Perspectives on Current Use of Some Virus Vaccines in the USA

Measles, Rubella, Poliomyelitis, and Influenza in the USA: Contrasts in Control by Vaccination

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The purpose of this presentation is to compare the achievements in the control of each of these diseases in relation to the nature and behavior of the etiologic agents and the different objectives and programs of vaccination.

MEASLES

The objective is to eliminate the disease and its complications among the vaccinated and to protect the irreducible minimum of susceptible, unvaccinated, and inadequately vaccinated by bringing about a break in the chain of transmission of the virus. When properly stored and given to children without residual maternal antibodies, the vaccine is highly immunogenic. Available evidence indicates that adequately immunized children lose their capacity to serve as links in the chain of transmission of naturally occurring measles virus. Thus, if enough children were vaccinated in a relatively short period of time, measles virus should quickly disappear from a community or a country. It should be possible then to maintain this measles-free status by immunizing the required proportion of new children at the optimum age. Fifteen years after licensure of the first live, attenuated measles virus vaccine in the USA and with more than 80 million doses of vaccine distributed since then, there has been an almost 75% reduction in the number of cases—but epidemics and hundreds of thousands of cases continue to occur annually. Why?

It has been estimated, on the basis of the number of children who acquired serologic evidence of immunity during the first 15 years of life in the prevaccine era, that there must have been about 4 million cases per average year, or 10 times more than were being reported.

The data in Table 1 show that the estimated numbers of measles cases in the USA in 1975 and 1976, based on Bureau of Census questionnaires, were 24 and 17 times higher, respectively, than the numbers officially reported. The data in Table 2, listing the number of officially reported cases during the period of 1963–1977, indicate the periodicity of low and high incidence years since 1968. Based on the extent of under-reporting in recent years (Table 1), it is probable that about 1 million cases of measles occurred in 1977. Although this represents a 75% reduction from prevaccine years, it is still 1 million cases and that is 1 million cases too many. As might be expected after 2 consecutive years of high incidence, the number reported thus far in 1978 is much lower.

Who is to blame? Is it the parents or physicians who in the USA are currently accused of growing apathy, or the nature of the public health program for getting the vaccine to the children who need it? The official annual US Immunization Survey data show that the percentage of 1- to 4-year old children with a history of measles vaccination from 1965–1976 (Table 3) has not changed. Instead of a decline, there has been a continuing small increase in

the percent of preschool children who received measles vaccine during recent years. It is also obvious that about one-third of 1- to 4-year old children in the USA are not receiving measles vaccine, and that vaccination of 66% of preschool children is not enough to break the chain of transmission of measles virus in the country. In 1977, 86% of the reported cases occurred in the 5- to 19-year-old age group. It is clear that the public health system of getting the measles vaccine to children who do not receive regular health care from private pediatricians has been inadequate. Because measles vaccination involves only one dose of vaccine, how does it compare in percent of 1- to 4-year-old children of different socioeconomic groups who have received at least one dose of vaccines which must be given in multiple doses, the first dose being given early during the first year of life? For whatever reason, is less measles vaccine than other vaccines being given to preschool children? The 1976 US Immunization Survey data (Table 4) indicate that: a) among 1- to 4-year-old white children, only 68% received measles vaccine compared to 97% for one dose of DPT (diphtheria-pertussis-tetanus) and 92% for one dose of oral polio vaccine (OPV); and b) among nonwhite children, only 55% received measles vaccine compared with 95% for at least one dose of DPT and 82% for OPV. It appears from the above data that approximately 45% of economically disadvantaged children probably do not receive regular health care and the accompanying vaccinations *after* the first year of life, when measles vaccine is effective in the largest proportion of children. Accordingly, something *special* needs to be done to supplement the existing program.

Recommendations for Supplementation of Present Measles Vaccination Program in the USA. Emphasis on increasing public information to motivate parents, as is now being done in the USA, will achieve very little because the fault is not with the parents, but with the public health program which does not sufficiently take into account the problems of parents in the lower socioeconomic groups. Existing public health clinics where children can be vaccinated free of charge are too few in number, too far from the areas inhabited by lower income groups, and open predominantly during the hours when parents are at work.

The compulsory school-entry immunization laws that are now in existence in all but a few states have had limited effectiveness because; 1) they apply only to those entering school and not to the unvaccinated children who have been in school for many years; 2) they rely on parents' statements that a child has had measles or has already been vaccinated; and 3) parental memory may be influenced by the fact that the child would have to be vaccinated by a private physician for a fee they cannot afford or at a health department clinic that is closed when they are not at work. The system of referring families to private physicians and the usual health department clinics is, in my judgment, the main reason for the continuing measles problem in the USA after 15 years of vaccine availability. In my judgment, the greatest impact on the

Table 1. *Discrepancy between reported and estimated actual number of measles cases in USA, 1975 and 1976 (6)*

	1975	1976
Number reported	24,374	41,126
Number estimated	588,000	685,000
Ratio estimated/reported	24.1	16.7

Table 2. *Periodic increases in number of reported cases of measles in USA since marked reduction in incidence that first appeared 5 yr after introduction of live measles virus vaccine in 1963 (6)*

Year	Reported Cases
1963	385,156
1964	458,083
1965	261,904
1966	204,136
1967	62,705
1968	22,231
1969	25,826
1970	47,351 ¹
1971	75,290 ¹
1972	32,275
1973	26,690
1974	22,094
1975	24,374
1976	41,126 ¹
1977	55,201 ¹

¹ Denotes increases.Table 3. *Percent of 1- to 4-yr old children with history of measles vaccination in USA, 1965-1976 (6)*

Year	%
1965	33.2
1966	45.4
1967	56.4
1968	58.8
1969	61.4
1970	57.2
1971	61.0
1972	62.2
1973	61.2
1974	64.5
1975	65.5
1976	65.9

Table 4. *Percent of 1- to 4-yr old children with history of receiving different vaccines white vs. other races, USA, 1976 (9)*

Vaccine	White	Other races
Measles	68	55
Rubella	64	52
Polio (Oral) 1 or more	92	82
2 or more	79	56
3 or more	66	40
DTP 1 or more	97	95
3 or more	75	53

immediate as well as long-range prevention of measles would result from the following supplementation of the present program:

1. Give the vaccine to all school children from kindergarten to high school inclusive, without reference to previous history of vaccination or natural infection, which is frequently unreliable. Such a program, to be effective, must be carried out in the schools on a regular school day, free of charge, with the aid of unpaid nonprofessional volunteers trained and organized by local health

officers, private physicians, nurses, and other paramedical personnel. Administration of measles vaccine by well-organized teams using disposable syringes and needles can be done almost as quickly as taking polio vaccine on a sugar cube.

2. For preschool children, expansion of the present program of vaccination as part of regular health care by private physicians or health department clinics is urgently needed, but in view of past failures among certain groups of children it should be supplemented as follows:

a) Unvaccinated children at nursery schools, day-care centers, Headstart preschool centers, etc. should receive the vaccine free of charge from public health nurses.

b) Once each year, on a Sunday, provide an opportunity for free measles vaccination administered by unpaid volunteer staffs at local schools that are close to the homes of needy families for all those who have not previously been vaccinated.

RUBELLA

In contrast to measles, there is no current rubella problem in the USA when it is recalled that rubella vaccination is aimed *not* at preventing the millions of cases of mild illness in children *but* at preventing the congenital rubella syndrome in children whose nonimmune mothers are infected early in pregnancy. Rubella congenital birth defects seem to be disproportionately prevalent during certain epidemics, the last of which occurred in the USA in 1964, when an estimated 20,000 children were born with various rubella defects. A national registry for rubella birth defects has been in existence since 1969 and the number of cases reported to the registry has been very small from the beginning (Table 5), even though the amount of rubella vaccine used after licensure in 1969 had little or no impact on the number of reported cases in children in 1969, 1970, and 1971 (Fig. 1). But reporting of rubella cases by physicians is even less than for measles. It is possible to estimate that in the prevaccine era there were on the average about 3.5 million rubella virus *infections* per annum with an estimated 1.4 million clinically recognizable illnesses. Accordingly, it is possible that there have been about 30 times more rubella cases than have been reported. By January 1977, more than 75 million doses of rubella vaccine were distributed in the USA. It is, therefore, astonishing to note in the 1976 US Immunization Survey that during the 12 months preceding September 1976, an estimated total of 1,011,634 of rubella cases only in the 0- to 12-year age group were reported by the surveyed parents even though the total number of officially reported cases for 1976 was 12,491 for all ages. Because there is evidence that 50% or more of rubella virus infections can be without clinical manifestations, nearly 2 million persons may have been infected with rubella virus during that year. Even if one greatly reduces this number because of the unreliability of the clinical diagnosis of rubella, it is evident that

Table 5. *National registry for congenital rubella reported cases by year of birth (10)*

Yr	Number of Cases	
	Reported	79% of reported ¹
1969	78	62
1970	90	71
1971	52	41
1972	40	32
1973	38	30
1974	28	22
1975	40 ²	32
1976	23 ²	18
1977	18 ²	14

¹ 79% of 351 cases reported from 1969-1975 MET CDC criteria for diagnosis.

² Reporting of these years still incomplete because some cases are not diagnosed until later in childhood.

Fig. 1. Reported cases of rubella, US 1966-1977 (10).

there is still a great deal of rubella virus in circulation. And yet, the total number of rubella birth defects that have been reported thus far to the national registry is 18 for 1976 and 14 for 1977. Does this small number of rubella birth defects among at least 60,000 other birth defects annually warrant an ongoing immunization program with rubella vaccine? For the USA, my answer at this time is not only yes, but more of it, to prevent the possible emergence of another specially teratogenic virus of the 1964 variety which was associated with thousands of tragic rubella birth defects. Between 20 and 30% of 10- to 19-year-old girls are currently estimated to be without rubella antibody in the USA and about 66% of reported cases of rubella occur in the 10-year and older age group.

In my judgment, the present vaccination program should be supplemented in preschool and schoolage children as I previously recommended for measles by administration of the combined measles and rubella vaccines. The hypothetical danger of giving rubella vaccine to postpubertal girls is not borne out by the fact that more than 60 susceptible women who inadvertently received rubella vaccine shortly before or shortly after conception gave birth to children without congenital rubella abnormalities (Center for Disease Control Morbidity and Mortality Weekly Report, November 25, 1977). The fact that rubella virus has been demonstrated in some artificially aborted fetuses of vaccinated women does not mean that the vaccine virus can multiply to the level required for the production of congenital defects. Previously unvaccinated childbearing women should receive rubella vaccine during the postpartum period while they are still in the hospital, without resorting to prior cumbersome and expensive serologic tests. The vaccine itself is inexpensive and cannot hurt the women who are already immune. It would also be helpful if, at the first diagnosis of pregnancy, obstetricians would give rubella vaccine to all previously unvaccinated children in the household of the pregnant woman.

POLIOMYELITIS

Oral polio vaccine is different from the other attenuated live virus vaccines in that it is given at the natural portal of entry where the vaccine strains multiply extensively and spread to unvaccinated persons in the family and the community. Thus, while the vaccine has the capacity of breaking the chain of transmission of the naturally occurring paralytic polioviruses when a sufficiently large number are vaccinated in a short period of time, it provides continuing dissemination of attenuated vaccine

strains as a source of immunizing infections for those who for various reasons receive no vaccine or an insufficient number of doses.

No other country with a comparable large population has achieved as good a record as the USA in the complete or almost complete elimination of paralytic poliomyelitis caused by polioviruses. I emphasize "caused by polioviruses" because long before successful vaccination was developed, it was established beyond doubt that a very small proportion of persistent paralytic poliomyelitis is caused by related nonpolioviruses against which the vaccine containing the three types of poliovirus cannot be expected to protect. Excluding the few imported poliovirus paralytic cases, the remaining unexpectedly small numbers that have been occurring in the USA during the past 9 years are, with perhaps very rare exceptions, in my judgment either misdiagnosed as regards the cause or nature of the disease. It is important to remember that this virtual elimination of paralytic poliomyelitis is being maintained despite the large annual immigration of families from Mexico where paralytic polioviruses are still highly prevalent.

The data in Table 6 show that 5 years (1956-1960) of extensive use of inactivated polio vaccine (IPV) in the USA reduced the paralytic attack rate from about 100 to about 28 per million total population. The ultimate reduction to what I regard as three questionable cases per 100 million total population followed extensive community mass campaigns from 1962-1964 during which about 90 million persons of all ages received OPV and an ongoing use of OPV in newborn children as part of their routine immunizations. This excellent record has been maintained despite the fact that, according to the 1976 US Immunization Survey, only 66% of 1- to 4-year-old white and 40% of the nonwhite children of this age had received 3 or more doses of trivalent OPV, although 92% of 10.1 million white children and 82% of 2.2 million nonwhite children of this age received one or more doses of trivalent OPV (Table 4). Serologic surveys recently carried out in the USA (Tables 7 and 8) show the high immune status among some 2- to 4-year-old children and young army recruits. It is necessary to stress here that serologic surveys do not completely measure the immune status of a population when undiluted sera are not tested or when the serum-virus mixtures are not incubated for 4 hours at 37° and overnight in the refrigerator, because infection immunity in poliomyelitis (including that after OPV) is associated in some persons with very low or undetectable levels of antibody in the presence of intestinal resistance to reinfection. A recent serologic survey in Rome using 1:2 and higher dilutions of serum in a cytopathic microneutralization test (Table 9) showed practically 100% immunity in all age groups from 6 months to over 70 years of age. This result was achieved in Italy by an initial OPV mass campaign (Fig. 2) followed by ongoing use of OPV in the new generations of children. This rapid elimination of paralytic poliomyelitis in the USA, Italy, and other countries by the strategy of initial mass vaccination followed by routine immunization of children is to be contrasted with the slow reduction and continuing occurrence of large numbers of measles and rubella cases in the USA because the chain of transmission of the naturally occurring measles and rubella viruses was never broken by extensive initial mass vaccination of all susceptible children and because the vaccination program that was used always left a sufficient number of unvaccinated children to maintain these viruses in circulation. The extra dividend from the use of OPV, i.e., immunization by spread of excreted vaccine viruses, which is not available from measles vaccine, imposes the need of much higher coverage in any plan to break the chain of transmission of measles.

POLIOMYELITIS AND MEASLES VACCINES IN SUBTROPICAL AND TROPICAL COUNTRIES

In economically underdeveloped countries, subtropical, and tropical countries, measles is a leading cause of death in young children and much of it occurs before 15 months of age, the age for administration of measles vaccine now recommended in temperate climates. To provide protection to the vast majority of

Table 6. *Paralytic Poliomyelitis Reported in USA, 1951-1976 (7)*

Era	Period	Total no. for 5 yr	Average no. per annum	Approximate no./million/annum
No vaccine + IPV ¹ , 1955	1951-1955	79,112	15,822	100
IPV only	1956-1960	22,291	4,584	28
IPV + OPV ² antiepidemic + later community programs	1961-1965	2,313	463	3
OPV only	1973-1976	24? (4 yr) (+6 imported)	6?	<3?/100 million

¹ IPV = inactivated polio vaccine (Salk). ² OPV = Oral polio vaccine (Sabin).

Table 7. *Antibodies to measles, rubella, and polioviruses in 2- to 4-yr old children, Shelby County (Memphis), Tennessee—1975 (7)¹*

Virus	No. tested	Percent positive	Percent vaccinated
Measles	353	76 at 1:5	80%
Rubella	334	69 at 1:8	80%
Polio 1	341	98 at 1:5	93%
2	341	99 at 1:5	Two or more doses
3	341	96 at 1:5	

¹ Unpublished data of David T. Karzon and Peter F. Wright, Vanderbilt University School of Medicine, Nashville, Tennessee.

Table 8. *Poliovirus neutralizing antibodies in 286 US army recruits before routine Army vaccinations: February, 1976 (7)^{1,2}*

Poliovirus type	% positive (1:4)
1	92
2	92
3	89

¹ Data from Walter Reed Army Institute of Research, Washington, D.C.

² US Immunization Survey showed that in 1975 in the 15- to 19- year age group, the percent that had received 1 or more, 2 or more, and 3 or more doses of oral polio vaccine was 88, 71, and 62, respectively, for whites and 77, 58, and 49, respectively, for nonwhites.

Table 9. *Antibodies of poliovirus in lower-middle socioeconomic population, Rome, Italy—1974 and 1975 (7) Oral Poliovaccine Used Since 1964^{1,2}*

Age group	No. persons tested	Percent positive for indicated type		
		1	2	3
6 months-4 yr	130	97.7	98.5	98.5
5-9 yr	67	98.5	100.0	98.5
10-19 yr	170	98.2	100.0	100.0
20-70 yr	195	99.0	98.0	98.5
Over 70 yr	40	100.0	100.0	100.0

¹ Proportion of vaccinated children in any 1 yr in Italy has varied between 80-90%.

² Data from Volpi, Ragona, Biondi, Rocchi, and Archetti: Bull, World Health Organization, 54: 3518 (1976).

infants who have already lost their maternal antibody by 6 months of age, it becomes necessary to give measles vaccine at 6 months or earlier and then give another dose at 15 months of age. The main difficulty, however, in achieving a marked reduction in the number of measles cases in economically underdeveloped countries is not immunologic, but administrative, because a very small proportion of infants are brought to clinics for routine immunizations especially at 6 months of age and later. Under these conditions only a strategy that includes *annual* mass vaccination of all children between 6 and 23 months of age without reference to previous history of clinical measles or vaccination, can be

expected to have a significant impact, and for this both cheap vaccine and disposable syringes and needles are needed as well as properly trained nonprofessional and professional personnel.

The magnitude of paralytic poliomyelitis as a public health problem, deserving special measures in economically underdeveloped countries is not adequately reflected by the number of officially reported cases. Clinical surveys for poliomyelitis lameness in schoolaged children, recently reported from Ghana, Burma, Egypt, and the Philippines, have shown how very high the average annual incidence can be in both rural and urban areas in the absence of epidemics. There is a great need for similar clinical surveys in many other countries. Paralytic rates higher than those during the peak prevaccine era in the USA have been found in countries with high infant mortality rates and continuing poverty with its undernutrition, malnutrition, and absence of basic sanitary facilities. Analysis of reports of the lower frequency of antibody response to one or two doses of OPV in infants in economically underdeveloped, subtropical, and tropical countries has shown that some of the factors are similar to those found in the lower seroconversion rates encountered in the early 1960's among older children and adults in the USA. The phenomenon is based on the fact that immunity after infection with polioviruses can in some persons consist of intestinal resistance to reinfection with very low or undetectable levels of antibody. Neutralization tests for antibody that begin with 1:8 or 1:10 dilutions of serum not only miss a certain proportion of persons that are already immune before receiving OPV, but also fail to detect those with a lower antibody response.

There is no question that a high prevalence of concurrent nonpoliovirus enteric infections can modify, delay, and lower the frequency of antibody response to one or two doses of OPV, even though some field studies have reported no such effect. It has, nevertheless, been established that this impediment to optimum effectiveness of OPV in some infants in the tropics is overcome by multiple doses of trivalent OPV. Prolonged breast-feeding, which is often mentioned as another impediment to the effectiveness of OPV, has been found to be without inhibitory effect in the routine use of OPV in infants in the USA and in the tropics.

The problem of eliminating poliomyelitis as a public health problem in economically underdeveloped countries is administrative and not immunologic or epidemiologic. It is also obvious that both a different and specially concentrated effort is needed in countries in which most of the cases occur during the first 2 years of life and paralytic polioviruses are propagating year-round in the intestinal tracts of a large proportion of the infant population. The problem is predominantly administrative because the highly desirable expanded routine infant immunization programs, which include OPV but reach at best only 20-40% of the total infant population with one or more doses of the vaccines that require multiple doses for maximum effectiveness, cannot be expected to protect the unvaccinated and inadequately vaccinated children in the community. Use of multiple doses of quadruple vaccine (DPT + IPV) would not only greatly increase the cost of routine immunizations, but would not achieve more or as much as the feeding of OPV at the time of the DPT injections.

In countries with small numbers of professional health personnel and many other year-round problems, the best results can be expected from *annual* mass vaccination campaigns on only 2 days of the year, 2 months apart, during which OPV is given to all

Fig. 2. Paralytic poliomyelitis in Italy 1962-1966 (4).

children under 2, 3, or 4 years of age (depending on the epidemiologic situation in the region) without reference to the number of doses they may have had before. I have recently described in some detail the procedures for such mass campaigns based on central national planning and decentralized regional and local implementation using large numbers of unpaid, unskilled, well-rehearsed volunteers.

INFLUENZA

The clinical syndrome that for centuries has been called influenza cannot be considered chiefly as a problem caused by influenza viruses that could be overcome by influenza virus vaccines. Natural influenza virus infections of human beings result in a spectrum of manifestations ranging from no illness and mild afebrile or febrile upper respiratory tract illnesses (*i.e.*, above the larynx) to febrile lower respiratory tract illnesses, affecting the larynx, trachea, bronchi, bronchioles, and lungs, accompanied by systemic symptoms of varying severity. Although it is generally agreed that all of these clinical manifestations can also be caused by other viruses, the dogma has developed that epidemics of influenza, which are indeed caused only by influenza viruses (usually antigenic variants of type A), are responsible for the major problem of influenza, and if that is indeed so, the major problem can best be dealt with by the proper use of optimum influenza virus vaccines. I also believed in this evaluation of the influenza problem until about 2 years ago when a study of the data accumulated continuously for many years by the US National Center for Health Statistics on morbidity (through its ongoing Health Interview Surveys) and on mortality separately for influenza, pneumonia, and various debilitating diseases during influenza virus epidemic and non-epidemic years led me to a totally different perspective.

Data on Morbidity from Health Interview Surveys. In the ongoing Health Interview Surveys, a statistically adequate and representative sample of families (*i.e.*, excluding those living in various types of institutions) throughout the USA are selected for evaluation

of the role of various acute and chronic conditions as causes of poor health. Trained interviewers visit these homes and obtain information only on the events of the *preceding 2 weeks*. For acute respiratory conditions, the information is categorized separately for "upper respiratory conditions", "influenza", "pneumonia", "bronchitis", and "other respiratory conditions". The available information includes the number of "days of bed disability", referring to the number of days a person was confined to bed, the total number of days of restricted activity, the number who were medically attended, incidence by sex, age, etc. I recently summarized the data for bed disability attributed to influenza, upper respiratory tract infections, and pneumonia and mortality data separately for influenza and pneumonia in the USA during the period of mid-1963 to mid-1976 (6). The magnitude of the bed-disabling clinical influenza problem during the years *without* national influenza A virus epidemics was astonishing, *e.g.*, during the 12 months of July 1973-June 1974, there were 61,841,000 bed-disabling clinical influenza illnesses with an average of 3.6 days of bed disability per illness. During the next 12-month period without a national influenza A virus epidemic, *i.e.*, July 1976-June 30, 1977 (the year when the predicted swine influenza virus epidemic did not materialize), there were a total of 65,232,000 of bed-disabling clinical influenza illnesses and in addition 65,543,000 bed-disabling upper respiratory tract illnesses (Table 10). When the equal numbers of bed-disabling clinical influenza and upper respiratory tract infections are combined, one discovers that 62% of the entire US population was affected, and yet the official information given out by the US Public Health Service was along the lines of "Thank God we did not have an influenza epidemic". Considering only morbidity, it is of interest to note how small is the impact of epidemics caused by new antigenic variants of influenza A virus. From July 1970-June 1977, the average bed-disabling morbidity for clinical influenza was 30% during the 3 non-epidemic years and 36% during the 4 epidemic years, but when combined with bed-disabling upper respiratory tract infections the total increase in morbidity is only 4% (Table 11).

Role of Influenza Viruses in Clinical Influenza. The respiratory

tract is an area in which hundreds of viruses and other microbial agents are struggling for territoriality. Since November 1972, the US Center for Disease Control in Atlanta, GA with the help of 43-58 collaborating laboratories, has accumulated virologic data on over 80,000 patients with "influenza-like" illnesses. The data in Table 12 show that the combined influenza A and B virus isolation rates during the two nonepidemic periods were 9.7% and 8.4% compared with 10.9% to 21.9% during the four influenza A virus epidemic periods. The influenza B viruses predominated during the nonepidemic years and practically disappeared during the influenza A virus epidemic years. Only a very small number of additional influenza virus infections have been detected by antibody tests on acute and convalescent phase serum specimens, and when these are taken into account it appears that there is no evidence of concurrent influenza A and B virus infections in about 90% of the huge number of bed-disabling clinical influenza illnesses during nonepidemic years and in 77-85% during different epidemic years. The actual etiology of this vast amount of "non-influenza virus" influenza remains unknown. Virologic studies on 3,115 acute lower respiratory tract infections in children under 16 years in Chapel Hill, North Carolina during the period of 1963-1969, which included the period of Hong Kong/68 influenza A virus prevalence in the community, yielded viruses in 25%, mycoplasma in another 3%, and 72% of the illnesses were in the category of undiagnosed viral disease (2). During this 6 year period, influenza A viruses (including Hong Kong/68) were recovered from only 0.8% and influenza B from 1.3% of the illnesses compared with 6.9% for respiratory syncytial virus, and 10.3% for parainfluenza 1 and 3 viruses. It is noteworthy that during a nonepidemic year the seasonal distribution of clinical influenza,

measured by the millions of days of bed disability, has the same January-March peak as during epidemic years, and that it is different from upper respiratory infections (peak during October to March) and other respiratory infections which are more or less evenly distributed throughout the year.

Excess Mortality Associated with Influenza Virus Epidemics in the USA Before and After 1971. It is obvious from this analysis that even if a 100% effective vaccine could be given to every man, woman and child in the USA, it would prevent only a small portion of this leading cause of morbidity assuming that the "vacuum" left by the influenza viruses would not be filled by the many known and as yet unknown viruses in the human respiratory tract, an assumption that cannot be made in the light of the 4% lower incidence of bed-disabling respiratory tract illnesses during nonepidemic years (Table 11). However, the objective of current recommendations for the annual use of influenza virus vaccines is not to reduce morbidity but rather to reduce influenza virus epidemic associated excess mortality in specified high risk groups. My analysis of mortality data for influenza (the primary or only diagnosis on the death certificate), pneumonia, various types of heart disease, emphysema, asthma, and other debilitating conditions during the period of mid-1963 to mid-1977, reported in greater detail elsewhere (5, 6) showed that the excess mortality from pneumonia and other high-risk conditions that regularly occurred during influenza A virus epidemic years in the USA before 1971, has practically disappeared since then. Beginning in 1971, pneumonia mortality has continued to decline without reference to influenza A virus epidemics which are associated with a varying increase in mortality directly attributed to influenza on the death certificates (Fig. 3). Based on information I received from the National Center for Health Statistics there has been no reduction in pneumonia morbidity since 1967 and the bed-disability rates have not varied significantly during influenza A virus epidemic and nonepidemic years (Table 13). It appears rather that an improvement in medical care for low-income groups may have reduced pneumonia mortality without affecting morbidity. The curves in Figure 4 for mortality from heart disease show that during the influenza A virus epidemic years up to and including the A/Hong Kong pandemic year of 1968-1969 the rates were regularly higher than those during nonepidemic years, but with the exception of one year (1972-1973) not thereafter, the curves of declining mortality being identical during nonepidemic and epidemic years including the 1975-1976 A/Victoria influenza virus year when the highest influenza mortality of 7770 cases (36 per million) was reported since the A/Hong Kong pandemic year of 1968-1969 with 8630 cases (43 per million). Figure 4 also shows the comparable declining curves for emphysema mortality since 1973-1974. The annual asthma mortality rates have also been declining at a rate that has not been influenced by influenza A virus epidemics during the entire 14-year period of mid-1963 to mid-1977, and has not been a so-called high risk condition during the years when heart disease and emphysema were high-risk conditions. The data for other individual high-risk conditions (available only for calendar years which, nevertheless, include the usual peak influenza A virus epidemic months of January and

Table 10. *Bed-disabling influenza and upper respiratory infections during nonepidemic 12-month period of July 1, 1976 to June 30, 1977 in noninstitutionalized population of USA (11)*

Illness	Millions of cases	No. of cases per 100 persons	Bed days per case
Influenza	65.2	30.9	3.1
Upper respiratory	65.5	31.0	2.6
Both	130.7	61.9	

Table 11. *Bed-disabling influenza and upper respiratory infections incidence during national influenza epidemic and nonepidemic yr in noninstitutionalized population of USA July 1, 1970 to June 30, 1977 (11)*

Average	No. cases/100 persons/yr		
	Influenza	Upper respiratory	Both
3 nonepidemic yr	30	28	58
4 epidemic yr	36	26	62
Difference	+6	-2	+4

Table 12. *Influenza virus isolations in USA reported by laboratories participating in WHO influenza program, 1972-1978 (10)*

Influenza A epidemic	Period	No. specimens tested	% specimens yielded		
			Influenza A	Influenza B	Influenza A + B
No	November 1973-April 1974	6,841	2.3	7.4	9.7
	December 1976-June 1977	29,709	1.5	6.9	8.4
	November 1972-February 1973	6,289	15.7	0.7	16.3
Yes	November 1974-April 1975	7,892	13.0	0	13.0
	November 1975-April 1976	13,296	21.4	0.5	21.9
	October 1977-March 1978	19,463	10.9 ¹	0.0003	10.9

¹ 8.4% of A (H3N2) + 2.5% of A (H1N1).

Fig. 3. Mortality rates from influenza and from pneumonia during nonepidemic years (N) and influenza A virus epidemic years from July 1–June 30, 1963–1977 (5).

February) indicate that during the calendar years of 1971–1975 there were continuing declines for some conditions (e.g., rheumatic and ischemic heart disease, cerebrovascular disease, bronchitis+emphysema+asthma, diabetes mellitus, chronic nephritis, tuberculosis of respiratory tract), steady states for some (e.g., leukemia), and increases for others (e.g., malignancies of the respiratory system) without relationship to influenza virus epidemics (Table 14).

Mortality from All Causes at Different Times of Year During Influenza A Virus Epidemic and Nonepidemic Years. The US Center for Disease Control, Atlanta, GA continues to report estimated excess mortality from all causes during recent influenza A virus epidemics based only on the increases observed during the peak weeks of the epidemics without reference to what happens during the remainder of the year. The epidemiologists of this Center believe that the real impact of an influenza A epidemic may be missed when 12-month mortality data are used although using such 12-month data there is clear evidence of excess from several causes, excluding influenza itself, before 1971, but not thereafter (3). Comparison of the mortality data from all causes during different months of the 3 nonepidemic and 4 epidemic years of 1970–1977 (Table 15) reveals the following interesting points:

Table 13. Seasonal distribution of bed disability associated with different respiratory conditions in absence of national influenza virus epidemic in USA, July 1973–June 1974 (6)

Respiratory condition	Millions of days of bed disability				
	July–September	October–December	January–March	April–June	Total yr
Influenza	17	48	128	31	224
Upper respiratory	24	49	52	20	145
Other respiratory (pneumonia, bronchitis, etc.)	11	14	15	10	50
					419

Fig. 4. Mortality from indicated diseases during nonepidemic and influenza A virus epidemic years in USA from July 1–June 30, 1963–1977 (5).

Table 14. *Mortality rates of indicated diseases per million US population in relation to influenza A virus epidemics, 1971-1975 (5)*

Disease (ICDA no.)	Calendar yr and occurrence of widespread influenza epidemic				
	1971 No	1972 Yes	1973 Yes	1974 No	1975 Yes
Influenza (470-474)	7	24	24	10	22
Pneumonia (480-486)	270	277	274	249	247
Diseases of heart					
Total (390-398, 402, 404, 410-429)	3605	3630	3608	3492	3390
Rheumatic (390-398)	71	68	65	63	58
Ischemic (410-413)	3270	3287	3260	3145	3043
Cerebrovascular diseases (430-438)	1014	1025	1021	981	918
Bronchopulmonary					
Total (490-493, 519.3)	178	187	196	195	not available
Bronchitis + emphysema + asthma (490-493)	147	148	142	127	119
Chronic obstructive lung disease without mention of asthma, bronchitis, or emphysema (519.3)	31	39	54	68	not available
Diabetes mellitus (250)	186	186	182	177	168
Chronic nephritis, etc. (582-584)	34	34	32	31	31
Malignant neoplasms					
Total (140-209)	1636	1660	1673	1705	1744
Respiratory system (160-163)	354	370	378	395	415
Leukemia (204-207)	70	69	69	69	70
Tuberculosis, respiratory (010-012)	17	17	14	13	12

Table 15. *Mortality from all causes at different times of yr during influenza A virus epidemic and nonepidemic yr, USA 1970-1977 (11)*

Year, 1 July-30 June	Actual mortality per million			
	Influenza A epidemic months	12 months	Epidemic months	Other months
1970-71	None	9,375	1,617 ¹	7,800
1971-72	January-February	9,378	1,741	7,673
1972-73	January-February	9,431	1,698	7,761
1973-74	None	9,255	1,556 ¹	7,723
1974-75	January-February	9,067	1,620	7,471
1975-76	February-April	8,917	2,386	6,543
1976-77	None	8,770	1,553 ¹	7,240

¹ These rates are for the months of January and February.

1. The 12-month data show a decline that has not been affected even by the severe 1976 A/Victoria epidemic which caused about 5700 excess deaths attributed specifically to influenza on the death certificates. When the data for the nonepidemic and epidemic years are plotted separately, the rates for the 1975 and 1976 epidemic years are precisely on the nonepidemic descending line.

2. There is a distinct increase in overall mortality during the January-February (on one occasion February-April) months of the epidemic years, but with an associated decrease in mortality during the remaining months of the year when compared with the rates obtained during the preceding nonepidemic years.

Thus, the assumption that mortality from all causes remains the same during the months of the year without influenza virus activity is not valid, and that counting only the excess observed during the epidemic months gives an erroneous impression of the real impact of an influenza A virus epidemic. These data do suggest, however, that some persons who would have died later in the year, die earlier during an influenza virus epidemic year. Data collected by the Metropolitan Life Insurance Company over many years indicate that a short-term increase in cancer mortality early during an influenza epidemic year is followed by a relative decrease in mortality in the balance of the year (1).

Influenza Mortality in Older Age Groups. All persons over 65

years of age, debilitated or healthy, are also included in current recommendations for annual administration of influenza virus vaccine. An analysis of age-specific influenza mortality data in older age groups during recent epidemic and nonepidemic years (Table 16) indeed shows that about 80% of the relatively small number of deaths specifically attributed to influenza in death certificates occur in the 65 years and older age group without reference to epidemics. It is also noteworthy, however, that 60% or more of the deaths occur in the much smaller group aged 75 years and over. There are no data on how many, if any, of these deaths occur in previously healthy older people. It seems highly desirable to obtain such data by examining an appropriate sample of recent influenza death certificates in younger and older age groups to determine how many were debilitated and bed-ridden before their fatal influenza episode and how many were healthy. This type of information should be obtained especially in view of the recent evidence that one expects one excess case of the paralytic Guillain-Barré syndrome per 100,000 persons receiving the killed influenza virus vaccine per annum, and this risk can be expected to exist each year the vaccine is taken and therefore greater over the years.

Comments on Use of Influenza Virus Vaccine—Annually and During Pandemics. For all the reasons given in the preceding

Table 16. *Percent of annual total influenza mortality in older age groups (5)*

Calendar yr	Influenza A epidemic	No. of deaths all ages	Percent of all deaths in		
			65+	65-74	75+
1971	No	1504	77	17	60
1972	Yes	4986	74	22	52
1973	Yes	5131	79	19	60
1974	No	2201	79	16	63
1975	Yes	4780	81	18	63

reassessment of the influenza problem, I question the validity of the recommendations for the continued use of influenza virus vaccine in the currently designated so-called high-risk groups, especially because vaccines containing new antigenic strains continue to be unavailable until after the new epidemic strains have had their major impact during the first year of their spread. Moreover, it seems incongruous to continue to include influenza B virus in the vaccine in view of the fact that its predominant prevalence is during the nonepidemic years (see Table 12) when there is apparently no excess mortality from influenza or other conditions. In my judgment, a continuing campaign to discourage the harmful widespread use of antibiotics in uncomplicated influenza and upper respiratory tract viral illnesses may be more beneficial than campaigns for increased use of influenza virus vaccines.

The oft-repeated statements that worldwide epidemics caused by totally new antigenic variants of influenza A virus can be expected approximately once every 11 years is incorrect. It happened only once between 1957 and 1968. The interval before 1957 was at least 27 years (or 39 years), and there is no way to predict when the next one will appear. The time interval between the first identification of an influenza A pandemic virus and its extensive spread in a country is so short that only the most heroic measures of preparedness for rapid mass production and *even more rapid mass administration of the vaccine* in prior well-planned and organized volunteer community programs, could be expected to have at best a partial impact on the spread of the virus and on the total incidence of influenza+upper respiratory tract illnesses. Studies carried out during the A/Hong Kong/1968 virus initial epidemics showed that even during the few weeks of major virus spread, a varying but large proportion of clinically diagnosed influenza was not caused by influenza viruses. In view of the special problems connected with rapid production and rapid administration even only to the 65 or 75 and older age groups, one can expect a very limited impact on the higher influenza mortality during pandemic periods.

SUMMARY

Measles, rubella, poliomyelitis, and influenza present different problems in control by vaccination. Thus, influenza is a disease of multiple etiology and influenza viruses are the cause of only about 10% of bed-disabling clinical influenza during nonepidemic years and about 15-20% during epidemic years. Contrary to general impressions, extensive epidemics of influenza, which are caused only by influenza A viruses, contribute relatively little to the overall massive annual incidence of bed-disabling influenza and upper respiratory tract infections, which together affect 58% of the US population during nonepidemic years and 62% during inter-pandemic epidemic years. Accordingly, even a 100% effective vaccine, which would be available before rather than after the appearance of new antigenic variants and which would be rapidly administered to the entire population, could be expected to have a very limited impact on the immense amount of bed-disabling, acute respiratory tract illness. The increase in mortality that continues to occur during influenza A virus epidemics is now quite

small in the USA. The unavailability of vaccine for new antigenic variants at the time of or shortly after their first appearance, has also precluded a significant impact of influenza virus vaccines on mortality.

The success of oral polio vaccine in countries with advanced health services and large populations, not all of whom are vaccinated, is dependent on the following factors: 1) although persistent paralytic poliomyelitis can occasionally be caused by enteroviruses that are not polioviruses, the three types of poliovirus caused *almost all*, if not all, of the paralytic disease; 2) mass vaccination in a short period of time quickly breaks the chain of transmission of the paralytic polioviruses, but the vaccine strains continue to spread and immunize many of the unvaccinated and incompletely vaccinated persons not only during the mass campaigns but also annually as part of the ongoing vaccination of the new children.

Only measles virus causes measles, and a rapid initial mass vaccination of all children could also break the chain of transmission of measles virus, but the proportion of the population that needs to be vaccinated initially and thereafter must be larger than with oral polio vaccine, because the special dividend of immunization by ongoing dissemination of attenuated viruses in the community is lacking. Moreover, the system of measles vaccination in the USA has always left enough unvaccinated susceptibles to maintain a continuing chain of transmission of measles virus, with continuing epidemics wherever and whenever the number of susceptibles increased in number.

Rubella vaccination was started in the USA not to eliminate the disease, but the congenital defects. It was assumed that the large number of congenital defects seen in association with certain epidemics represents an invariable consequence of rubella virus infection early in pregnancy. It is evident, however, that extensive dissemination of rubella virus occurs also during the many non-epidemic years, and that the number of congenital defects reported to the National Registry in the USA since 1969 was very small even before the extensive use of rubella vaccine has partly diminished the dissemination of rubella virus in the country. This very low incidence of rubella congenital defects in the USA is in line with the failure even of certain epidemics in other countries to give rise to large numbers of children with the special rubella congenital defects. Many countries have chosen not to give rubella vaccine to children on the ground that the small numbers of rubella congenital defects do not warrant the extensive effort that would be required to bring about a significant break in the chain of transmission of the rubella virus by vaccinating all the children, and vaccination limited to women of child bearing age was initially regarded with justifiable uncertainty. If one assumes that rubella viruses with special properties, not just special virulence, are needed to produce congenital defects—and, in my judgment, there are good reasons for such an assumption—a break in the chain of transmission of rubella virus in a country could be expected not only to prevent the emergence of such a special strain, but also to prevent its spread if it should be introduced from outside. For this reason, there is good reason for expansion of the present rubella vaccination program concurrently with the expanded measles vaccination program in the USA by administering the combined measles-rubella vaccine to a sufficiently large

number of preschool and schoolage children to effect a complete or almost complete break in the chain of transmission of both of these viruses. An expanded program of vaccination of women of child bearing age is also indicated in the USA.

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