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PREVENTION OF INFLUENZA AND OTHER RESPIRATORY DISEASES (U)

ANNUAL PROGRESS REPORT

BY

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

August, 1974
(For the period 1 June 1973 to 31 May 1974)

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Influenza A
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Hemagglutinin
Neuraminidase
Field trial

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

1. Tests for H.I. antibody response to test lots of B/HK/72 in September, 1973, containing 250, 500, or 1000 CCA units showed good seroconversion rates and elevation of titers when late (E 22) egg passage virus was used. A second injection of vaccine evoked little further increase. The 500 CCA unit vaccine subsequently used in the Air Force also evoked a highly satisfactory response.
2. Vaccine of standard military formula, containing A2/Eng/72 and B/Mass/71 evoked a highly satisfactory response to A2/Eng/72 and to

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the more recent A/Port Chalmers/73 and a moderate response to B/HK/72.

3. Significant systemic or local reactions were not observed following vaccination, even when the standard bivalent 1000 CCA unit vaccine and the 500 CCA unit B/HK/72 vaccine were given simultaneously.

4. A volunteer field trial designed to compare the incidence of influenza A or B in men receiving bivalent vaccine containing A_2/Eng/42 and B/Mass/71 with that in men who received only B/HK/72 vaccine was set up.

5. A small outbreak of influenza B, caused by strains closely related to B/HK/72 occurred in February and March, 1974. The number of cases in the study groups was very small and significant differences in incidence were not demonstrated between those who received earlier (B/Mass/71) and those who received recent influenza B (B/HK/72) vaccines.

6. A small outbreak of influenza A caused by strains closely related to A/Eng/72 and A/Port Chalmers/73 occurred in late March and April, 1974. The number of cases was small in the study group and, while there was a suggestion of a protective effect, the differences between those who had received influenza A vaccine and those who had not was not significant.

7. No cases of adenovirus illness due to Types 4 or 7 were found among 400 men with febrile U.R.I. The results of tests for neutralizing antibody suggested that vaccination alone could not be credited for disappearance of these viruses.

8. The incidence of febrile U.R.I. at Lowry Air Force Base in the 1973-74 season never exceeded 10.8/1000/week and was the lowest observed during the past 20 years

SUMMARY

1. Tests for H.I. antibody response to test lots of B/HK/72 in September, 1973, containing 250, 500 or 1000 CCA units showed good seroconversion rates and elevation of titers when late (E 22) egg passage virus was used. A second injection of vaccine evoked little further increase. The 500 CCA unit vaccine subsequently used in the Air Force also evoked a highly satisfactory response.

2. Vaccine of standard military formula, containing A_2/Eng/72 and B/Mass/71 evoked a highly satisfactory response to A_2/Eng/72 and to the more recent A/Port Chalmers/73 and a moderate response to B/HK/72.

3. Significant systemic or local reactions were not observed following vaccination, even when the standard bivalent 1000 CCA unit vaccine and the 500 CCA unit B/HK/72 vaccine were given simultaneously.

4. A volunteer field trial designed to compare the incidence of influenza A or B in men receiving bivalent vaccine containing A_2/Eng/42 and B/Mass/71 with that in men who received only B/HK/72 vaccine was set up.

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8. The incidence of febrile U.R.I. at Lowry Air Force Base in the 1973-74 season never exceeded 10.8/1000/week and was the lowest observed during the past 20 years.

KEY WORDS

Influenza A

Influenza B

Adenovirus

Vaccination

Hemagglutinin

Neuraminidase

Field trial

PURPOSES

A. General Aim

The purposes of the studies carried out during the winter of 1973-74 were to obtain further knowledge about febrile respiratory diseases in newly inducted military personnel and to improve methods for reducing their incidence or eliminating their occurrence. Influenza, with its ever-changing antigenic patterns, presented a new problem. In contrast to the previous year, when an antigenic change in the influenza A_2 virus (A_2/Eng/42, H_3N_2) had posed the major threat, during the current year interest centered on influenza B strains because of the appearance of a new antigenic variant (B/HK/5/72). For the first time in many years, influenza B appeared to pose a more formidable problem than influenza A, and the question of whether the information learned about influenza A could be directly transferred to influenza B required an answer.

Secondly, adenovirus disease due to types 4 and 7 which, during the past two decades, has been the major cause of febrile disease at Lowry Air Force Base had fallen to very low levels during the preceding season, but it was not clear how much of this decline in incidence could be attributed to the introduction of universal immunization of incoming troops. Further information was clearly needed. Major efforts were direct to these two problems. At the same time, surveillance of all febrile respiratory diseases was continued in the student population at Lowry Air Force Base in order to detect other previously unrecognized problems.

B. Specific Aims

1. Influenza Vaccine

a. Influenza B

The behavior of influenza B has differed rom influenza A over the years in that antigenic change has occurred by gradual drift without the sharp changes, or antigenic shifts, such as those noted in the influenza A epidemics of 1957, 1968 and 1972. The drift has been sufficient to warrant changes in the composition of influenza vaccine at relatively long intervals, incorporating most recently the strains B/Mass/66 and, subsequently, B/Mass/71 in the military formula. The Armed Services have escaped large outbreaks of influenza B during this period although there have been a number of outbreaks in surrounding civilian personnel. This may have been due to protection afforded by the vaccine, but there are no clear cut field trials during this period to provide hard evidence to support this interpretation.

The appearance of the new B/HK/5/72 strains, which differ very sharply in their hemagglutinin from earlier strains and represent a major antigenic shift, raised the possibility of large influenza B outbreaks. The majority of the populations screened in this country lacked hemagglutination inhibiting antibody for these strains and appeared to comprise a highly susceptible population. On the other hand, the behavior of the new strains in those parts of the world where outbreaks had occurred did not appear to be particularly alarming since the outbreaks had not been massive and had not been accompanied by sharp increases in morbidity or mortality. Nonetheless, it appeared wise to anticipate trouble and to prepare vaccines against the new strains. These vaccines clearly needed

evaluation both in terms of their antigenic characteristics and their protective efficacy. Studies were consequently planned to (1) determine prevailing antibody levels in the population, (2) assess the effect of single injections of vaccines of varying potencies, (3) evaluate the effectiveness of second injections of vaccine (4) set up a field trial to measure vaccine effectiveness and, (5) observe the behavior of the new influenza B virus strains in the military and, secondarily, in civilian populations.

b. Influenza A

The 1972-73 studies at Lowry Air Force Base had clearly demonstrated that influenza vaccines prepared against A_2/Aichi/68 (H_3N_2) provided some protection, approximately 60%, against the A_2/Eng/72 strains but pointed to the need for a change in the influenza A_2 component of the vaccine. This was accomplished during the intervening period, and the new military formula contained 700 CCA units of A_2/Eng/72 and 300 CCA units of B/Mass/71. In the meantime, further antigenic drift had been observed in influenza A viruses, and the newer strains had caused outbreaks, notably in Australia and New Zealand. Information was sought on the antibody response which the current vaccines would provide not only against homologous virus but also against the newer influenza A_2 strains.

c. Adenovirus Disease

Adenovirus diseases fell to very low levels during the preceding year, and it was of interest to determine whether this pattern would be repeated in 1973-74. It has earlier been noted that, while the administration of vaccine for both types 4 and 7 had been carried out during the earlier year, there had been serious questions about the potency of the vaccine, particularly the type 4 component. Antibody studies carried out on incoming personnel at Lowry Air Force Base had failed to demonstrate neutralizing antibody in a high proportion of the men. Nonetheless, the incidence of diseases was extremely low. With the administration of vaccine of higher potency during the summer of 1973, it was again important to follow adenovirus incidence and to attempt to determine whether the diminution of diseases rates could be attributed to the immunization procedure or was due to other factors. With the elimination of types 4 and 7, it was of particular interest to determine whether they would be replaced by other adenovirus types which, at the present time, have not been significant causes of illness in American military personnel. Concern over this possibility has been a major factor in delaying the implementation of a policy for immunization of all recruits.

d. Surveillance of Other Respiratory Diseases

There continues to be a segment of febrile acute respiratory disease which has not been classified with respect to etiology. Even after infections caused by known agents such as influenza, adenoviruses, streptococci and rubella have been identified, 30% to 50% of illnesses still fall into unclassified categories. None of these have occurred in large epidemic peaks during the years of study at Lowry Air Force Base. Searches have been made for infections due to mycoplasma, coronaviruses and parainfluenza viruses in order to define the roles of these agents and, while all have been present, they have not proved to be major causes of febrile disease. In the process of following the major infectious agents, the specimens of throat washings and sera were collected in order to provide materials for identifying any clear-cut outbreaks which might occur or to provide material for the identification of previously unrecognized infectious agents.

C. Antibody Response Following Vaccination

1. Observations on Early Monovalent Influenza B Vaccines

When influenza B/HK/5/72 strains were first received and distributed in this country, screening of earlier sera and tests of sera of military personnel from the preceding year at Lowry Air Force Base suggested that the population was virtually devoid of hemagglutination inhibiting antibody, confirming an earlier observation by Dr. Fred Davenport. This indicated a need for the prompt development of vaccine against the new strain, and the rapid acquisition of information necessary to determine an appropriate vaccine unitage. These preliminary studies were done with early egg passage (6th passage) virus and suggested that not only was antibody virtually absent in the pre-vaccination sera but also that the response to vaccine even in high unitage was disappointingly low. It became clear after the virus was further passed in chick embryos that the early tests were meaningless because the virus was in a non-avid stage. Tests with later passage material (egg passages 22 and 23) produced a totally different picture. This phenomenon has long been recognized with influenza A strains and was, in fact, used in the past in the U.S.S.R. for the selection of strains for live intra-nasal vaccines. As will be shown later, monkey kidney isolated virus, in passage as early as the second, provided an antigen which would have provided answers comparable to the later egg passage material if it had been used at the beginning of the study.

a. Tests with Early Passage B/HK/72 Strains

Monovalent vaccines containing 250, 500 and 1,000 CCA units (lots 6599600, 6599700 and 6599800) prepared by Merck, Sharp and Dohme were administered to groups of 73 - 80 men on September 4, 1973. The stated potency of the vaccine was checked in Dr. Fred Davenport's laboratory and found to relate closely to the stated content. Serum specimens were collected before and three weeks after vaccination (in a few instances, two weeks following vaccination). Because there has been concern in the past about possible severe pyrogenic reactions to influenza B vaccines, these men were checked for temperature elevations or other systemic or local reactions 24 and 48 hours following vaccination. There were, in several instances, minor local reactions and low-grade temperature elevations (not more than one degree). These were in no instance troublesome, and there was, furthermore, no difference between the degree of reactions in men given 1,000 CCA units of vaccine and that in men receiving the smaller amounts.

The results of H.I. tests against B/HK/72 are presented in Table 1. These results were promptly forwarded to Colonel Buescher at WRAIR, as well as to Dr. Parkman at the Division of Biologics, to Dr. Walter Dowdle at the Center for Disease Control and to other members of the influenza committee. They show a very mediocre response at all levels. With 250 CCA unit vaccine, only 33% of the men showed a four-fold or greater rise in titer; with 500 CCA unit vaccine, only 37%; and with 1,000 CCA unit vaccine, only 46%.

The same sera were also tested against B/Mass/71 in order to obtain information on the amount of crossing between the new and the older strain contained in current military vaccines (Table 2). The pre-vaccination antibody titers in this group of men are relatively high, reflecting their response to standard military vaccine administered several months earlier. Results are presented in Table 2. The B/HK/72 vaccine evoked a four-fold or greater response in 35% of the men who received 250 CCA units, in 40% of those receiving 500 CCA units and in 56% of those receiving 1,000 CCA units. Following vaccination, only a very small number of men continued to have titers of 1:16 or less, and most of the men

had titers in a range between 128 and 1024. There was a trend toward a greater increase in antibody titer with increasing antigenic mass.

Tests with a 1973 influenza B strain isolated in Denver by the State Health Department laboratory (B/Denver/452/73) are presented in Table 3. The results are intermediate between the two described above but closer to those obtained with B/Mass/71. A somewhat larger proportion of men were seronegative prior to vaccination, and the magnitude of the antibody response was less than that observed with B/Mass/71. There was, again, some trend toward improved antibody response with increasing antigenic vaccine content.

b. Tests with Later Egg Passage B/HK/72 Strain

When the same serum pairs were tested with later egg passage material (E-22, E-23), the results were strikingly different (Table 4). Among the pre-vaccination sera, instead of a virtual lack of antibody, approximately 1/3 of the men had H.I. antibody titers of 1:16 or greater, though the majority still had titers of less than 1:8. Following vaccination, there was a substantial increase in antibody titer with the amount of response clearly related to the antigenic content. At the 250 CCA unit level, 52% of the men had increases in titer of four fold or more, at 500 CCA units 66% and at 1,000 units 78%. There were still a significant number of seronegative (titers less than 1:8 or 8) men following vaccination, but the ratio of men at these levels between pre- and post-vaccination specimens was reduced by approximately 5 or 6 to 1.

c. Test with Early Monkey Kidney Passage Virus Strain (B/Den/1/74)

Later in the season when a number of influenza B strains had been isolated from the small outbreak which occurred in the spring of 1974, paired sera of men who had received vaccine containing 500 CCA units were re-tested with second monkey kidney passage fluid of one of the newly isolated strains (Table 5). These strains grew readily in monkey kidney cells, and the titer of the tissue culture (B/Den/1/74) fluid was sufficient to permit its use at a 1:2 dilution in a standard H.I. test. The results of this test are shown in Table 5. The percent of men showing antibody increases of four fold or greater was 94%. Considerable uncertainty about the desirable course of action could have been avoided if this observation had been made in the fall of 1973.

d. Tests Following Second Injection of Vaccine

When the early studies which suggested a very poor antibody response to the monovalent B/HK/72 vaccine were obtained, it seemed desirable to find out whether a second injection of vaccine would produce significant enhancement of effect. The number of men available for this second vaccine injection was relatively small, but the results are of some interest (Table 6). Men from each of the three groups, namely, those who had received 250, 500 or 1,000 CCA units, were given a booster injection in each instance of 500 CCA units. As in earlier studies with aqueous influenza vaccine, there was relatively little response to the booster injection. In the group which had received 250 CCA units, 15% showed a four-fold or greater increase in titer, in the 500 CCA unit group, 15%, and in the 1,000 CCA unit group, 11%. The only notable change was the reduction in the seronegative group from 5 to 1 persons in the groups which had initially received 500 or 1,000 CCA units.

2. Observations on Current Military Vaccines (1973-74)

a. Bivalent Vaccine

Results obtained with sera of men who received polyvalent vaccine (Wyeth, lot 133701) which contained 700 CCA units of A2/Eng/42 and 300 CCA units of B/Mass/71 are presented in Table 7. The response to the influenza A component was highly satisfactory. A number of men already had antibody in high titer. Of those whose titers were initially low, virtually all showed significant rises. The proportion of men with four-fold or greater increase in antibody level was 57%. The response to the B/Mass/1/71 was again satisfactory in this population which already had relatively high antibody levels. In tests with B/Den/452/73 it was noted that while a similar proportion of men had four fold or greater increases in titer, a significant proportion remained seronegative, and the range of post-vaccination titers was considerably lower than had been observed with homologous strain B/Mass/71. This difference was further accentuated in tests with the 22nd or 23rd egg passage of B/HK/72. Here, 69% of the men were seronegative prior to vaccination and, after vaccination, 46% continued to have titers of 1:8 or less. Only 27% of the men showed significant increases in antibody titer. It can be concluded that, while there is clearly crossing between B/Mass/71 and B/HK/72 in human sera, the response to B/Mass/71 vaccine is less than optimal when measured against the new variant.

b. Monovalent B/HK/5/72 Vaccine

At the time when the field trial subsequently described was begun, a small group of men who received only the monovalent B/HK/72 (Merck, Sharp and Dohme lot 4708G) vaccine was bled on two occasions, and their antibody response was determined (Table 8). When the sera were tested against the homologous B/HK/5/72 strain, the antibody response was remarkably good and 91% of the men showed four-fold or greater increases in antibody titer. The pre-vaccination titers in this group were lower than those observed in other groups, and the response seemed to be inordinately high. For this reason, it was checked on two additional occasions without significant change in the results.

In tests with B/Den/452/72, this group showed considerably higher levels in their pre-vaccination sera and responded well to the injection of B/HK/72 vaccine. Fifty-four percent of the men showed four-fold or greater rises in antibody titer and virtually all men had titers of 1:16 or higher following vaccination. With B/Mass/1/71 the response was even more satisfactory. Sixty-six percent of the men showed four-fold or greater increases in titer following vaccination, and almost all of the men had titers in the range between 128 and 1024. These sera were also tested against A/Den/1/72 in order to provide a check on the validity of the hemagglutination inhibition tests. These tests showed a highly satisfactory degree of reproducibility in that titers usually changed not at all or only two fold, and none of the men showed four-fold increases in titer.

3. Observations on Simultaneously Administered Bivalent and Monovalent Vaccines in Civilians

Since most men in the Armed Services received both polyvalent and monovalent vaccines during the winter of 1973-74, it was of considerable interest to observe antibody response in people who had received both preparations. It was for local reasons impractical to obtain serum from double recipients among the military personnel, but it proved possible to collect a civilian group who

had received simultaneously polyvalent vaccine containing standard formula of 700 CCA units of A_2/Eng/72 and 300 CCA units of B/Mass/71 (lot NDC 0071-1568-01) and also a monovalent preparation containing 500 CCA units of B/HK/72. The vaccine used was prepared by Parke-Davis under the commercial name of "Fluogen" (lot NDC 0071-1600-01) and was an ether-split product. No significant complaints regarding reactions were received. This civilian population clearly differed in a number of respects from the military population, notably, in age, history of prior immunization and, presumably, prior exposure to various influenza strains.

Results are presented in Table 9. With the homologous A/Den/1/72 strain, the response was remarkably good with 86% of individuals showing a four-fold increase in titer, and virtually all individuals having titers of greater than 1:256 following vaccinations. With the recently isolated A/Port Chalmers/73 and A/Dynedin/73 which show some antigenic shift and have caused considerable concern, the response was, again, highly satisfactory with approximately 80% of men showing four-fold or greater increases in antibody titer. Again, the proportion of men remaining seronegative following vaccination was relatively small. These results suggest that the current vaccine should have provided a relatively high level of protection in the event that outbreaks due to the newer variants of A_2/Eng/72 occurred.

With the influenza B strains, the response to B/Mass/71 was moderately satisfactory with 60% of men showing a four-fold or greater rise in titer. With B/452/73, the situation was somewhat different. Even though 50% of the men showed increases in titer of four-fold or more, a large proportion continued to be seronegative following vaccination. With B/HK/72, 70% of the men showed four-fold or greater increases in titer, and a large proportion rose to relatively high levels. However, 14% remained seronegative following vaccination. This represented a reduction from 68% to 14% seronegative individuals and was similar to the rates of seroconversion seen in military recipients of the monovalent B/HK/72 vaccine.

D. Field Trial of Vaccine Effectiveness

1. General Plan of Studies

As in previous years, the withholding of influenza vaccine during the period from July 1 to October 1 at Lackland Air Force Base provided a sizable pool of men who had not received influenza vaccine following entrance into the Air Force. The situation differed in that arrangements had been made to give vaccine only on the basis of men volunteering and indicating that they had entered the study following adequate explanation and following the signing of an informed consent form. Furthermore, no arrangements were made to give placebo injections to any men. The two vaccines available, namely, the polyvalent vaccine which contained A_2/Eng/72 and B/Mass/71 and the monovalent B/HK/72 vaccine presented a problem since the use of the vaccines might be expected to provide a clear difference in the event of an influenza A (H_3N_2) outbreak but could not be expected to demonstrate vaccine effectiveness as effectively in the event of an influenza B outbreak because the comparison would be not between B/HK/72 and nothing but between B/HK/72 and B/Mass/71. Recognizing the limitations, it was decided to endeavor to enlist all students, particularly those in long study programs, in a volunteer study and to alternate volunteers on the basis of their serial number between recipients of the polyvalent vaccine and the monovalent B/HK/72 vaccine.

At the time when vaccine was received late in November, 1973, there were 4,297 men enrolled in student squadrons. Vaccine was given on two successive days with both morning and afternoon sessions in order to meet the convenience of those students who were enrolled on different shifts. At these sessions, 2,568 men appeared; 1,728 men failed to report. A considerable portion of the latter represented men who were enrolled in either temporary duty units or in an officer squadron. Of the 2,568 men who reported, 1,087 indicated that they did not wish to volunteer and, consequently, were given simultaneously polyvalent vaccine in one arm and monovalent B/HK/72 vaccine in the other arm. This left 1,382 men of whom 362 had already received polyvalent vaccine at Lackland prior to July 1 or, in a few instances, after October 1. These men were given an additional injection of monovalent B/HK/72 vaccine.

This left 1,020 men who were divided into two groups on the basis of the terminal digit of their Social Security number with one group receiving monovalent B/HK/72 vaccine and the other standard military polyvalent vaccine. There were 488 men in the monovalent B vaccine group and 632 men in the polyvalent vaccine group. The reason for this discrepancy remains unclear.

The effectiveness of enlisting the student population in a volunteer study of this kind could undoubtedly have been increased by more careful preparation. The attained figure of 55% left the study groups too small and might well have been increased to a considerably higher level. The notion spread among many of the students that, if they enrolled in the study, they would be bled on two occasions, and this seriously deterred volunteering during one morning of the vaccination administration. The final group of 1,382 men might have been adequate to obtain significant results had the attack rates of either influenza B or influenza A had been high, but the number was certainly marginal. It was further reduced during succeeding months and had reached a level far below the point where any significant answers might have been obtained when influenza B occurred in late February and influenza A in March and April.

2. Method of Follow Up

All men reporting to the dispensary with temperatures of 99° or higher and symptoms of respiratory illness were asked to report at the influenza office. There, a brief notation was made of date of onset and clinical symptoms, serum specimens were collected, and arrangements were made for a second specimen to be collected three weeks later. Throat washings were collected in broth from all individuals whose reporting temperature was 101° or higher. The serum pairs were tested by complement fixation tests for influenza A and B, for adenovirus and mycoplasma. During the periods when influenza was prevalent, all specimens were also tested by hemagglutination inhibition tests with influenza B strains B/Mass/71, B/452/73 and B/HK/72. The influenza A strains used were A/Denver/2/72 and A/Port Chalmers/73. Individuals showing a complement fixation antibody rise for adenovirus were tested for neutralizing antibody for types 4 and 7 in a Hela cell tissue culture test. There were only two isolates (Adeno 1 and 5), and they were tested for neutralizing antibody rises to their homologous viruses.

3. Occurrence of Influenza

Influenza B first appeared on the Base during the week beginning 25 February and continued for the next four weeks. The outbreak was very minor with a total of only 26 cases detected of which only 19 were in the study groups. This caused a barely noticeable rise in the overall incidence of febrile respiratory disease on the Base.

Influenza A appeared in the week beginning March 18 and continued through the week beginning April 22. A total of 24 cases were detected on the Base with no more than seven cases occurring in any week. Again, the effect on the overall rate of febrile respiratory disease was imperceptible. Some of the cases occurred in men who had arrived at the Base subsequent to the establishment of the study and, for this reason, are not included in the analysis of attack rates in the various study groups. When these were eliminated, there remained a total of 19 cases of influenza B and 15 cases of influenza A distributed through the various components of the study.

4. Incidence of Influenza in the Different Vaccine Groups

a. Influenza B (Table 10)

Among the 1,392 men who were enrolled in the volunteer study, there were only three cases of influenza, with two cases occurring in the 270 men who had received polyvalent vaccine only, and 1 case occurring in the 437 men who had received either the monovalent B/HK/72 vaccine or both bivalent vaccine and monovalent vaccine. If one breaks down the incidence among the total number of 2,145 men whose vaccination status was known, the overall attack rate was 0.88%. Among men who had received B/HK/72 vaccine either alone or combined with bivalent vaccine, there were six cases among 914 men, an attack rate of 0.65%. The number of cases among 949 men was 11 among men who had received polyvalent vaccine only or had received no vaccine at all, a rate of 1.16%. This difference is clearly not significant.

b. Influenza A (Table 11)

The number of cases of influenza A among the 1,497 men who were present on the Base at the peak of the influenza A outbreak was 15, an attack rate of 1.00%. Within the volunteer study there were four cases among the 164 men who had received only the B/HK/72 vaccine, a rate of 2.44%. Among the 318 men who had received bivalent vaccine, there were no cases. If one takes the total population of 1,497 men, there were seven cases among 1,155 men who had received polyvalent vaccine, a rate of 0.60%. Among 338 men who had received no vaccine containing A_2/Eng/72, there were eight cases, a rate of 2.37%. The data suggest a protective effect, but the numbers of cases are too small to carry any significance.

E. Laboratory Investigations

1. Isolation of Virus Strains

a. Influenza B

Throat washings from men reporting with temperatures of 101° or higher were tested throughout the season. In all, 70 such specimens were received. No influenza strains were isolated until March 4 when the first influenza B isolate was obtained in Rhesus monkey kidney tissue culture. During the course of the small outbreak, seven throat washings were tested from individuals who showed serologic evidence of influenza B, and in all instances virus strains were recovered. Simultaneous efforts to isolate these strains in chick embryos incubated at 35° C. were unsuccessful. To date, adaptation to chick embryos has been successful only when strains isolated in monkey kidney tissue culture have been passed in chick embryo inoculated at 33° C.

These strains grew readily to high titer in monkey kidney tissue culture and appeared to have the characteristics of the B/HK/5/72 strain in that the results of H.I. antibody tests with the serum from the cases of influenza were very similar when B/HK/72 and strain B/Den/4/74 were used. Homologous antisera against the Denver strains have not yet been prepared, and further data are needed. It is obvious from the results presented in Table 8 that the new strains differed widely from B/Mass/71 and B/Den/452/73.

b. Influenza A

Influenza A strains were first isolated on March 21 and, thereafter, 11 of 12 throat washings from serologically confirmed cases of influenza A which were tested in monkey kidney and, in a few instances, in chick embryos yielded virus strains. These strains appeared to grow readily and rapidly when inoculated by the allantoic route into chick embryos as have other strains since the appearance of the A/HK/68 variants. Identification of the local strains has not yet been accomplished, but the results of serologic tests using both the A/Eng/42/72 and A/Port Chalmers/73 suggest that they resemble these viruses.

Comment The consistency with which influenza strains have been isolated from cases during this outbreak and during last year's outbreak when, again, more than 90% of confirmed cases of influenza A yielded virus, raises the possibility of conducting vaccine efficacy trials using virus isolation rather than serologic diagnosis as a criterion of clinical infection. Carriers do not appear to have been a problem since last year no isolations of virus were made from 26 individuals who failed to show antibody rises during the epidemic and, during this year's experience, 12 throat washings were tested from individuals who had no antibody rise and no virus strains were isolated. Nonetheless, it should be noted that virus isolation attempts have been limited to individuals who have temperatures of 100° or 101° and higher and might not be so uniformly successful if individuals with less severe infections were tested. In view of the difficulty of obtaining consent or of instituting a mandatory system of collecting blood specimens from all cases, however, this possibility deserves investigation.

2. Neuraminidase Antibody Studies

One of the fascinating and unsolved questions in influenza epidemiology is why virus strains differ in their capacity to spread and why clinical attack rates vary widely from outbreak to outbreak. Obviously, something is different either in the virus or in the host or in the interaction between the virus and the host. During the current year, influenza A virus was present on the base over a period of six weeks, yet attack rates were extremely low. This could be reasonably explained by the fact that the great bulk of the population had moderately or markedly elevated hemagglutination inhibiting antibody titers for the current strains. This, however, was not the case for influenza B which was prevalent for a period of approximately four weeks in the military population and considerably longer in the adjoining civilian population. At the end of the season, in May of 1974, screening of men at Lowry Air Force Base who had not received B/HK/5/72 vaccine indicated that there was still a large segment of the population which had either no antibody or antibody in very low titer only (Table 12). It is logical to assume that either these men had no exposure to the virus or they were protected by some mechanism other than hemagglutination inhibiting antibody.

One of the interesting hypotheses which deserves investigation in the field is that developed by Kilbourne and Schulman who suggest that antibody against the viral neuraminidase may modify or prevent clinical illness even though not preventing infection. For this reason, studies of neuraminidase antibody in various population groups have been begun using recombinants of recent influenza A strains prepared in Dr. Kilbourne's laboratories. Many technical obstacles were encountered initially, but the test, following the technique described by the CDC, now appears to be working in a highly satisfactory and reproducible manner.

A comparison of the results of the neuraminidase inhibiting antibody test with those of other serologic tests in 25 cases of influenza A during the 1972-73 outbreak is presented in Table 12. It is noteworthy that 21 of the 25 cases lacked N.I. antibody at the lowest level tested. The other four had antibody at relatively low levels, notably, 16 or 32. There was a striking rise in N.I. antibody in virtually all cases which closely paralleled the H.I. rise in antibody titer when tested with epidemic strains. H.I. antibody for the current strains and complement fixing antibody for the current strains were also absent in the acute phase sera of virtually all individuals, suggesting that they had not had recent contact with influenza A viruses. Preliminary screening of three other population groups at a 1:16 serum dilution (Table 14) suggested that, in this population, approximately one-half had N.I. antibody and one-half did not. Following vaccination, roughly one-half of the men who had previously lacked antibody appeared to have acquired antibody titers of greater than 1:16, but the remainder continued to have titers below that level.

There is, obviously, much to be learned from the sera collected during the outbreaks of recent years, and current efforts are directed to these investigations. Hopefully, suitable influenza B recombinants will be available for parallel studies.

3. Serologic Diagnosis of Influenza B

It has been noted earlier that the degree of egg adaptation had major effects on the usefulness of influenza B strains in H.I. tests for determination of antibody levels or confirmation of vaccine response or infection. Even when the virus had been well adapted to eggs by more than 20 passages, the results of serologic tests were less consistent than have been observed in the past with influenza A (Table 15). Specifically, occasional sera appeared to have very high titers in acute phase sera when run in tests with allantoic fluid but showed either low titers or virtually no antibody when tested with monkey kidney tissue culture. This suggested that inhibitors were present in these sera, but to date no satisfactory method has been found to eliminate these. Heat, periodate RDE and carbon dioxide have been tried without appreciable effect on the results. This clearly requires further investigation.

F. Adenovirus Disease

The 1973-74 season was extraordinary in that no cases of adenovirus disease due to types 4 or 7 were detected between November, 1973 and June, 1974. Two serologically confirmed cases of adenovirus disease were found, and virus strains were isolated which were neutralized by convalescent sera from the patients from whom the strains originated. Neither of these could be neutralized by either type 4 or type 7 antiserum, and they were subsequently identified in Dr. Lennette's laboratory as, respectively, type 1 and type 5 strains.

It is attractive to attribute this disappearance of the adenovirus problem to the institution of routine immunization of incoming recruits. The available data do not completely support this interpretation. Sera were collected in the fall of 1973 from unvaccinated men who had arrived at Lowry Air Force Base early in the fall and again during the respiratory season from men who had received vaccination following induction into the Air Force. Results are presented in Table 15. It is clear that the proportion of men showing antibody for type 7 was greater in the vaccinated group, but there was only a minor increase in the number of sero-positive men in the recipients of type 4 vaccine. In previous years, when adenovirus outbreaks were prevalent, a very large proportion of the men developed antibody during the course of the season, many as a result of either sub-clinical or totally inapparent infections. This was clearly not the case during the past season. If the prevention of illness and transmission is to be attributed to vaccination, then antibody response must have been relatively low and transient in order to explain the large proportion of seronegative individuals present at the end of the season.

Concern has been expressed in the past that, if types 4 and 7 were eliminated by universal vaccination, there was a high likelihood that they would be replaced by other adenovirus types which have not hitherto been a problem in the Armed Services. This replacement phenomenon clearly did not occur during the 1973-74 season or in preceding years. There will undoubtedly be arguments that there is no longer need to use the live type 4 and type 7 vaccines since the adenovirus problem has disappeared. However, the opposite view clearly has more validity, and it seems highly desirable to continue to administer these two vaccines, hopefully of adequate potency, to all recruits in the future.

G. Surveillance of Acute Febrile Respiratory Disease

The 1973-74 season was remarkable for the low incidence of febrile respiratory disease and for the absence of significant epidemic peaks (Table 17). For the whole season, the rate was approximately 5 per 1000 per week. On only two occasions did the rate reach 10.8 per 1000 per week. The previous season when the A/Eng/42/72 strain struck the Base was similar with the exception of the pre-Christmas influenza peak. The A_2/Eng/72 outbreak reached 60 per 1000 per week and would undoubtedly have been considerably higher had not vaccine been used which provided approximately 60% protection against clinical illness. The spring outbreaks which, in the past, were attributable almost entirely to adenovirus disease had frequently reached levels between 40 and 60 per 1000 per week. This virtual elimination of the more severe respiratory illnesses caused by influenza and adenoviruses is obviously highly satisfactory but should not be interpreted as grounds for cessation of investigations designed to improve the situation further and to deal with presently undefined problems.

A breakdown of the 400 cases which were studied by serologic tests is presented in the final table (Table 18).

TABLE I

Results of Vaccination with B/HK/5/72 on
HI Antibody Response to B/HK/5/72
(Egg Passage 6)

Vaccine Group	No.		Percent with HI Antibody Titer to B/HK/5/72								% with 4 x rise
			≤ 8	8	16	32	64	128	256	≥256	
250 CCA units	48	Pre-	98	0	0	0	2	0	0	0	33
		Post-	58	6	13	15	2	2	2	2	
500 CCA units	60	Pre-	93	4	1	0	0	0	1	0	37
		Post-	50	10	18	5	5	3	3	5	
1000 CCA units	41	Pre-	98	0	0	0	0	0	2	0	46
		Post-	51	0	5	10	12	10	10	2	

TABLE 2

Results of Vaccination with B/HK/5/72 on
HI Antibody Response to B/Mass/71

Vaccine Group	No.		Percent with HI Antibody Titer to B/Mass/71								% with 4 x rise
			< 8	8	16	32	64	128	256	>256	
250 CCA units	48	Pre-	17	2	6	10	10	25	10	19	35
		Post-	2	0	0	15	6	15	17	46	
500 CCA units	60	Pre-	15	2	8	8	7	25	12	23	40
		Post-	3	0	2	5	7	18	15	50	
1000 CCA units	41	Pre-	20	0	0	10	10	20	17	24	56
		Post-	5	0	0	2	0	15	10	68	

TABLE 3

Results of Vaccination with B/HK/5/72 on HI Antibody Response to B/452/73

Vaccine Group	No.		Percent with HI Antibody Titer to B/452/73								% with 4 x rise
			< 8	8	16	32	64	128	256	>256	
250 CCA units	48	Pre-	25	6	10	21	10	8	17	2	33
		Post-	6	0	8	17	19	17	25	8	
500 CCA units	60	Pre-	27	2	7	17	23	8	5	7	30
		Post-	12	0	2	17	17	20	13	20	
1000 CCA units	41	Pre-	27	0	7	20	12	17	10	7	61
		Post-	5	0	2	7	15	15	24	32	

No. of CCA units	Persons	Serum	Percent with HI Titer of < 8	8	16	32	64	128	256	512	1024	% with 4 x ris
250	73	Pre-	53	10	16	10	3	7	1	-	-	
		Post-	11	8	12	22	21	8	10	4	4	52
500	80	Pre-	61	3	10	10	6	6	1	1	1	
		Post-	9	3	13	16	18	18	10	9	6	66
1000	73	Pre-	64	8	11	10	4	1	-	1	-	
		Post-	10	3	8	10	15	23	12	11	8	78

TABLE 4 HI antibody response for B/HK/5/72 following administration of 250, 500 or 1000 CCA units of monovalent aqueous B/HK/5/72 vaccine (Egg passage 22, 23).

Test Strain	No. of Persons	Sera	Percent with HI Titer of: < 8	8	16	32	64	128	256	512	1024	% with 4 x ris
B/Den/1/74	35	Pre-	60	20	6	6	6	-	-	3	-	86
	35	Post-	--	3	6	9	14	9	29	11	20	

TABLE 5 H.I. antibody titers of 35 men before and 3 weeks after receiving 500 CCA units of B/HK/5/72 vaccine. (Tested with second monkey passage tissue culture fluid of strain isolated at Lowry Air Force Base in March, 1974).

Vaccine Group	No. of Persons	Serum	Percent with H.I. titer of ≤ 8	8	16	32	64	128	256	512	1024	% with 4 x rise
250 CCA units	13	Pre-	8	0	1	1	-	3	-	-	-	
		2nd	1	1	2	3	2	3	-	-	1	46
		3rd	1	1	1	2	2	3	2	1	0	15
500 CCA units	20	Pre-	14	1	-	2	2	1	-	-	-	
		2nd	2	1	2	2	1	2	2	4	4	80
		3rd	1	0	2	1	4	2	2	1	7	15
1,000 CCA units	17	Pre-	11	1	1	4	0	0	0	0	0	
		2nd	2	0	0	0	3	5	3	3	1	82
		3rd	0	0	2	1	2	5	3	1	3	11

TABLE 6 H.I. antibody response to B/HK/5/72 of 3 groups of men who had received initially either 250, 500 or 1,000 CCA units of monovalent aqueous B/HK/5/72 vaccine followed by a booster injection of 500 CCA units of the same B/HK/5/72 vaccine.

Test Strain	No. of Persons	Serum	Percent with H.I. titer of ≤ 8	8	16	32	64	128	256	512	1024	% with 4 x ris
A_2/Den/1/72	65	Pre-	25	9	9	14	8	5	3	6	22	
		Post-	2	2	-	3	11	11	8	11	54	57
B/Mass/71	65	Pre-	14	5	20	12	17	9	11	6	6	
		Post-	-	2	8	12	14	17	23	12	12	42
B/452/73	65	Pre-	25	14	17	19	5	8	8	5	2	
		Post-	6	8	6	11	28	22	11	5	5	42
B/HK/72	65	Pre-	55	14	14	6	5	3	2	2	-	
		Post-	27	19	19	13	8	8	3	3	2	27

TABLE 7 H.I. antibody response for influenza A_2/Den/1/72 and B/Mass/71, B/452/73 and B/HK/72 of men who received standard military vaccine containing 700 CCA units of A_2/Eng/72 and B/Mass/71.

Test Strain	No. of Persons	Serum	Percent with H.I. titer of ≤ 8	8	16	32	64	128	256	512	1024	% with 4 x ri
B/HK/5/72	35	Pre-	74	11	-	9	3	-	-	3	-	
		Post-	-	3	6	6	11	14	17	11	31	91
B/452/72	35	Pre-	23	17	11	9	17	11	3	3	6	
		Post-	3	-	3	6	20	17	9	11	31	54
B/Mass/1/71	35	Pre-	11	9	29	3	17	17	3	3	9	
		Post-	-	-	--	6	6	23	14	6	46	66
A/Den/1/72	35	Pre-	20	3	9	14	11	9	6	3	26	
		Post-	17	6	9	17	6	11	6	3	26	0

TABLE 8 H.I. antibody response for B/HK/72, B/452/72 and B/Mass/71 of men who received 500 CCA units of aqueous monovalent B/HK/72 vaccine. Lack of response to strain A_2/Den/1/71 is included for comparison.

Test Strain	No. of Persons	Serum	Percent with H.I. titer of < 8	8	16	32	64	128	256	512	1024	% with 4 x ri
A/Den/1/72	43	Pre-	37	19	16	9	9	9	-	-	-	
		Post-	-	-	7	-	9	5	16	21	42	86
A/Port Ch/1/73	43	Pre-	58	19	14	2	2	5	-	-	-	
		Post-	2	7	-	5	12	23	28	9	14	81
A/Dynedon/4/73	43	Pre-	54	19	19	2	7	-	-	-	-	
		Post-	2	7	-	5	14	35	16	5	16	79
B/Mass/71	43	Pre-	42	7	12	23	7	7	-	-	2	
		Post-	9	5	5	9	19	26	16	-	12	60
B/452/73	43	Pre-	68	7	14	5	2	2	-	-	-	
		Post-	30	5	7	23	19	5	9	2	-	50
B/HK/72	37	Pre-	65	3	3	8	16	-	3	3	-	
		Post-	11	3	3	11	22	16	3	16	16	70

TABLE 9 H.I. antibody titers of civilian volunteers for 3 influenza A and 3 influenza B strains before and 2 weeks after 2 injections of vaccine (polyvalent containing 700 CCA units of A_2/Eng/42/72 and 300 CCA units of B/Mass/71 and monovalent containing 500 CCA units of B/HK/72 given at same time).

Volunteer Study	Vaccine Received	No. of Persons	No. of Cases	Rate/100
	Bivalent	270	2	0.74
	Bivalent and Monovalent B	205	0	0.00
	Monovalent B	233	1	0.43
Non-volunteer Study	Bivalent	691	9	1.32
	Bivalent and Monovalent B	477	5	1.04
	No Vaccine	282	2	0.71
Total Student Population	Monovalent B	914	6	0.65
	Bivalent only or no vaccine	1231	13	1.06
		2145	19	0.88

TABLE 10 Incidence of influenza B in different vaccine groups during February and March, 1974.

Volunteer Study	Vaccine Received	No. of Persons	No. of Cases	Rate/100
	Bivalent	197	0	0.0
	Bivalent and Monovalent B	121	0	0.0
	Monovalent B	164	4	2.44
Non-volunteer Study	Bivalent	480	4	0.83
	Bivalent and Monovalent B	361	3	0.83
	No Vaccine	174	4	2.29
Total Student Population	Polyvalent ± Monovalent B	1155	7	0.60
	Monovalent B or no vaccine	338	8	2.37
		1497	15	1.00

TABLE 11 Incidence of influenza A in different vaccine groups during March and April, 1974.

Vaccine Received	Number of Persons	Percent of men with HI titer for B/HK/72 of								
		< 8	8	16	32	64	128	256	512	1024
Bivalent (B/Mass/71)	28	46	18	4	14	7	7	-	-	4
Monovalent (B/HK/72)	22	14	9	14	27	5	14	14	-	5
Total	50	32	14	8	20	4	10	6	-	4

TABLE 12 Distribution of HI antibody titers for B/HK/72 of 50 men in May, 1974, who had received either bivalent vaccine containing 300 CCA units of B/Mass/71 or monovalent vaccine containing 500 CCA units of B/HK/72.

TABLE 13

Number	Date Bled	Antibody Titer N.I. X-38 (H Eq$_1$N$_2$)	N.I. A/HK/68	N.I. A/Port/72	C.F.
1	11/6	< 16	< 8	< 8	< 8
	11/28	512	128	256	128
2	11/7	< 16	16	< 8	< 8
	11/28	64	512	1024	256
3	11/6	32	256	< 8	< 8
	12/1	256	256	64	256
4	11/6	< 16	32	< 8	< 8
	11/28	64	128	64	< 8
5	11/6	< 16	< 8	< 8	< 8
	11/28	32	64	128	16
6	11/6	< 16	512	< 8	< 8
	11/20	256	512	1024	256
7	11/7	< 16	< 8	< 8	< 8
	11/29	512	32	256	64
8	11/7	< 16	< 8	< 8	< 8
	11/29	256	32	512	64
9	11/7	< 16	< 8	< 8	< 8
	11/29	< 16	64	256	64
10	11/7	< 16	8	< 8	< 8
	11/29	256	64	256	32
11	11/7	< 16	16	< 8	< 8
	11/29	256	512	1024	64
12	11/8	< 16	16	< 8	< 8
	12/1	16	256	256	256
13	11/8	< 16	< 8	< 8	< 8
	11/29	32	16	64	64
14	11/8	< 16	8	< 8	< 8
	11/30	64	32	64	32
15	11/9	< 16	< 8	< 8	< 8
	11/30	256	128	128	128
16	11/9	< 16	16	< 8	< 8
	11/29	32	32	256	256
17	11/9	< 16	8	< 8	< 8
	11/30	128	88	8	32
18	11/10	32	64	< 8	< 8
	12/1	64	256	64	64
19	11/11	< 16	< 8	< 8	< 8
	12/4	256	256	256	64
20	11/11	< 16	64	< 8	8
	12/6	256	512	256	128
21	11/12	64	1024	< 8	< 8
	12/4	512	1024	256	32
22	11/12	< 16	< 8	< 8	< 8
	12/1	256	256	256	256
23	11/12	< 16	16	< 8	< 8
	12/12	32	128	512	32
24	11/13	< 16	8	< 8	< 8
	12/4	256	32	32	128
25	11/13	32	16	< 8	< 8
	12/6	>1024	32	256	64

Comparison of results of neuraminidase inhibitor titers with X-38 (H Eq$_1$N$_2$) with titers in H.I. and C.F. tests in 25 cases of Influenza A$_2$ (A/Eng/42/72).

TABLE 14

Population Group	Number	Percent with N.I. titer	
		< 16	≥ 16
Cases of Influenza A	25	84	16
Non-influenzal A.R.D.	24	46	54
Pre-vaccination	25	44	56
Post-vaccination	25	24	76

No.	Patient	C.F. Test	Acute and Convalescent Titers in HI Test with B/Mass/71	B/452/73	B/HK/5/72 (E-23)	B/Den/1/74 (M.K.-2)
1	J.M.	< 8/128	256/1024	512/1024	64/1024	16/256
2	D.D.	< 8/64	32/128	32/256	64/256	16/64
3	G.D.	8/256	< 8/32	< 8/32	< 8/64	< 8/128
4	G.M.	< 8/256	32/128	32/256	< 8/32	< 8/128
5	S.K.	< 8/128	8/256	8/128	< 8/256	< 8/128
6	R.P.	< 8/256	256/1024	128/1024	32/1024	32/512
7	D.S.	< 8/64	16/16	16/32	< 8/16	< 8/< 8
8	W.S.	< 8/64	1024/1024	1024/1024	1024/1024	8/64
9	M.W.	< 8/32	128/256	128/128	64/256	16/64
10	R.D.	< 8/128	64/128	32/256	< 8/64	< 8/64
11	D.J.	< 8/32	32/64	32/32	< 8/32	< 8/16
12	E.M.	< 8/64	32/64	64/64	8/32	< 8/16
13	P.B.	< 8/128	16/32	16/64	< 8/32	8/32
14	D.M.	< 8/64	64/128	64/128	< 8/8	< 8/16
15	C.W.	< 8/128	32/128	64/128	< 8/64	16/64
16	J.D.	< 8/32	32/64	32/128	< 8/8	< 8/16
Four-fold rise(total)		16/16	7/16	8/16	13/16	15/16

TABLE 15

Comparison of results of serologic tests for influenza B in 16 cases of influenza.

Tested with	Vacc. Status	Date Bled	No. of Men	Percent with Neutralizing Antibody Titer of							
				< 4	4	8	16	32	64	128	256
Type 4	Unvacc.	9/4/73	41	80	20	10	-	-	-	-	-
	Vacc.	9/4/73	50	76	20	4	-	-	-	-	-
	Vacc.	12/1/73 - 3/6/74	100	60	32	4	2	1	1	-	-
	Vacc.	5/1/74 - 6/1/74	50	64	---------- 36 * ----------						
Type 7	Unvacc.	9/4/73	41	30	17	17	10	14	10	2	-
	Vacc.	9/4/73	50	16	---------- 84 * ----------						
	Vacc.	12/1/73 - 3/6/74	100	37	40	14	6	1	-	1	1
	Vacc.	5/1/74 - 6/13/74	50	40	26	12	18	4	-	-	-

* Titer 1:4 or greater. Not tested at further dilution.

TABLE 16 Results of tests for Type 4 and Type 7 adenovirus neutralizing antibody of vaccinated and unvaccinated men bled in September, 1973, and of 2 groups of vaccinated men bled during spring of 1974.

TABLE 17

Week Starting	Total number of Illnesses	Illness/ 1000/wk	No. Cases Influenza B	No. Cases Influenza A
3 Sept.	8	2.0	-	-
10 "	19	4.8	-	-
17 "	22	5.5	-	-
24 "	20	5.0	-	-
1 Oct.	19	4.8	-	-
8 "	25	6.3	-	-
15 "	24	6.0	-	-
22 "	6	1.5	-	-
29 "	24	6.0	-	-
5 Nov.	25	6.3	-	-
12 "	26	6.5	-	-
19 "	19	4.8	-	-
26 "	43	10.8	-	-
3 Dec.	24	6.0	-	-
10 "	19	4.8	-	-
17 "	21	5.3	-	-
24 "	1	-	-	-
31 "	0	-	-	-
7 Jan.	14	3.5	-	-
14 "	18	4.5	-	-
21 "	20	5.0	-	-
28 "	15	3.8	-	-
4 Feb.	24	6.0	-	-
11 "	20	5.0	-	-
18 "	21	5.3	-	-
25 "	30	7.5	6	-
4 March	43	10.8	13	-
11 "	35	8.8	5	-
18 "	26	6.5	4	1
25 "	22	5.5	-	3
1 April	30.	7.5	-	6
8 "	24	6.0	-	7
15 "	20	5.0	-	5
22 "	18	4.5	-	2
29 "	11	2.8	-	-
6 May	14	3.5	-	-
13 "	8	2.0	-	-
20 "	7	1.8	-	-
27 "	11	2.8	-	-
3 June	5	1.3	-	-
10 "	5	1.3	-	-
Total	786	4.91	28	24

Infecting Agent	Number of Cases	Percent of Cases
Group A Streptococci	64	16.0
Influenza B	27	6.8
Influenza A	24	6.0
Rubella	16	4.0
Adenovirus	2	0.5
Unknown	267	66.7

TABLE 18 Etiology of febrile U.R.I. among 400 students tested between 10 September 1973 and 10 June 1974 at Lowry Air Force Base.

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