persons more than 30 years old. At the time of writing, data on influenza B are still incomplete.

8. Antibody Response in Cases of Influenza

Influenza A

The antibody response of students with influenza A is shown in Table 5. Complement-fixing antibodies tended to be low in the acute phase sera and rose moderately in the convalescent sera. Eighty-nine percent of individuals showed a four-fold increase in C.F. antibody.

H.I. tests with A/Brazil were of interest because this is the virus from which the vaccine was prepared. Thirteen of the 18 cases occurred in individuals with titers of 8 or less, even though tests with post-vaccination sera suggested that this represented less than 15% of the population. The remaining cases occurred in individuals with slightly higher titers with only one occurring in an individual with a titer of 128. Titers rose very sharply following infection and the H.I. test with A/Brazil showed four-fold increase in titer in 94% of persons. This is in marked contrast to the results obtained with A/USSR in 1978, when lack of avidity made H.I. tests a remarkably insensitive measure of infection. Ether-split antigens at that time proved to be a more useful diagnostic tool but it is difficult to see how they could exceed the sensitivity of the whole virus H.I. test in this particular year.

H.I. tests for A/Bangkok showed a relatively high level of antibody in acute phase sera with no significant rise in titers. This obviously was expected and is presented simply as a control for the serologic procedures.

In Table 6, similar data are presented on 23 members of the permanent party. Results are generally similar. Complement-fixation tests showed significant rises in titer in 70% of individuals and H.I. tests with A/Brazil in 91%. Titers of A/Bangkok in this group were slightly lower than in the student population. This was explained in part by the fact that this group included a number of individuals who had not been vaccinated in 1981 and of those who had been vaccinated, a number had received only a single injection of 7 µg vaccine.

Influenza B

Table 7 presents the results of complement-fixation and H.I. tests on 22 persons with influenza B. These include four students and 18 members of the permanent party. The results, as in the recent past with influenza B, have been highly unsatisfactory. Complement-fixation tests have proved to be the most sensitive diagnostic procedure with four-fold rise in titer obtained in 97%. Virus isolation, it might be stated parenthetically, was successful in 86%.

H.I. tests with whole virus B/Singapore antigen were extraordinarily insensitive. The great majority (17/22) of persons had titers of 8 or less in their acute phase sera and titers rose only modestly in convalescent sera. In all, only 36% of this group had four-fold or greater increases in titer.

In the hope that ether-split antigen would provide a more sensitive diagnostic procedure, the same sera were tested with ether-split B/Singapore antigen. With this antigen, the acute phase titer spread over a wide range and one-third of individuals had titers of 64 or higher. There was a further boost in titer in many individuals following infections, but the percent of individuals with a four-fold rise in titer was a disappointing 59%. These data suggest that the use of this antigen does not solve the problem of obtaining a satisfactory diagnostic procedure with B/Singapore.

It should be recalled that when the Russian strain of H1N1 first appeared, the same difficulty with avidity was observed with early egg passage antigens and the problem was only resolved when A/Brazil was used in relatively late egg passage. Whole virus antigens have the great advantage of relating results to those obtained in earlier years.

B/HongKong antigen was also tested. The titers were somewhat higher than with B/Singapore in the acute phase sera and 45% of individuals had four-fold increases in antibody titer.

9. Comments on Vaccine Effectiveness

While it is impossible to obtain an exact estimate of the protective efficacy of a vaccine in the absence of a control group, useful information can be obtained by observing the incidence of influenza in a totally vaccinated recruit population. Both the H1N1 virus and influenza B virus have been shown to be capable of causing explosive epidemics in recruit populations. In 1978 at Lowry Air Force Base, when the Russian strain of H1N1 appeared and no vaccine was available, over 30% of the recruit population had influenza within a four-week period. Influenza B, which has been a minor cause of illness in military populations since vaccination was adopted as a routine procedure, in the years before vaccination was used, caused sharp epidemics with attack rates of more than 10%. Comparable rates are seen in civilian school populations.

In the fall of 1981, almost one-half of the recruits were seronegative (≤ 8) for H1N1 influenza before vaccination and a sharp outbreak would have been anticipated. Vaccination produced an excellent antibody response. Only 5% of persons remained seronegative and 90% had titers of ≥ 32. In this setting,

the attack rate was only 0.37%, even though there was continuing challenge by infected persons on the Base over a 9-week period. With one exception, all cases occurred in persons whose acute phase titers were ≤16, confirming the general opinion that, with this strain, a titer of ≥32 is protective.

The incidence of influenza B (0.1%) was even lower, despite the fact that cases occurred over a 12-week period, mainly in the permanent party. Protective antibody titers with this virus are more difficult to define due to the technical problems with the H.I. tests with whole viruses. Almost no cases occurred in persons with H.I. titers of ≥16 when tested with whole virus or titers of ≥64 when tested with ether-split virus.

It appears that a single injection of 15 µg potency whole virus vaccine provided adequate antibody response for currently circulating type A H1N1 influenza and for influenza B. The vaccine appears to have provided a high level of protection during outbreaks of H1N1 influenza and influenza B. An additional shot would be costly and would add little protection.

10. Comparison of Different Laboratory Procedures for Diagnosis of Influenza

Influenza B

Table 8 presents a summary of the results of various diagnostic tests used in establishing a diagnosis of infection. With influenza B, of the 22 patients with confirmed influenza B virus was isolated from 19, a rate of 82%. The complement-fixation test was positive in 77%. In H.I. tests, B/Singapore in its 18th egg passage was positive in 36%, ether-split B/Singapore in 59%, and B/HongKong in 27th egg passage in 45%. The H.I. tests were clearly unsatisfactory, as they have been in the past. Virus isolated with remarkable consistency in monkey tissue culture. The few attempts to isolate virus in eggs were unsuccessful. Complement fixation tests again were the successful serologic tests but missed almost a quarter of the cases.

Influenza A

Virus isolation was far less successful with H1N1 influenza than with influenza B. Viruses were isolated from only 59% of patients. Complement-fixation tests had a 78% success rate, comparable to that of influenza B, H.I tests with A/Brazil in its 11th egg passage were the most useful diagnostic procedures with four-fold rises being demonstrated on 93 percent of patients. It is obvious that A/Brazil performs better in this setting than the earlier A/USSR virus which caused us difficulty in this system in 1978.

11. Estimates of Protective H.I. Antibody Levels

The occurrence of both influenza A and B, even though cases were few in number, provided again an opportunity to evaluate protective antibody levels. Pre-epidemic antibody levels had been measured in three groups. The first (Group 1) consisted of students who had received single injections of 15 µg potency vaccine at Lackland Air Force Base in November and had been bled three weeks later. They did not fairly represent the whole student population, however, at the time when influenza appeared because many students who had been at

Lowry Air Force Base prior to that time had followed the former vaccine schedule of two injections of 7 µg vaccine. Response to the latter regimen had been shown to be slightly less favorable than to the single injection of double potency.

The second group (Group 2) consisted of 40 students who reported with febrile U.R.I. to the dispensary before the first case of influenza appeared. All but four had received either the 15 µg vaccine or 2 shots of 7 µg (occasionally 15 µg) vaccine. This group provided a reasonable, though small, representative sample of the distribution of titers in the student population prior to the epidemics.

The third group (Group 3) consisted of 36 members of the permanent party who had reported ill before the epidemic. They were of particular interest because influenza B occurred almost entirely in the permanent party. They were a heterogenous group with respect to vaccination history. Twenty-four had received 2 injections of 7 µg vaccine or a single shot of 15 µg vaccine. Seven had received no influenza vaccine for more than a year. There is no way of knowing how well this group represented the antibody studies of the permanent party as a whole.

The distribution of antibody titers in the three groups for influenza A is shown in Table 9, which also shows the distribution of acute phase antibody titers of all cases of influenza. Precise calculations are not justified, but it is obvious that the great majority of cases occurred in the relatively small proportion of persons with low titers and that very few cases occurred among the very large segment of the population which had high titers. The cut-off titer for H1N1 influenza appeared to be 64.

Data for B/Singapore are less clear-cut and are still incomplete. It appears that the protective titer when B/Singapore whole virus was used in H.I. tests was 16. With ether-split antigen the corresponding titer was 128.

12. Comparison of Severity in H1N1 Influenza A and in Influenza B

There is a general impression that H3N2 is more severe than H1N1 influenza and that H1N1, in turn, is more severe than influenza B. Clinical data observed at Lowry are relatively sketchy and consist of a single oral temperature reading taken at the time when individuals report to the dispensary. Patients are not hospitalized and there are no data available on subsequent febrile course or on the duration of illness. With these reservations, it is of some interest to compare the temperatures of 44 patients with influenza A with those of 29 patients with influenza B. These include both student and permanent party personnel (Table 10).

With influenza A, 45% of the confirmed cases reported with temperatures in excess of 101° in contrast to 38% of those with influenza B. Twenty-five percent of the influenza A cases had temperatures of less than 100 compared to 37% of those with influenza B. There, thus, appears to be a suggestion that influenza A produces higher febrile response than influenza B, but the differences are very minor. When one considers the vagaries of a single

temperature reading, these results cannot be given much weight. Factors such as outside temperature, whether the patient is mouth-breathing because of nasal obstruction and other factors could influence these results.

13. Analysis of Febrile U.R.I. by Etiology

In order to get a better perspective on what agents were causing disease and the severity of the illness which they caused, Table 11 was prepared. The diagnosis of streptococcal pharyngitis and on those individuals classified as negative were negative in tests for the three diseases previously listed.

In patients with temperatures of less than 100, no etiology was established in 53% and in those with temperatures between 100 and 100.9 in only 52%. It was only in patients with temperatures of >101 that a diagnosis was established in approximately 70% of individuals. It is noteworthy that in the student population, the percentage of undiagnosed cases was far larger than in the permanent party. The latter, it appeared, remained away from the dispensary except when they had influenza or streptococcal disease. In all, 46% of the patients remained undiagnosed during the period from January 1 until April 9.

This class of undiagnosed febrile U.R.I. has been observed for many years and indicated that one or more other agents are infecting the student population. Attempts to identify enteroviruses, Coxsackie viruses, parainfluenza viruses as significant cause of illness have been unsuccessful though it might be noted that two Echo viruses and one Coxsackie virus were isolated during the past winter. Adenovirus disease has been remarkable for its absence since type 4 and type 7 vaccines have been given to recruits at Lackland. Type 21 adenovirus has to this date not been identified at Lowry for reasons which are not clear.

A further effort to identify other agents in order to explain this discrepancy is undoubtedly in order, although they have never caused sharp epidemics and the relatively small number of cases does not appear to warrant a major effort at this time.

14. Antibody Response to A/Shanghai/31/80

When decisions were being made about the possible need for a change in the H3N2 component of the vaccine, strain A/Shanghai/30/80 was considered as a substitute for A/Bangkok/79. In tests with ferret antisera, this strain had shown some (slight) drift away from earlier H3N2 strains.

Accordingly, 25 serum pairs of recruits who had received standard military vaccine in November, 1981, which contained 15 µg of A/Bangkok/79 were simultaneously tested against A/Texas/77, A/Bangkok/79 and A/Shanghai/80. Results are shown in Table 12. With these human sera the antigenic drift appears minor. In 28% of persons post-vaccination, titers were $\geq$four-fold lower, in 72% $\geq$two-fold lower to A/Shanghai than to A/Bangkok. Nevertheless, with 92% of persons having A/Shanghai/80 post-vaccination titers of $\geq$32, a high degree of protection would be expected if a strain of this type became prevalent.

15. Collaborating Activities

Air Force. Lt. Colonel David Gremillion at Wilford Hall USAF Medical Center in San Antonio, where he is Chief of Infectious Diseases, has been most helpful during the past two years in obtaining serum specimens from newly vaccinated recruits. Serologic work on these sera has been done in our laboratory. Dr. Gremillion has presented data from these studies at a regional meeting of the American College of Physicians and has also prepared a manuscript for publication. Since we had not only antibody data but also observations on infection rates during epidemics of H1N1 influenza and influenza B, we suggested that the manuscript be altered to include protection data as well as antibody data. A revised manuscript has now been virtually completed and will shortly be submitted for publication with Dr. Gremillion as senior author. A copy of this manuscript accompanies the Annual Report.

Lt. Colonel Gremillion also has suggested collaborative studies in other areas and we are now exploring these with him. We are most anxious to be helpful in any studies directed towards the further reduction of viral disease in the Air Force.

Walter Reed Army Institute for Research. Major Charles Hoke, a former fellow in this Division, has remained in close contact with our laboratory and has received paired sera from vaccinated individuals who subsequently developed influneza. He is interested in modification of antibody measurement techniques which might explain vaccine failures.

Bureau of Biologics. Dr. Bruce Brulington, also a former fellow, is now in the Influenza Section at the Bureau of Biologics of Bethesda. He is continuing the work with sera obtained here in an effort to devise an ELISA test which will be more useful than conventional H.I. tests in measuring antibody response. To assist in this project, we have provided sera from patients who had influneza in 1978 (H1N1) and 1957 (H2N2) as primary infections.

Center for Disease Control. We remain in close contact with Drs. Gary Noble and Alan P. Kendal at CDC during the influenza seasons. This year, as in the past, we have sent them a number of strains of both H1N1 influenza and influenza B in order to further characterize them and to detect any evidence of antigenic drift.

World Health Organization. The principal investigator annually passes through Geneva and exchanges information with Dr. Assad there who is in charge of the Influenza Unit of the Virus Section. During the past year, he had the opportunity to visit the W.H.O. supported laboratory at St. Mary's Hospital in HongKong, which has been the source of several interesting influenza strains, both A and B. During the coming summer, he will also spend a month in Thailand where he will contact the virus laboratory. Interesting virus strains have been isolated there, such as contained in the current vaccine and also A/Bangkok/2/1979, A/Bangkok/1/79 which is a strain with considerable antigenic drift. Up the presnt time, this strain has not been responsible for any recognized outbreaks of significant size.

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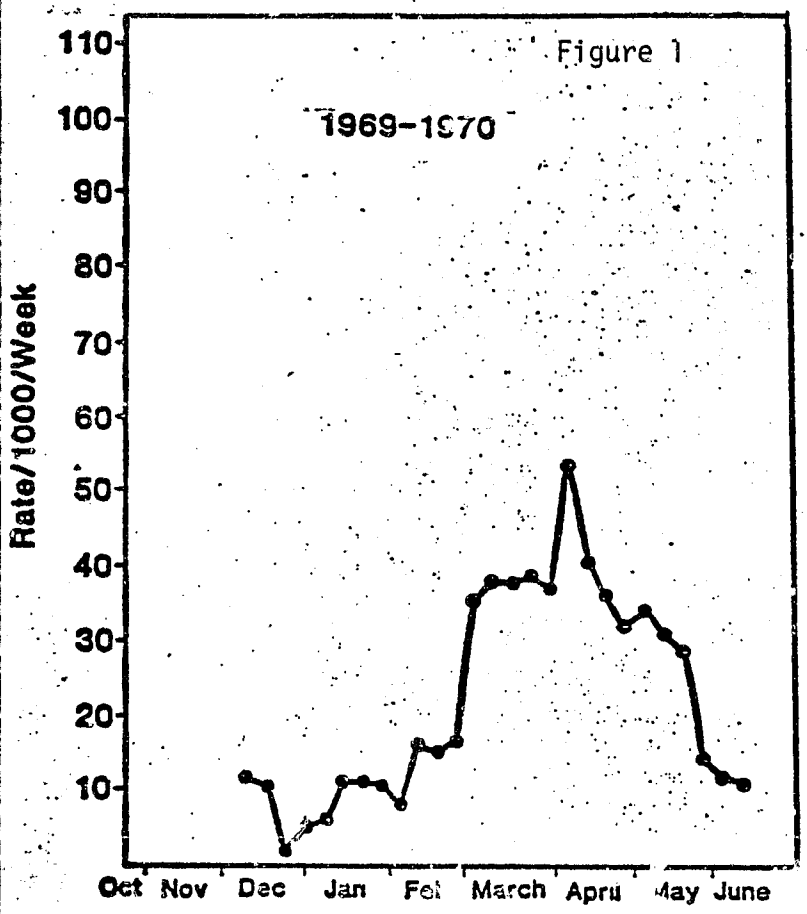
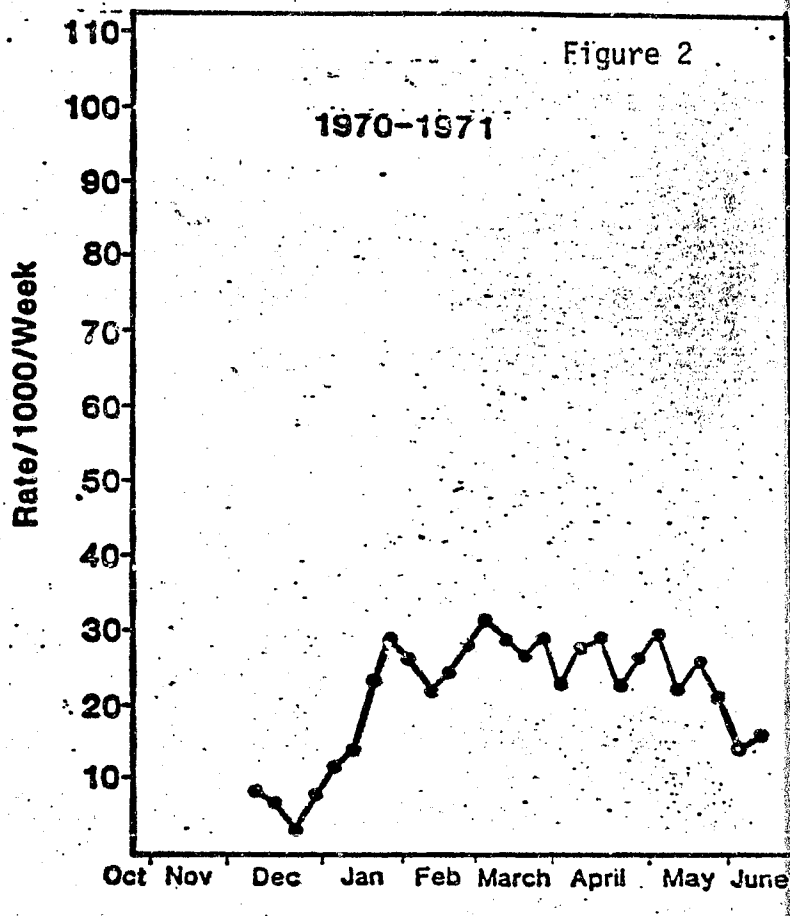
Col. George G. Lathrop, USAF MC, USAF SAM-ES, Brooks AFB

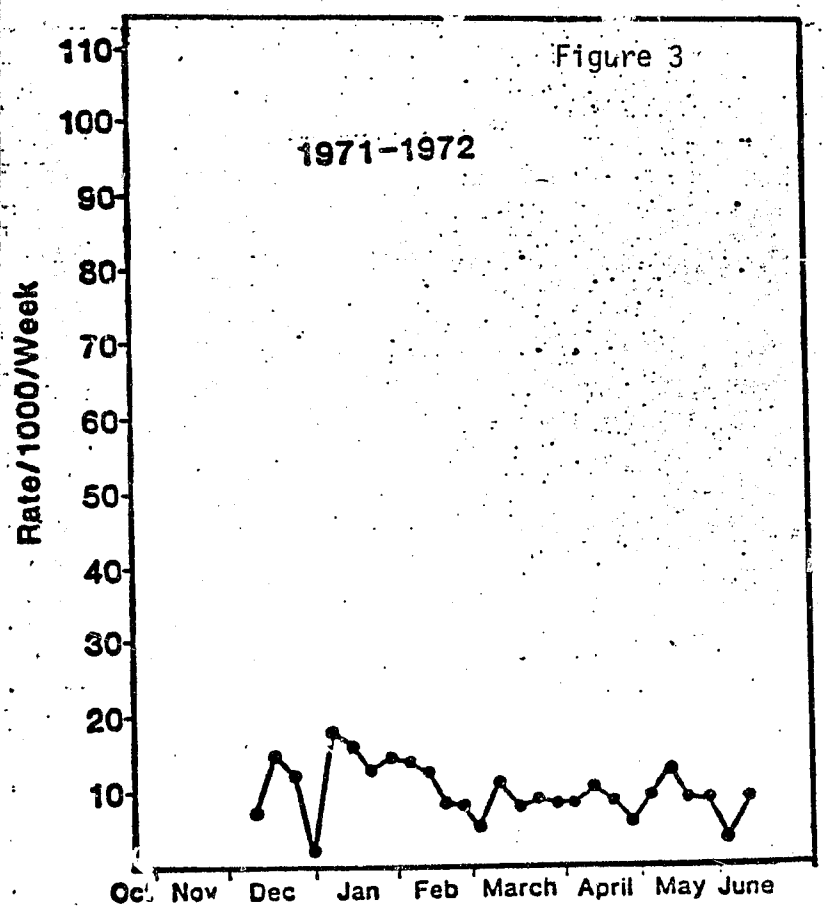
Lt. Col. David Gremillion, USAF MC, Chief, Infectious Diseases Service, Wilford Hall USAF Medical Center, Lackland AFB

Josephine I and Patricia S. Graves, University of Colorado School of Medicine

Weekly Rates of Febrile Upper Respiratory Infection
Study Population, Lowry Air Force Base







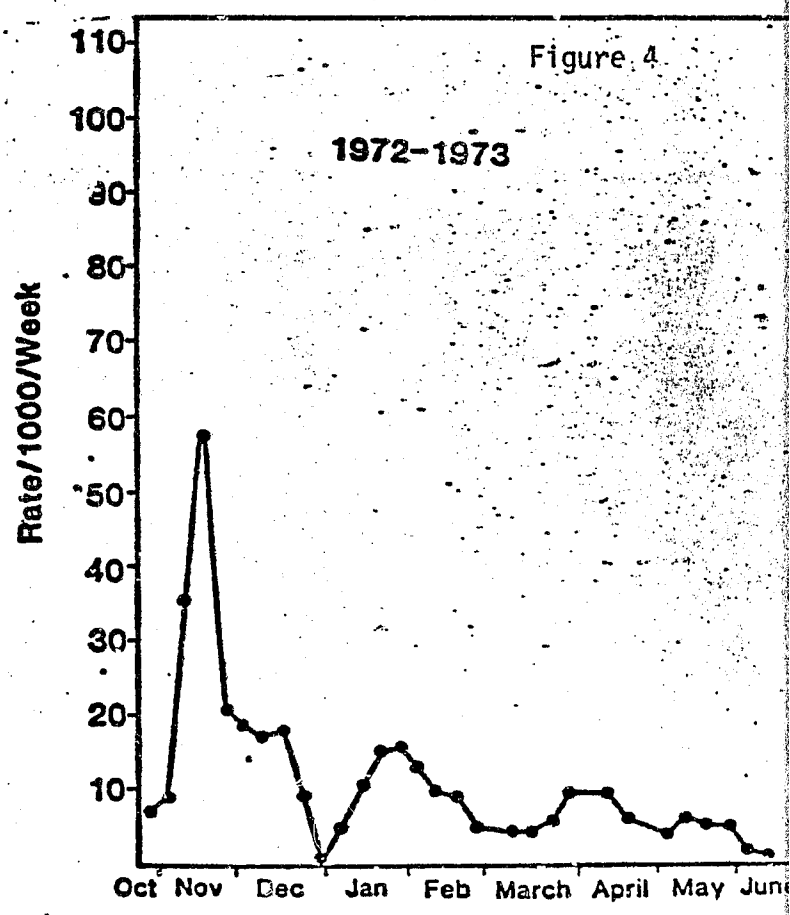
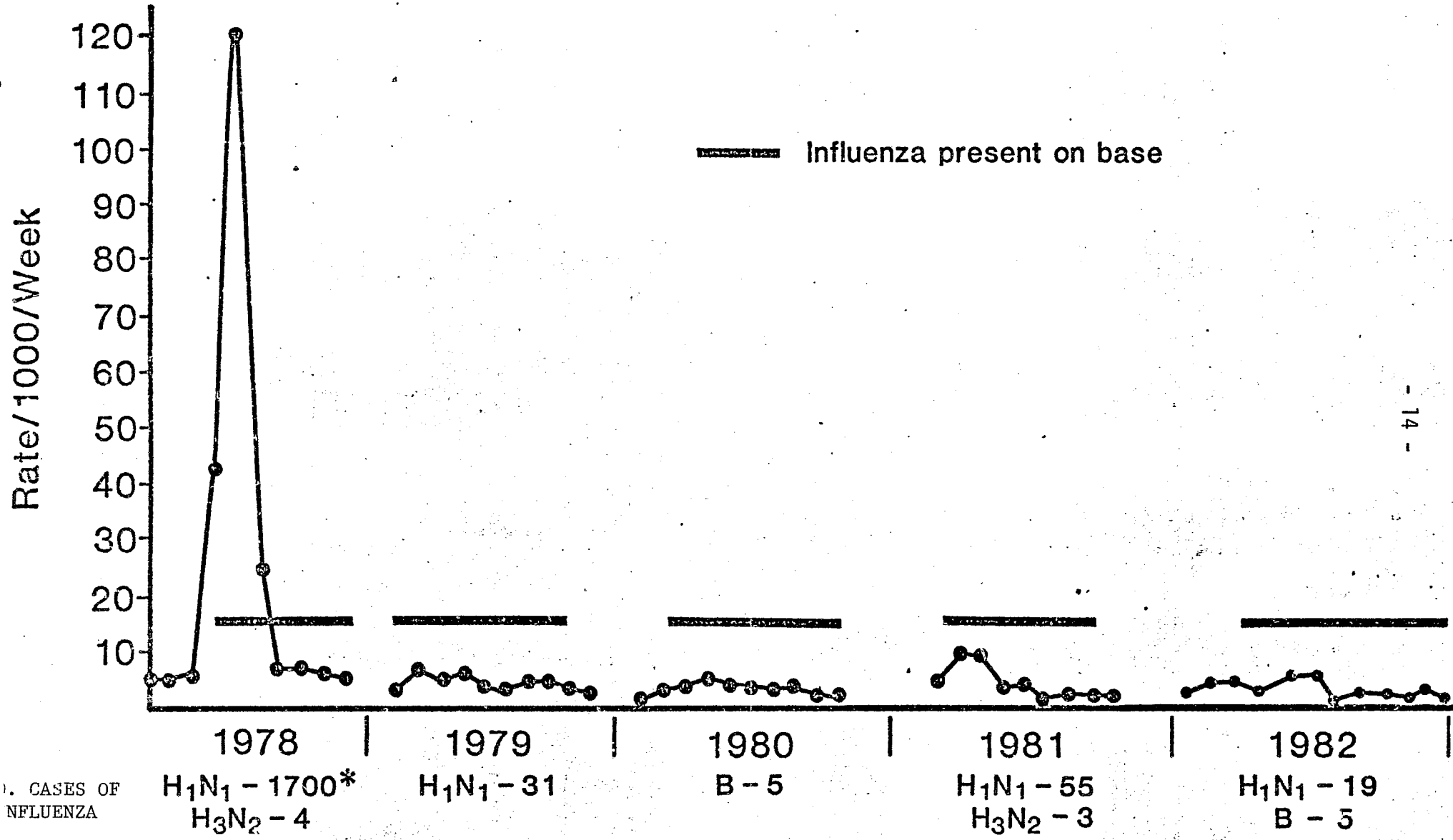


Figure 5

Weekly Rates of Febrile URI in Student Population at Lowry A.F.B. 1978-1982



I). CASES OF NFLUENZA

* Estimate based on excess clinic visits

Table 1. Distribution of H.I. Titers of 81 Air Force Recruits Before and After Receiving Influenza Vaccine Containing 15 µg Each of Hemagglutinin of A/Brazil/11/78, A/Bangkok/1/79 and B/Singapore/222/79

Test Virus	Serum Specimen	Cumulative percent with H.I. titer of > <8	8	16	32	64	128	256	512	1024
A/Brazil/78	Pre-	43	57	30	13	2	1	0	0	0
	Post-	5	95	91	90	88	73	57	34	20
A/Bangkok/79	Pre-	57	49	24	6	2	1	0	0	0
	Post-	1	100	100	95	74	60	40	23	9
B/Singapore/79	Pre-	59	41	11	1	0	0	0	0	0
	Post-	6	93	83	45	20	2	1	1	0

Comment: The responses to A/Brazil/78 and A/Bangkok/79 are very good, as they were in the group studied in May of 1981. The influenza B response appears less satisfactory, but this may be in part a technical problem. See accompanying table for results of tests using ether-split B/Singapore/79 antigen.

Table 2. H.I. Antibody Response to Influenza B Component (15 μg of B/Singapore/79) of 25 Air Force Recruits Using Three Different Antigens

Test Strain	Type of Antigen	Serum Specimen	Cumulative Percent with H.I. Titer of ≥ <8	8	16	32	64	128	256	512	1024	% with 4X rise
B/Singapore/79	Whole Virus	Pre-	68	32	8	4	0	0	0	0	0	
		Post-	4	96	92	60	24	0	0	0	0	76
B/Singapore/79	Ether-Split	Pre-	16	84	76	60	40	16	4	0	0	
		Post-	0	100	100	100	100	100	64	40	12	88
B/HongKong/72	Whole Virus	Pre-	32	68	60	24	12	0	0	0	0	
		Post-	0	100	96	80	64	24	8	4	0	68

Comment: The response appears to be far better with the ether-split B/Singapore antigen, but the baseline (pre-vaccination titer) is far higher. The titer measured with the whole virus antigen has been more useful in predicting protection against infection.

Table 3. Complement-Fixing Antibody Response of 80 Students to Vaccine Containing 15 µg Each of A/Brazil, A/Bangkok and B/Singapore

		Cumulative Percent with Titer of								% with
	Serum	<8	8	16	32	64	124	256	512	1024	4 X rise
Influenza A	Pre-	31	68	36	13	1	1	1	1	-	
	Post-	11	88	71	44	23	3	2	1	-	32
Influenza B	Pre-	25	75	58	23	3	1	1	-	-	
	Post-	1	98	97	79	31	5	1	-	-	28

Table 4. Rates of Febrile U.R.I. in Student Population and Number of Confirmed Cases of Influenza A (H1N1), Influenza B, Adenovirus and Streptococcal Infections in Students (S.) and Permanent Party (P.P.), 1981-82

Week beginning	Cases/1000/wk (Students only)	Influenza A		Influenza B		Adenovirus		Streptococcal	
		S.	P.P.	S.	P.P.	S.	P.P.	S.	P.P.
16 Nov	0.2	-	-	-	-	1	-	-	-
23 "	0.9	-	-	-	-	-	-	-	3
30 "	0.9	-	-	-	-	1	-	-	-
7 Dec	0.8	-	-	-	-	1	2	-	-
13 "	1.2	-	-	-	-	1	-	-	1
20 "	0.2	-	-	-	-	-	-	1	1
27 "	-	-	-	-	-	-	-	-	1
4 Jan	0.5	-	-	-	-	-	-	-	-
11 "	2.6	3	1	-	1	-	-	1	2
18 "	2.7	1	3	-	-	-	-	2	2
25 "	2.4	4	1	-	-	-	-	1	2
1 Feb	4.5	4	5	1	2	-	-	-	-
8 "	4.5	2	8	-	3	-	-	-	-
15 "	1.8	1	5	-	1	-	-	1	-
22 "	2.0	2	2	-	2	-	-	-	-
1 Mar	2.1	1	1	1	1	-	-	-	1
8 "	1.4	1	1	1	4	-	1	3	1
15 "	1.9	-	-	1	6	-	-	-	1
22 "	1.4	-	-	1	2	-	-	-	-
29 "	1.5	-	-	-	2	-	-	-	1
5 Apr	1.9	-	-	-	-	-	-	1	-
12 "	1.9	-	-	-	-	-	-	-	-
Sub-Total		19	27	5	24	4	3	10	16
Total		46		29		7		26	

Table 5. Antibody responses of 18 students* with Influenza A in Complement-Fixation Tests and H.I. Tests with Two Antigens

Test	Antigen	Serum	Number of persons with titer of <8	8	16	32	64	128	256	512	1024	Percent with 4 X rise
C.F.	A/Brazil	Acute	9	4	3	2	-	-	-	-	-	89
		Conv.	-	-	3	2	6	7	-	-	-	
H.I.	A/Brazil	Acute	8	5	3	1	-	1	-	-	-	9
		Conv.	-	-	1	2	1	3	5	3	3	
H.I.	A/Brazil	Acute	1	-	2	2	2	-	4	1	6	
		Conv.	1	-	2	3	1	2	2	2	5	

*One additional virus was isolated from a person from whom no convalescent serum was available.

Table 6. Antibody Responses of 23 Permanent Party* with Influenza A in Complement Fixation Tests and H.I. Tests with Two Antigens

Test	Antigen	Serum	<8	8	16	32	64	128	256	512	1024	Percent with 4 X rise
C.F.	A/Brazil	Acute	9	3	6	4	1	-	-	-	-	70
		Conv.	2	-	1	7	4	8	1	-	-	
H.I.	A/Brazil	Acute	9	4	6	3	-	-	1	-	-	91
		Conv.	-	-	2	4	6	2	6	1	2	
H.I.	A/Bangkok	Acute	1	7	6	4	3	-	1	-	1	0
		Conv.	1	8	6	4	3	-	-	-	1	

*Viruses were isolated from an additional 4 persons from whom convalescent sera were not available.

Table 7. Antibody Response of 22 Persons with Influenza B in Complement-Fixation Tests and in H.I. Tests with Three Antigens

Test	Antigen	Serum	No. of persons with titer of								Percent with 4 X rise
			<8	8	16	32	64	128	256	512	1024	
C.F.	B/Singapore	Acute	4	8	8	2	-	-	-	-	-	
	Whole Virus	Conv.	-	1	2	3	8	4	3	1	-	77
H.I.	B/Singapore	Acute	8	9	2	1	1	1	-	-	-	
	Whole Virus	Conv.	1	5	5	4	4	2	-	-	1	36
H.I.	B/Singapore	Acute	4	1	9	1	5	1	1	-	-	
	Ether-Split	Conv.	1	2	1	3	2	3	3	5	2	59
H.I.	B/HongKong	Acute	4	7	7	2	1	1	-	-	-	
	Whole Virus	Conv.	1	2	3	5	2	7	2	-	-	45

Viruses were isolated from 19 of these 22 (86%) persons. In two instances where viruses were isolated, there was no significant rise in titer in any test. These may represent carriers or laboratory contaminants rather than cases.

Table 8. Comparison of Diagnostic Sensitivity of Various Tests in Confirmed Cases of Influenza B (B/Singapore) and Influenza A (A/Brazil)

	Test	No.Positive/No.Tested	Percent Positive
Influenza B	Virus isolation	19/22	86
	C.F.	17/22	77
	H.I. - Whole virus B/Sing E-19	8/22	36
	- Ether-split B/Sing	13/22	59
	- B/HK/5/72 E-27	10/22	45
Influenza A	Virus isolation	24/41	59
	C.F.	32/41	78
	H.I. - A/Brazil E-11	38/41	93

Table 9. Comparison of H.I. Antibody Titers of 3 Population Groups with the Acute Phase Titer of 41 Patients with Influenza A

Percent with Titer of	Group* 1	2	3	Cases of Influenza A
<8-8	9	20	6	63
16-32	3	10	30	32
≥64	88	71	64	5

*See text.

Table 10. Oral Temperatures of Patients with Confirmed Influenza A or B

Temperature	Influenza A			Influenza B		
	Students	P.P.	Total (%)	Students	P.P.	Total (%)
<100	3	8	11 (25)	0	10	10 (37)
100-101	7	6	13 (34)	1	7	8 (29)
>101	8	12	20 (45)	3	8	11 (38)
Total	18	26	44	4	25	29

P.P. = Permanent party

Table 11. Percent of Illness Caused by Influenza A and B and Group A β Hemolytic Streptocci in Persons with Different Oral Temperatures 4 January - 9 April, 1982

Temperature	Total No.	Influenza A	Influenza B	Strep Pharyngitis	Negative	% Negative
<100	89	11	10	7	31	53
100-100[9]	61	13	10	6	32	52
>101	52	21	9	6	16	31
Total	172	45	29	19	79	46
Percent of illness		26	17	11	46	

Table 12. H.I. Antibody Response of 25 Students to Three H3N2 Strains A/Texas/1/77, A/Bangkok/1/79 and A/Shanghai/31/80 to Trivalent 15 µg Vaccine Containing A/Bangkok/1/79

Test Strain	Serum	Cumulative % with titer of <8	8	16	32	64	128	256	512	1024	% with 4 X rise
A/Texas/77	Pre-	8	92	80	36	16	4	4	-	-	
	Post-	-	-	-	-	100	88	64	52	32	100
A/Bangkok/79	Pre-	8	92	28	12	4	-	-	-	-	
	Post-	-	-	-	100	88	64	60	24	12	100
A/Shanghai/80	Pre-	20	80	16	4	-	-	-	-	-	
	Post-	-	-	100	92	76	40	24	8	4	96

Comment: Pre-vaccination titers are highest to A/Texas and lowest to A/Shanghai. Post-vaccination titers are higher to A/Texas than to A/Bangkok, the vaccine strain, which one would expect in a population which has presumably been previously infected with virus strains resembling A/Texas

The A/Shanghai titers are about 2-fold lower, but the response to vaccine is good, with 92% having post-vaccination titers of $\geq$32.

The data support the decision to continue using the A/Bangkok strain in the vaccine rather than changing to A/Shanghai.