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Evaluation of vaccination against viral respiratory disease

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EVALUATION OF VACCINATION AGAINST VIRAL RESPIRATORY DISEASE

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The subject under consideration is the evaluation of vaccination against viruses causing respiratory infections. It will be necessary first to evaluate the relative importance of these viruses, influenza, parainfluenza, adenovirus, respiratory syncytial, and some of the less severe viruses such as coryza. Much of the discussion of vaccination will be limited to influenza and adenovirus since they represent the primary viruses for which vaccination trials have been made. Consideration of the newer and in some cases more minor viruses is made so that the future polyvalent vaccines may include protection for a wide spectrum of viruses.

Viruses of influenza were first isolated in 1931 and 1933. The benefical effect of vaccination was shown decisively in 1943. Further studies revealed the probable usefulness of emulsification of antigens for influenza vaccines in 1944-45 with further extention in the early 1950s. The need for a broad-spectrum coverage has been apparent since 1947. Widespread epidemics of influenza continue to occur in 1960. The obvious question as stated by Jonas E. Salk is "why, when the course of action was clear, so little was done so late?[46]

Influenza has small focal outbreaks which coalesce to produce epidemics or pandemics. Early autum and late spring are the times in which 20 to 40% of the population is affected. Outbreaks peak in 3 weeks and subside in another 3 to 4 weeks. The incidence is highest in children, 5 to 9

years old, lowest in 15 to 24 age range, rising again in the 25 to 34 age range and with a decreased incidence after 40 years of age apparently due to resistence accumulated. After an incubation of 18 to 36 hours the symptoms arise abruptly with fever, chills, and backache. Weakness, fatigue, and possible prostration follow. Minor symptoms of ocular tenderness, conjuntival infection, watery eyes, throat pain, and mild nazal discharge may be present. On the second day the temperature is 101° to 104° F. with a rapid fall on the third to fourth day if no pulmonary complications appear. If tachycardia, cyanosis, or hemoptysis appear there is a possible fatal outcome. The symptoms for influenza A (1937, 39, and 41), influenza A1 (1950,51,53, and 56), and Influenza A2 (1957) all showed essentally the same characteristics. Likewise the physical signs of influenza show remarkably little variation from one epidemic to the next.[2 3]

The virus shows a selective affinity for respiratory epithelium. In fatal cases there is inflamation of air passages and necrotizing tracheobronchitis and bronchiolitis with a foci or squamous metaplasia. There is congestion and edema of the lungs with a varable degree of intra-alveolar hemorrage.[47 48]

Laboratory methods for virus isolation are done by serologic demonstration of increasing antibody titers using throat or nazal washings innuculated into eggs 2 to 3 hours after collection. If after 48 hours chicken erthrocytes agglutinate, influenza virus is persumed to be present.

A type specific sera is used to identify the particular virus. Blood specimens collected in the acute stage and again 10 to 14 days later are used for anti-body testing. The compliment-fixation test is used to differentiate the A and B types. The hemagglutination-inhibition test identifies the specific subtypes of A. A four fold increase in titer in the second (convalescent) serum indicates infection of influenza virus.[49]

Type A, asian, viruses tend to occur every 2 to 3 years with great regularity, and the respiratory infections between these years have been shown to be caused by a variety of viruses. In a study by Hilleman of serodiagnoses of respiratory infections among children in 1959-60 approximately 40% of the total were defined etiologically in terms of the following eleven different viruses:[4]

Myxovirus Influenza		
A1	.6%	
A2	1.3%	
B	0.1%	..... 2.6%
C	0.6%	
Myxovirus Parainfluenza		
1	1.2%	
2	2.1%	
3	1.9%	..... 5.5%
1 or 3	0.3%	
Reo Virus		0.1%
Adenovirus		5.1%
Respiratory Syncytial		17.2%
Multiple Serological Rises		5.1%
Coryza		4.8%
Total:		
Diagnosed	40.4%	
Undiagnosed	59.6%	

Influenza was not highly epidemic in the general population in 1959 and 1960 and this fact was reflected by the relatively small contribution of influenza to the total respiratory disease problem.[4]

Serologic studies were made of the occurence of influenza A2 (Asian) infection in Navajo school children in Arizona and in Medical students in New York City. Evidence was obtained that influenza A2 has occured during every year since the 1957 epidemic in both groups of subjects in the absence of recognized community epidemics.[26] Thus there seems to be evidence that even in the non-epidemic years there are endemic year-around cases of respiratory infection caused by influenza virus.

Adenoviruses are another important cause of endemic year-round disease. From the experience with army recruits it appears that although adenovirus is present year round, the high hospitalization rates result only during the respiratory disease season. The disease is indistinguishable from acute respiratory disease caused by other viruses. It has a wide clinical spectrum ranging from inapparent infections manifest only by increases in complement fixation antibody titer through mild illness to extensive pneumonia. Of at least 23 different adenoviruses types 4 and 7 have been found to be associated with most adenovirus disease in the Army recruits.[13]

The study of Hilleman indicates that in children the respiratory syncytial virus is an important agent for

bronchiolitis and pneumonia. This agent has been isolated from chimpanzees with coryza and inoculated by nasopharynegal swab to produce symptoms of the common cold-like syndrorne in 20 or 41 adult volunteers. The incubation period averaged 4.9 days and the illness 5.5 days. It was noted that in adults the illness was milder than that associated with respiratory syncytial (R.S.) virus infection in children. This suggests that a protective effect results from previous infections.[35 36] A controlled study in Washington D. C. recovered the R.S. virus from 57% of young infants with bronchiolitis or pneumonia during a 5 month period. R.S. was recovered in 12% of older infants and children with milder febril respiratory diseases. They also discovered that R.S. virus infection occurs in sharp outbreaks, lasting 3 to 5 months and coinciding with peak occurences of bronchiolitis and pneumonia. Thus it is suggestive that R.S. is a respiratory pathogen of major significance during early life.[33] Other studies appear to support this statement. Pannott et al. did serologic studies over a 34 month period of children with bronchiolitis, pneumonia, and minor respiratory respiratory disease from October, 1957, to July, 1960. They found R.S. virus infection present in 11% of 1,038 infants and children hospitalized with pneumonia, bronchiolitis, croup, or pharngitis with bronchitis. This was 5.5 times greater than among the control group free of respiratory tract symptoms. Most striking findings were in infants than in older children,

particulary patients with bronchilitis (estimated 36%) or bronchopneumonia (21%).[34] Clearly this would seem to be an area where considerable more work in developing an effective vaccine would be beneficial.

Having briefly examined etiology, pathology, symptoms, and laboratory diagnosis of respiratory diseases, we now examine the costs in lives and dollars resulting from respiratory diseases. It is estimated that influenza alone has resulted in a total of 86,000 deaths in excess of the normally expected numbers as a result of the two epidemics in the United States from 1957 to 1960. Over two-thirds of the excess mortality occured in persons aged 65 years and over.[10 6] A national health survey from July 1957 to June 1958 indicated that about 3.7 days of work loss and 5.7 days of school loss per person per year in the United States were attributable to acute respiratory disease. These figures were greater than the losses from all acute conditions combined. The results of the past 3 decades research have indicated that viruses are the principal cause of actue respiratory illness.[4]

The standardized, commercially prepared, type 4 and 7 adenovirus vaccine used during the respiratory disease season of 1960-1961 at all recruit training stations is estimated to have saved the Army about $5,000,000. This vaccine was about 50% effective in reducing hospitalizations resulting from adenovirus disease.[13]

As was noted in the mortality statistics there is a

marked excess mortality clustered in the "high risk" groups. These "high risk" persons are defined as follows:

1. Persons of all ages who suffer from chronic debilitating disease, e.g. chronic cardiovascular, pulmonary, renal, or metabolic disorders; in particular, patients with (a) rheumatic heart disease, (b) arteriosclerotic heart disease, and hypertension, (c) chronic bronchopulmonary disease, (d) diabetes millitus, and (e) Addison's disease.

2. Pregnant women.

3. Persons in older age groups; those over 45 and particularly those over 65 years of age.[5]

It thus seems apparent that the costs in lives, dollars, and time are remarkable enough to warrant the development and use of vaccines for respiratory diseases.

The earliest adenovirus field trials were carried out in 1956 at Fort Dix, New Jersey using an adenovirus vaccine containing types 4 and 7. Hilleman used 311 subjects in this first trial. A recruit population of the military services was used for this test and most subsequent tests because it is easily randomized into various study groups that are highly comparable except for the variable being investigated. This similarity includes age, sex, race, activity, diet, socioeconomic status, and geographic origin. Thus the data derived from vaccine studies on recruit population can be gained through well matched control groups. Cross sectional-type surveys, involving a total of over 25,000 recruits in all stages of training during a three year period indicate that 50-70% of the recruits have respiratory symptoms at

any one time. Much of the illness is afebrile in character.[9]

Hilleman in 1956 developed a bivalent vaccine containing adenoviruses types 4 and 7 grown in monkey kidney cell culture and killed with formalin. The results of his small field trial of 311 subjects showed a reduction in hospital admissions for adenoviruses by 98%.[11]

In the following year, 1957, Hilleman used 8,238 subjects at Fort Leonardwood, Missouri for a 90% reduction in hospitalization from adenovirus.[12 13] Results at Fort Dix, New Jersey by Cooch and Rose in 1957 found the same high effectiveness with another adenovirus vaccine.[13 39] Gundelfinger ran a comparative trial of trivalent adenovirus and influenza vaccine in 1957 at Great Lakes, Illinois. His study used 339 men receiving 1 ml influenza vaccine only, 411 men receiving 1 ml adenovirus only, and 419 men receiving a placebo. Results showed an apparent protection of influenza and adenovirus of 68%; influenza vaccine only, 28%; and adenovirus only, 60%.[8 25] Gudelfinger's figures indicate first the importance of adenovirus as the cause of epidemic respiratory disease in these recruits and secondly that adequate comparisons of relative reductions appear to be conditioned in part by the intensity and character of the epidemic and the prevalence of each agent.

Based on the clearly established effectiveness of the adenovirus vaccine the Preventative Medicine Division of the Surgeon General, Department of Army planned to immunize against adenovirus infections as a routine measure for

recruits prior to the winter of 1958-1959. Production upset this plan, and limited supplies of vaccine were available through the commission of influenza of the Armed Forces Epidemiological Board. This was followed with a field trial at Fort Ord, California, in 1958 with 8 recruit companies (2,162 subjects). This adenovirus vaccine produced a 58% reduction in all medically attended respiratory disease, and when adenovirus infections alone were considered, effectiveness was estimated to be 90%.[31]

In summary the six field trials of adenovirus vaccine have all provided the recruits with a protective reduction of adenovirus infection of greater than 80% with the exception of Culvers at Fort Ord who achieved a 70% reduction.[30]

Results of field trials on vaccination against influenza A conducted by the Commission on Influenza, Armed Forces Epidemological Board have demonstrated the effectiveness of aqueous influenza vaccine. This is shown in the following data:[28 14]

YEAR	PREVAILING VIRUS	PROTECTION RATIO (# of control cases: # of vaccine cases.)
1943	A	3.6
1947	A 1	1.1
1950	A 1	3.1
1951	A 1	4.0
1953	A 1	8.1
1953	A 1	4.5
1957	A 1	5.5
1957	Asian	Results of different series: 1.7, 2.5, 3.0, 2.3, 4.4, 4.1
1945	B	12.9
1952	B	2.7

1955	B 1	1.6
1958	B 1	5.8

During the past two decades, 22 successful field trials have been carried out on the efficacy of influenza virus vaccines by the Commission of Influenza of the Armed Forces Epidemological Board. The results are as follows:[5 14 28]

(a) 18 epidemological experiments with influenza A, Influenza A1, and Asian influenza. Average protections was 78%. (range from 41% to 94%)

(b) Four trials against influenza B and influenaz B1. Average protections was 90%. (range from 63% to 96%)

From the foregoing field trials of adenovirus and influenza vaccines it is apparent that their effectiveness has been well documented and proven. We shall now examine some of the problems encountered in the production, administration, and distribution of the vaccine.

One of the foremost problems to be met in the future is how to provide at all times by vaccination effective protection against viruses which have the unique characteristic of seldom appearing twice wearing precisely the same antigenic overcoat. There are two basic thoughts as to the best approach to this problem. One approach views the variation as a progressive or linear process in which old antigens are lost and new ones arise by mutation. Those with this approach would advocate vaccination with the most recent isolates of influenza A and B obtainable.[15] This would require endless crash programs designed to capture, process, and distribute each new minor antigenic variant as it is first discovered. Such an approach would be very impracticable in view of

current methods and technology.

The unidirectional multation hypothesis has met some opposition. Those who oppose the above hypothesis point out that with the passage of time old antigens are not commonly dropped nor do new ones, completely unrelated serologically to their predecessors, commonly arise. Their work on antigenic variation has shown the mechanism to be a shifting in dominance of a few of the antigens that apparently the majority of strains of a type contain in lessor amounts. Such a view pictures the number of antigens, though large, an finite.[14 15 16] Thus the alternative to crash programs of uncertain reliability and potential shortness problems is the stockpiling of "old formula" vaccine. Davenport and Gundelfinger feel this would probably yield better results than no vaccine at all in the hypothetical case wherein an important new strain could be captured and tamed in time.[14]

It has been demonstrated by Davenport that a vaccination with either A, A1, B, or B1 monovalent vaccine in general yields high levels of antibody against all other members of the corresponding family or set of strains. From his studies it would appear that the response of man to vaccination is at least "family-specific" not "strain-specific".[14 19] In support of these findings are the 1956 field trials of the British Committee on Influenza which showed that a preparation containing a 1947 isolate was just as effective as one containing a 1955 strain.[18] Gundelfinger and

and associates in 1957 reported that a vaccine containing merely a swine and A1 strain yielded aignificant protection against Asian influenza in a field trial.[20]

The current preparation of vaccine contains 6 strains of influenza and 2 adenovirus. Other viruses can be readily added to this basic influenza formula.[14] If indications arise that a change of formula is desirable, consultations are held and the available information on the antigenic vacination is assessed. Prototype isolates are furnished vaccine manufacturers who then test the vaccines as to dosage and capacity to induce neutralizing antibody. Prior to its release potency checks are made and thus the vaccine is of proved efficancy.[5]

As is frequently the case with commercially produced vaccines, the effectiveness of adenovirus vaccine has not been as remarkable in reducing hospital admissions for acute respiratory disease as were some of the field trials tested several years ago. Sherwood et al. believes that reduced potency of the commercial vaccines can possibly be explained on the basis of techniques for producing vaccines from infected animal cell cultures. They believe alternate methods of producing an acceptable adenovirus vaccine, or alternate methods for processing the presently produced vaccine should be explored by manufacturers and a regulating agency. Their goal should be not only to meet established safety standards, but also to increase the final product potency.[13]

In 1957 when the demands for influenza vaccine became great, a real control problem was encountered in the development

of requirements of vaccine manufacturers. In particular the question of potency of vaccine arose under conditions of extreme urgency at a time when there was very little definite information. The public Health Service Act engaged and licensed six firms for the manufacture of influenza vaccine. In order to produce the greatest quantity of vaccine at the earliest possible time requirements were modified, whenever possible, with an attempt to still maintain the safety, purity, and potency of the product. In the interest of expediency, potency was determined on the basis of chicken erythrocyte agglutination (CCA) content and the requirements for a mouse antigenicy test, which required four or more weeks to complete, were temporarily suspended. A committee met at the National Institute of Health in September, 1957 and advised that 200 CCA units of Asian monovalent is sufficient for producing detectable antibodies in the majority of persons and presumably of protecting against clinical disease. They added however that 400 CCA units produced antibodies in more people and to a higher level. By November 1957 they advised returning to a polyvalent vaccine. Based on experience that people show a disinclination to accept the local and general reactions which sometimes follow the administration of more than 500 CCA units two different polyvalent vaccines were developed. A civilian vaccine contained the following:[44]

STRAIN	CCA UNITS
Asian	200

Great Lakes	1	100
PR - 8		100
PR - 301		100
Total		500

A military vaccine contained the Following:

STRAIN	CCA UNITS
Asian	400
Great Lakes	200
PR - 8	200
PR - 301	200
Total	1000

Since it was felt that the 400 CCA units of the Asian strain was still the preferred dosage, the single dose was changed to a series of two doses given not less than two weeks apart in the case of persons who had had no previous immunization with Asian Strain material. The only changes in the formula made since that time has been the substitution of the Ann Arbor 1/57 strain for the PR - 8, since the former seemed superior as an antigen.[44]

There appears to be some question as to the significance of titer rises as a factor of protection, at least the titer level of significance. Rose in 1957 ran a field trial on 5,000 persons divided into a control group, a group receiving 200 CCA units and a group receiving 750 CCA units. His results were a 60% reduction in respiratory disease in those receiving 200 CCA units and a 77.5% reduction in those of the 750 CCA unit group. This was inspite of a four fold increase in titers by H-I tests in the 750 CCA unit group. Apparently both groups were given a significant protective effect.[46]

This type of result had caused some investigators such as Stuart-Harris to question the reliability of the H-I test

in measuring the protective antibodies. He believes there is a possibility that the H-I test may actually be measuring some other antibody not concerned with protection.[46] Dealing with the problem of potency, McLean of Parke, Davis and Co. feels it is difficult to evaluate the potency of a new influenza variant on the basis of CCA activity because of a market variation between different passage lines of the same strain until the lines become stabilized in eggs. The ratio of hemagglutinating activity to antigenieity will also be a variable factor. His feeling is that when stable adopted lines are available, a meaningful CCA concentration factor can be established based on animal studies and clinical trials.[45]

One of the early questions that arose in the production of the vaccines was that of mineral oil-arlacel adjuvant vaccine virsus aqueous vaccine. Advantages of the mineral oil adjuvant can be classified as follows:

(a) Less antigen is used.
(b) Comparable or greater increases in antibody titer are achieved.
(c) Antibody titers are increased for a longer time
(d) Immediate reactions are decreased in frequency and severity
(e) Numerous antigens can be injected in a small volume

A controlled field trial in the winter of 1959-60 was made to evaluate the effectiveness of polyvalent influenza and adenovirus vaccine containing eight antigens in a mineral oil adjuvant. Timing for the test was good in that outbreaks of Influenza A2 and Adenovirus 7 occured approximately two months after the vaccine was given. No undesirable

reactions occured in the vaccinated half of the 5,000 men. Protection ratios for Influenza A2 was reported as 94% and the protection ratio for adenovirus was 90%.[28]

In some of the earlier tests with mineral oil adjuvant there were cysts at the injection site; they were not seen in this study. Sensitization to materials such, as chick embryo proteins has not been a problem. The hypothetical possibility of long continued overstimulation the antibody production mechanism with consequent serious organic or systemic disease has not been substantiated to date.[28]

The data accumulated over the past decade on the efficancy of mineral oil emulsions as adjuvants would seem to clearly indicate that when proper oils and emulsifiers are used and when small volumes are injected, they are well tolerated and at a great conservation of antigen. The major benafit is the apparent long duration of antibody levels. Remaining for at least three years it is reasonable to assume that this may be the device to obviate the necessity for annual vaccination against influenza.[14]

The successful field trials reported in this review of the literature were carried out using the subcutaneous route of injection. Almost all proven protection is based on this route of inoculation. There has been a limited amount of work done on the benefits of intradermal injection. Sanger in 1959 ran a small field trial of 275 persons utilizing both routes of inoculation. His criteria for a significant rise in titer was an increase of 1:4 or greater as measured by the

hemagglutination-inhibition (H-I) test and/or complement fixation (C-F) test. His results are as follows:[23]

	A^1	B^2	C^3
204 Intradermal (0.1cc)	41%	45%	12%
72 Subcutaneous (1cc) (note:200 CCA units/cc)	66%	25%	8.7%

A^1 Rise in titer with HI and CF
B^2 Rise in titer 1 of the tests
C^3 Failed to rise 1:4 or Greater
(2% had previous immunization)

From these results one might interpret that the intradermal injection of 0.10 cc Asian influenza vaccine (200 CCA/cc) produces a rise in antibody titer comparable so that achieved with the 1.0 cc subcutaneous injection of the same vaccine when measured by both C-F and H-I tests. If this is true then in time of short supply, the intradermal technique would permit the available stocks of vaccine to be increased ten-fold. Sigel et al. reported good results in his adults injected intradermally, particularly when booster injections were given five weeks after initial vaccination. He also reported that he felt the results of the intradermal method were actually superior to the subeutaneous results in children. Again it should be pointed out that this success is in terms of titer increased using both H-I test and C-F tests and apparently does not reflect actual protection success.[38]

In trials utilizing only the H-I test only 8 of 22 elderly patients showed a rise in antibody titer four weeks

after intradermal injection whereas 20 of 22 showed response with the subeutaneous injection. A vaccine of 500 CCA units per cc was used in this trial by Bogen and Liu.[32] It is generally held by most investigators that the subeutaneous route is the proven and recommended route of inoculation. They further feel that intradermal results conducted post epidemic cannot be considered valid assuming the antibody titers as measured by the C-F and H-I tests are actually measuring the protective antibody.[2 5 6 44] Davenport specifically stated that the antibody response is largely dependent upon the mass or dose of antigen given and is not significantly influenced by the route of administration. Using amounts of vaccine less than those recommended abolishes or greatly reduces the protective effect obtainable with the full dosage.[5]

In the October 6, 1962 JAMA, Davenport presented the following generally accepted dosage and schedule for inoculation:[5]

	(Previously Vaccinated)		(Not Previously Vaccinated)		
Subject	Vol.(cc)	Frequency	Vol.(cc)	Frequency	Interval
Adult	1.0	once	1.0	twice	2 mos.
Child (6-12)	0.5	once	0.5	twice	2 mos.
Child (3 Mos.) (to Pre-School)	0.1 or 0.2	once	0.1 or 0.2	twice three	1 to 2 wks. vs 1st and 2nd dose 2 mos. vs 1st and last dose

A prompt first dose should be given to those unvaccinated

persons presenting themselves too late to receive their "booster" dose before mid December. A single dose is better than none, and may confer adequate protection for most persons. The only known contraindication presented by Davenport is the use of the vaccine in persons known to be allergic to eggs.[5]

Since influenza viruses are toxic they produce reactions when given in sufficiently high concentration. Systemic reactions of fever, chillness, myalgia, headache, and lassitude occur in the majority of patients between 6 and 18 hours after inoculation and disappear in most cases within 24 hours. At the site of inoculation it is common to have a burning or stinging sensation; thés may be followed by stiffness and soreness.[5 7 24] The rates of reactions to influenza vaccine compare very favorably with other vaccines as shown in the following:[24]

Reactions/1,000

Vaccine	Total	Mild	Moderate	Severe
Influenza	6.29	6.10	0.16	0.03
Typhoid (B)	6.86	6.37	0.47	0.02
Smallpox (P)	39.30	38.20	0.90	0.21
Smallpox (R)	24.43	22.29	2.05	0.10
Tetanus (B)	7.18	6.92	0.24	0.03

Note: B=Booster, P=Primary, R=Revaccination

REACTION CLASSIFICATION:

(A) Mild--Tolerated reactions by patent on duty status.
(B) Moderate--Reactions caused entry to excused from duty status for more than 48 hours.
(C) Severe--Exceeded above limits (more than two days lost up to and including fatal reactions.)

In present vaccines no antibotic agents or silk filters are used. It is estimated that over 90% of the vaccine is extraneous material which includes allantoic fluid, egg protein, red cell detritus, and other non-viral materials. Even if this non-viral material is less antigenic than the virus component, it could still be responsible for many reactions because of its quantity.[24] The future vaccines will apeculatively be more refined products which will be less toxic than whole virus vaccine.

SUMMARY

From reviewing the literature it is apparent that much progress against our ultra small enemy, the virus, has been made in the past two decades. The major viruses or respiratory infection, influenza and adenovirus have been isolated and harnesed. The vaccines to control them have been developed, tested, and found capable of successfully reducing their respective respiratory diseases by at least 50 per cent.

Production problems of potency, adjuvants, purity, and strains to be included in the vaccines have progressed to the point of relative agreement. The stockpiling of a basic vaccine representative of each of the four families of influenza A and of the two families of influenza B viruses will bring a great deal of stability to our vaccination program. Additional strains and variants can be added as they emerge. The current preparation of vaccine contains six

strains of influenza and two adenoviruses, type 4 and 7 with a mineral oil adjuvant. Future goals of the vaccine manufacturers will be to not only meet established safety standards, but also to increase the final product potency and purity.

Specific recommendations as to dosage and administration of the vaccine have been set forth in the body of this review. General recommendations at this time call for annual vaccinations in the fall of the year as soon as practicable after September and should be completed by December 15th. This will necessitate one vaccination if previously vaccinated and two vaccinations if not previously vaccinated. Vaccine dosage recommendations at this time call for 1.0cc injected subcutaneously for adults, 0.5 cc for children 6-12 years old, and 0.1 or 0.2 cc for children 3 months to preschool.

Epidemiologic studies of influenza show that the highest age-specific attack rates occurred in school age students and that these students may constitute the most important source of infection to the family.[21] Those of the "high risk" group acquire their infection later than more active people such as school children. Since the number one objective of the vaccine program should be to prevent the high mortality of the "high risk" group, the vaccination of the school age may be the most successful preventive medicine approach. Certainly all members of the "high risk" group are highest on the priorty list for the vaccine.

The future calls for further research on viruses such as the respiratory syncytial virus which is apparently an important agent for bronchiolitis and pneumonia in children. The development of a respiratory syncytial vaccine would be very beneficial in the preventive medicine aspect of pediatrics.

The future also calls for a job of "selling" on the part of the medical profession. Needless to say there will always be more to be known about any subject, but the time does come when we know enough to decide that something can be done to reduce the problem of a given disease. Epidemics of serious respiratory diseases will continue to occur and mortality rates will continue to be in excess of the expected unless we emphasize in our communities and to our patients, particularily the "high risk" group, that there are available vaccines to vaccinate against this disease.

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