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# Vaccination Against Virus Diseases

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**Benefits of vaccination against virus diseases are highlighted and reasons for the apparent lack of *the effect of influenza virus vaccines are discussed* and ascribed to immunization strategy, poor understanding of the importance of the immunogenicity of the various types of vaccines available, and the unjustified expectations that influenza virus vaccines should be effective against non-influenza virus causes of influenza-like illnesses.**

## Introduction[2]

Infectious diseases are the cause for every fifth visit to physicians [15]. Over 2.5 billion dollars were spent in the United States for medical care during the influenza outbreak in 1968–9. The rubella epidemic in 1964–5 was estimated to have resulted in approximately 20'000 children with congenital diseases, and almost as many fetal deaths, with an overall economic loss of 1.5 billion dollars. Prior to the licensing of measles vaccine in 1963 the United States had approximately 4 million cases of measles each year [58] with about 4000 cases of measles encephalitis and 400–500 deaths [1, 16].

It was estimated that during the ten years between 1963 and 1972 about 24 million cases of measles were prevented through vaccination, 2400 lives were saved and almost 8000 cases of retardation averted [58] with net economic savings of 1.3 billion dollars. Similarly, the economic burden of poliomyelitis was considerable: It was estimated that in the span of six years (1955–61) 12'464 deaths and 100'000 moderate to severe disabilities would have occurred at an estimated health care cost of over 326 million dollars, had there not been vaccination [16].

During the past hundred years the most important and most lasting benefit of medicine to human health and health expenditure has been the interruption of the vicious cycle of infectious diseases such as smallpox [37, 67], yellow fever [55, 62], and poliomyelitis [8]. A variety of factors have contributed. Eradication of pathogen reservoirs [6, 31], suppression of insect vectors and other carriers [20, 27, 35, 43, 44, 53, 63], improvement of socioeconomical conditions accompanied by reduced crowding [49] and improved education, sanitation and nutrition, all have played a role. However, one of the most important factors probably was the reduction of the number of susceptibles in a given population. In a natural situation such a reduction is achieved by disappearance of those least resistant to the contagion and development of immunity in the more resistant survivors [25, 45]. Today, planned vaccination programs are employed to reduce the population of susceptibles with great efficacy.

## Benefits of Vaccination

Surely, if we want to understand the benefits of vaccination, smallpox must be the outstanding example. One of the great scourges of mankind for centuries, more than 2.5 million cases ten years ago, it is gone today completely. There has been no natural smallpox case reported anywhere in the world since October 1977. How about poliomylitis today? How often do we see poliomyelitis cases, and where is the pressure to vaccinate and keep up the guard against this disease? Maybe it would be interesting to look back over our experiences with immunoprophylaxis against virus diseases.

The data I am going to discuss are based on US statistics *(Table 1)*. The conclusions I shall draw from them are unencumbered from considerations such as changes in the US population density (105.7 millions in 1920 to 215 millions today), social behaviour and life styles, diagnostic capabilities, changes in reporting emphases and procedures, adaptive changes in virus–host relationships, and advances of modern medicine outside the area of prophylactic immunology.

In this first table I have listed all the major communicable diseases in the US ranked by their change in incidence over the years. The diease that has shown maximum increase since 1951 is on top and the one with maximum incidence reduction is at the bottom of the list. A space is left where the incidence went below 30 % of that in 1951. Only diseases for which vaccines exist show a reduction of greater than 70 % from the prevaccination era.

In the following table *(Table 2)* I present the diseases with available immunoprophylaxis in relation to the time point at which vaccine licensing suggested widespread use of immunization. The right-hand column gives the percentage reduction in incidence and mortality since onset of vaccination. Of course, the longer a program of effective vaccination has been in existence, and the more conscientiously it has been carried out, the more effective it has been.

As control of the vaccine-independent influences on the spread of communicable diseases, I have listed those infectious diseases against which there are no vaccines available *(Table 3)*. Except for one, there is

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no similar decrease in incidence. The one exception, Syphilis, may be a combination of poor reporting and effective use of antibiotics. Mortalities, however, were markedly reduced, indicating the progress made in the treatment of disease and the effective use of antibacterial drugs. By contrast, hepatitis, a virus disease still without vaccine and refractory to the effects of antibiotics, shows only marginal reduction in mortality *(Table 4)*.

*Table 4* summarizes the overall picture from these two sets of data. Of all the diseases with vaccines the overall yearly incidence has been reduced by more than a million cases, a reduction by 90 % from before the onset of vaccination. Every year more than 100,000 lives are saved. Contrary to that, the incidence of diseases without vaccines increased by nearly one million over the past twenty-five years.

Additional evidence for the benefits of vaccination is the direct relationship between the reduction in incidence of virus diseases and the number of vaccine doses distributed. Within ten years after onset of the distribution of poliomyelitis virus vaccines the polio incidence was practically reduced to zero *(Fig. 1)*. The measles incidence between 400,000 and 760,000 in the fifties was down to 22,000 in 1974 and deaths due to measles declined from between 340 and 680 in the fifties to 20 *(Fig. 2)*. If we assume a mental retardation rate of 1 per 3000 of measles diseased [12] we can calculate the yearly saving of about 200 children from permanent damage. *Krugman* [38] reported the parallel decrease of subacute sclerosing panencephalitis with the distribution of increasing numbers of vaccine doses. Rubella, which at the time of vaccine license had touched nearly 50,000 in the US and produced nearly 90 congenitally deprived children was down by a factor of greater than five in both incidence and congenital syndrome cases *(Fig. 3)*. A similar positive relationship between vaccine distributed and disease incidence holds also with mumps *(Fig. 4)*.

**Lack of Effect of Immunoprophylaxis against Influenza**

As we now consider the overwhelming evidence for the success of immunoprophylaxis against viral diseases we rightly wonder why influenza virus vaccines, available in the US for more than thirty years, could not stem the cyclical tides of excess influenza mortalities. In *Fig. 5* we see not only the impact of influenza virus epidemics on deaths from pneumonia but also on deaths from all causes. More than 20 million people died in the 1918–20 pandemic caused by a virus similar to the one isolated a couple of years ago in New Jersey. The 1957–8 epidemic in the US cost nearly 70,000 lives and in the 1968–9 season approximately 33,000 died of influenza [13].

Of course, we know of the variability of influenza virus and its facility to adapt to the immunological environment, progressively selecting out and establishing that antigen variant against which there is no suppressive antibody. Some say, therefore, that influenza vaccines are inadequate and always a step behind–preventing last year's disease. Is this really the case? Or is it, that

*Table 1. Incidence of specified acute infectious diseases (U.S. 1951–76) Ranked by per cent increase in incidence*

| Disease | Causative agent | Case reports in year | | 1976 incidence as % of 1951 |
|---|---|---|---|---|
| | | 1951 | 1976 | |
| Salmonellosis | Salmonella | 1,773 | 22,937 | 1294 |
| Hepatitis | HV types A and B | 7,349 | 55,749 | 759 |
| Gonorrhea | Neisseria | 254,057 | 1,001,994 | 394 |
| Leprosy | Mycobacterium | 57 | 145 | 254 |
| Streptococcal disease | Streptococci | 324,195[1] | 436,632[2] | 134.6[2] |
| "Aseptic" meningitis, encephalitis | Many different viruses | 3,934 | 3,510 | 89 |
| Influenza | Influenza virus | (6,946)[3] | (4,277)[3] | (62)[3] |
| Bacillary dysentery | Shigella | 32,215 | 13,140 | 41 |
| Syphilis (all stages) | Treponema | 174,924 | 71,761 | 41 |
| Meningitis | Neisseria | 4,164 | 1,605 | 39 |
| Tuberculosis | Mycobacterium | 118,491 | 32,105 | 27 |
| Rubella | Rubella virus | 46,986[4] | 12,521 | 27 |
| Typhus fever | Rickettsiae | 3,952[6] | 1,006 | 25 |
| Mumps | Mumps virus | 152,209[5] | 38,492 | 25 |
| Typhoid fever | Salmonella | 2,128 | 419 | 20 |
| Tetanus | Clostridium | 506 | 75 | 15 |
| Measles | Measles virus | 530,118 | 41,126 | 8 |
| Whooping cough | Bordetella | 68,687 | 1,010 | 1.5 |
| Poliomyelitis | Poliovirus | 28,386[7] | 14 | 0.05 |
| Diphtheria | Corynebacterium | ≈ 400,000 | 128 | 0 |
| Smallpox | Smallpox virus | 11 | 0 | 0 |

[1] data from 1960 [3] (deaths) [5] data from 1965 [7] data from 1920
[2] data from 1970 [4] data from 1966 [6] data from 1946

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vaccination has not been carried far enough and does not reach a significant portion of the high-risk population and the population particularly likely to spread the disease [26, 40, 33, 29]?

Are the physician and the potential victim to blame, their disregard for "harmless influenza" and the consequent lack of urgency to vaccinate? Or are the vaccines employed not sufficiently potent? By definition, a vaccine should immunize a nonimmune individual. It is difficult to find nonimmune populations, and often in-

*Table 2. Diseases with existing immunization programs*

| Disease | year[1]: ≤ 1920[2] | 1930[2] | 1940[2] | 1947 | 1952 | 1957 | 1962 | 1967 | 1972 | 1975 | Per Cent Reduction[3] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Smallpox** | | | | | | | | | | | |
| Incidence | ■ **102,128** | > 48,907 | >2,795 | 176 | 21 | 0 | 0 | 0 | 0 | **0** | >99 |
| Deaths | **634** | 123 | NR | NR | 0 | 0 | 0 | 0 | 0 | **0** | >99 |
| **Typhoid fever** | | | | | | | | | | | |
| Incidence | ■ **35,994** | 27,201 | 9,809 | 3,075 | 2,341 | 1,231 | 608 | 396 | 398 | **375** | 99 |
| Deaths | **8,033** | 5,894 | 145 | NR | 78 | 34 | 15 | 12 | 8 | **3** | >99 |
| **Diphtheria** | | | | | | | | | | | |
| Incidence | **211,400** ■ | 72,452 | 18,438 | 12,262 | 2,960 | 1,211 | 444 | 219 | 152 | **307** | >99 |
| Deaths | **15,855** | 6,140 | 1,580 | NR | 217 | 81 | 41 | 32 | 10 | **5** | >99 |
| **Tetanus** | | | | | | | | | | | |
| Incidence | 1,585 | **1,289** ■ | 658 | 560 | 484 | 447 | 322 | 263 | 128 | **102** | 92 |
| Deaths | NR | NR | NR | NR | 360 | 279 | 215 | 144 | 58 | **45** | 87 |
| **Typhus fever** | | | | | | | | | | | |
| Incidence | NR | NR | **2,335** ■ | 2,646 | 532 | 353 | 272 | 357 | 541 | **888** | 62 |
| Dieaths | NR | NR | **263** | NR | 20 | 20 | 12 | 28 | 50 | **29** | 89 |
| **Influenza** | | | | | | | | | | | |
| Incidence | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | – |
| Deaths | 74,519 | 23,823 | **20,150** ■ | NR | 5,631 | 7,463 | 3,431 | 7,062[5] | 4,986 | **4,277** | 79 |
| **Whooping cough** | | | | | | | | | | | |
| Incidence | 168,120 | 196,480 | 210,720 | **156,517** ■ | 45,030 | 28,295 | 17,49 | 9,718 | 3,287 | **1,738** | 99 |
| Deaths | 8,456 | 7,982 | 3,029 | NR | **402** | 183 | 83 | 37 | 6 | **8** | 98 |
| **Tuberculosis** | | | | | | | | | | | |
| Incidence | NR | NR | 102,984 | **134,946** ■ | 85,607 | 66,437 | 53,315 | 45,647 | 32,932 | **33,989** | 75 |
| Deaths | 119,547 | 87,311 | 60,450 | NR | **24,621** | 13,324 | 9,506 | 6,901 | 4,376 | **3,333** | 86 |
| **Poliomyelitis** | | | | | | | | | | | |
| Incidence | NR | 9,220 | 9,804 | 10,927 | **57,879** ■ | 5,485 | 910 | 82 | 60 | **8** | >99 |
| Deaths | 951 | 1,474 | 1,054 | NR | **3,145** | 221 | 60 | 16 | 2 | **9** | >99 |
| **Measles** | | | | | | 486,799 | | | | | |
| Incidence | >469,924 | 419,465 | 291,162 | 222,375 | 683,077 | | **481,530** ■ | 62,705 | 32,275 | **24,374** | 95 |
| Deaths | 9,302 | 3,930 | 659 | NR | 618 | 389 | **408** | 81 | 24 | **20** | 95 |
| **Mumps** | | | | | | | | | | | |
| Incidence | NR | NR | NR | NR | NR | NR | NR | **152,209**[5] ■ | 74,215 | **59,647** | 61 |
| Deaths | NR | NR | NR | NR | NR | NR | NR | **37** | 16 | **8** | 78 |
| **Rubella** | | | | | | | | | | | |
| Incidence | NR | NR | NR | NR | NR | NR | NR | **46,898** ■ | 25,549 | **16,652** | 64 |
| Deaths | NR | NR | NR | NR | NR | NR | NR | **16** | 14 | **21** | 0 |

[1] Year of vaccine license

[2] Figures calculated from rates per 100,000: 105.7 million population in 1920
122.8 million population in 1930
131.7 million population in 1940

■ Denotes time period during which immunization program was instituted

[3] Per cent reduction since onset of immunization

[4] All data with > represent fewer than all states reporting

[5] 1968 data

NR: Not reported

From CDC Morbidity and Mortality Weekly Report Annual Summarie (US-DHEW)

*Table 3. Incidence and deaths of major bacterial diseases without existing immunization programs (U.S. 1947–75)*

| Disease | Parameter | Case reports in year 1947 | 1952 | 1957 | 1962 | 1967 | 1972 | 1975 | Reduction per cent[1] |
|---|---|---|---|---|---|---|---|---|---|
| Gonorrhea | Incidence | 380,666 | **253,839** | 214,496 | 263,708 | 404,836 | 767,215 | **999,937** | **0** |
| | Deaths | ND | **45** | 21 | 23 | 11 | 8 | **1** | **98** |
| Streptococcal complex | Incidence | 93,595 | **113,677** | 233,400 | 323,786 | 457,336 | 436,632[2] | ND | **0** |
| | Deaths | ND | **3,517** | 2,013 | 652 | 423 | 196 | **170** | **95** |
| Syphilis (all stages) | Incidence | 355,592 | **169,198** | 123,758 | 126,245 | 102,581 | 91,149 | **80,356** | **77** |
| | Deaths | ND | **5,719** | 3,825 | 2,811 | 2,381 | 344 | **272** | **95** |
| Salmonellosis | Incidence | 951 | **2,596** | 6,693 | 9,680 | 18,120 | 22,151 | **22,612** | **0** |
| | Deaths | ND | **42** | 60 | 62 | 63 | 68 | **67** | **0** |
| Bacillary dysentery | Incidence | 17,048 | **23,197** | 9,822 | 12,443 | 13,474 | 20,207 | **16,584** | **3** |
| | Deaths | ND | **334** | 156 | 134 | 62 | 69 | **69** | **79** |
| Meningococcal Infections | Incidence | 3,420 | **4,884** | 2,691 | 2,150 | 2,161 | 1,323 | **1,478** | **57** |
| | Deaths | ND | **1,386** | 785 | 649 | 635 | 350 | **308** | **78** |

ND: No data [1] Per cent as of 1952 [2] Data 1970
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*Table 4. Overall change in incidence and mortality of all major communicable diseases with and without immunization programs*

| Year report | Diseases without Bacterial Disease | Death | Immunization Viral (hepatitis) Disease | Death | Diseases with immunization Disease | Death |
|---|---|---|---|---|---|---|
| 1952 (VL)[1] | 567,448 | 11,047 | 17,428 | 794 | 1,383,125 | 112,020 |
| 1975 | 1,557,599 | 887 | 56,134 | 612 | 138,080 | 7,758 |
| Incidence in 1975 | 275 % | 8 % | 322 % | 77 % | 10 % | 7 % |

(VL)[1]: year of vaccine license for diseases with immunization

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*Table 5. Occurrence of HswN1 antibody in various age groups* [52]

| Age group | n | Percent with HAI AB to: A/Swine/31 | A/NJ/76 | A/Vic/75 |
|---|---|---|---|---|
| 17–24 | 710 | 3.8 | 5.5 | 65.0 |
| 25–34 | 864 | 20.2 | 15.4 | 59.0 |
| 35–51 | 716 | 37.0 | 28.1 | 52.5 |
| ≧52 | 899 | 92.2 | 94.9 | 58.0 |

*Parkman, P. D.*, et al., 1977, J. Inf. Dis. *136*, S722–S730.

*Table 6. Antigenicity of influenza virus vaccines containing 30 µg HA/Dose (IEP)* [46]

| Vaccine | Percent Seroconversion (≧1/40) Whole virus | Split Virus |
|---|---|---|
| 1 | 82 | 45 |
| 2 | 50 | 35 |

*Mayner, R. E.*, et al., DBS *39*, 169–78 (1977).

fluenza virus vaccines are tested in individuals who have had prior contact with influenza viruses of more or less similar antigenic composition. Thus, one often deals more with an anamnestic-like response than with a true primary immune reaction: not a very practical way to test the antigenic potency of influenza vaccines. Past vaccination failures, of course, are no reason to doubt the usefulness of influenza immunoprophylaxis unless one can demonstrate that the vaccines then employed had been antigenic.

**Antigenicity of Available Types of Influenza Vaccines**

With the swine influenza scare in 1976 and the resulting US National Influenza Immunization Program [57] it became possible to test, maybe for the first time on such as scale, influenza vaccines in a large susceptible population. Under this program A/New Jersey/76 (HswN1) vaccines were produced[1], tested and distributed to wide segments of the population. Results of this work are summarized in a supplement to the Journal of Infections Diseases (December 1977). The study consisted of a population of greater than 7500 individuals of which about 3500 were less than 25 years old [71, 52].

The following data are extracted from these studies and are limited to the population below the age of 25, of which about 95 % appeared not to have had prior contact with the HswN1 influenza A subtype as indicated by absence of antibody to this virus *(Table 5)*. This study showed that the whole virus vaccines were much more antigenic than the split vaccines. Indeed, 200 CCA units of the whole virus vaccines produced a level of immunity which even four times as much split virus antigen (800 CCA/dose) could not reach *(Fig. 6)*. Moreover antibody levels induced by the split virus

[1] Whole virus vaccines (Merck, Sharp, and Dohme; Merell-National) and split virus vaccines (Parke, Davis; Wyeth).

vaccine barely reached a geometric mean titer of 1:20 and this only when 800 CCA units per dose were given *(Fig. 7)*.

Not only are whole virus vaccines more efficient in stimulating antibody development, they also stimulate a different type of response. They produce IgM antibody, which is an early immune response to infection, in man [7] as well as in rabbits [24]. IgM has greater avidity and wider cross reactivity than IgG and binds more effectively and to a wider spectrum of influenza virus variants than IgG antibody [66].

Finally, antibody induced by the whole virus persists longer than that developing after vaccination with the split vaccine. Thus, antibody levels of $\geqq 1/40$ persisted in 13/15 children given one dose of whole virus for more than nine months, while none of 16 children vaccinated twice with split vaccine had any antibody after that time period [51]. All this points to the likelyhood, as already suggested by *Berendt* [4], that whole virus induces an immune cell population different to that stimulated by split virus antigens.

In view of its greater antigenicity, whole virus was added to subunit vaccines. In both, animal and man, this resulted in higher conversion rates and antibody titers [42, 28, 4, 65].

These described differences were not due to differences in assayability of the different vaccines. It had been suggested that haemagglutination might not be a reliable measure of antigenic content especially for split vaccines of different manufacture [17, 50, 3].

*Mayner* et al. [46] correlated therefore antigenicity with haemagglutinin content as measured by quantitative immunoelectrophoresis [41] and demonstrated again the antigenic superiority of whole virus vaccines *(Table 6)*.

Nor were these differences a result of the particular lots or vaccine strains used in the US National Influenza Immunization Program. Better antigenicity of one dose of whole virus vaccine against a dose of split vaccine was reported with a vaccine made from influenza A/Ann Arbor/31 [72]. *Stones* [64] found that in 13- to 19-year old schoolboys nearly twice as many

*Fig. 1. Decrease in poliomyelitis incidence with increasing use of the vaccine* [14].

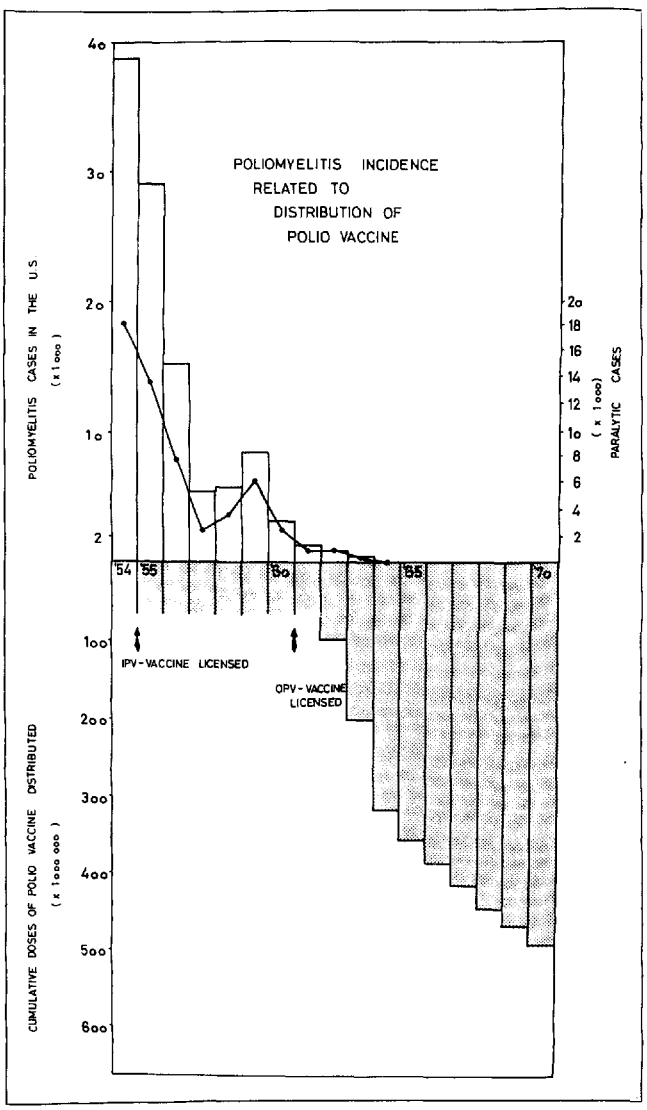
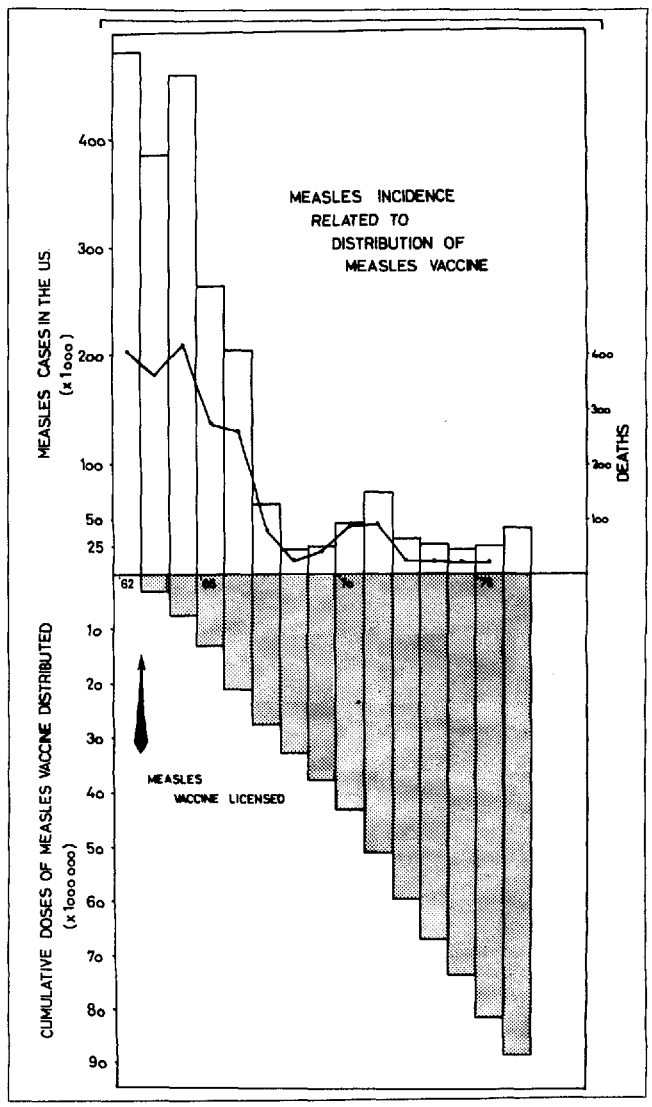



*Fig. 2. Decrease in measles incidence and deaths with increasing use of the vaccine* [12].



developed antibody when given the whole virus vaccine than when given a split product and antibody mean titers were four times as high. A vaccine, consisting of selectively solubilized haemagglutinin and neuraminidase [2] was markedly less antigenic than the whole virus control vaccine [39]. Today's A/USSR/77 vaccine has also been shown to be more antigenic in the whole virus form than when split [68].

That whole virus vaccines might be more antigenic than the ones made from split virus is not new [65, 24, 42]. Whole virus vaccines induce higher antibody titers in mice and hamsters than the split products [47], and provide greater protection *(Fig. 8)* against a challenge lethal to nonvaccinated mice [22]. The same was observed in rabbits, where antibody was not only higher in quantity but also was more avid for the inducing antigen [65]. Of squirrel monkeys, only those developed significant haemagglutination inhibiting antibody which had received the whole virus vaccine. After challenge only they showed a typical anamnestic response.

*Fig. 3. Decrease of rubella incidence with increasing use of the vaccine* [10].

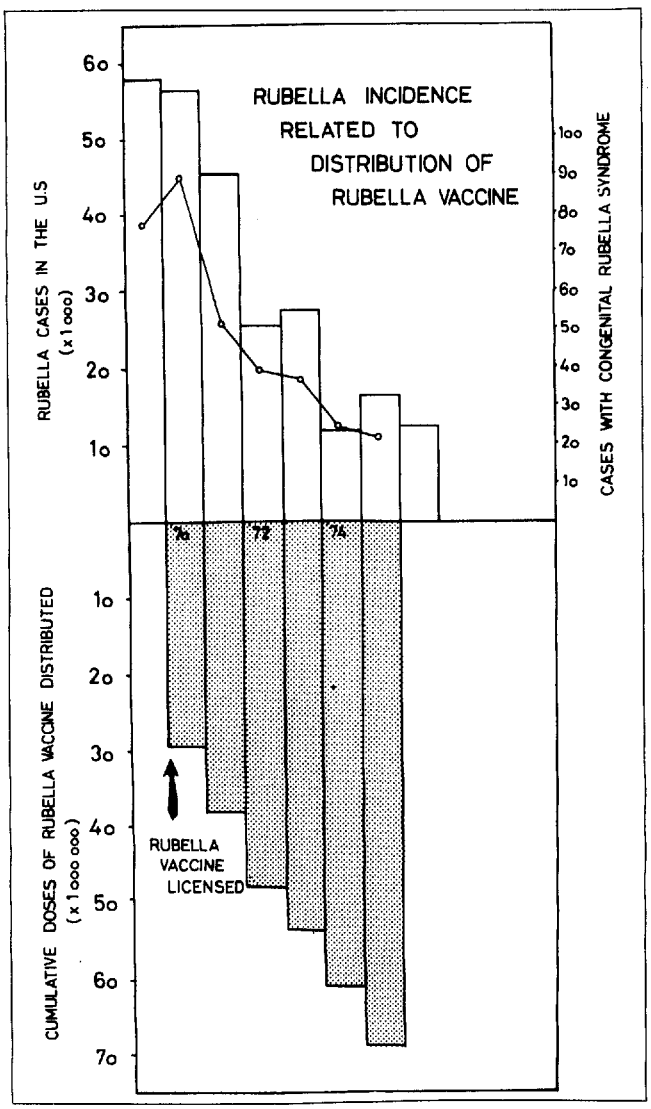



*Fig. 4. Decrease of mumps incidence with increasing use of the vaccine* [9].

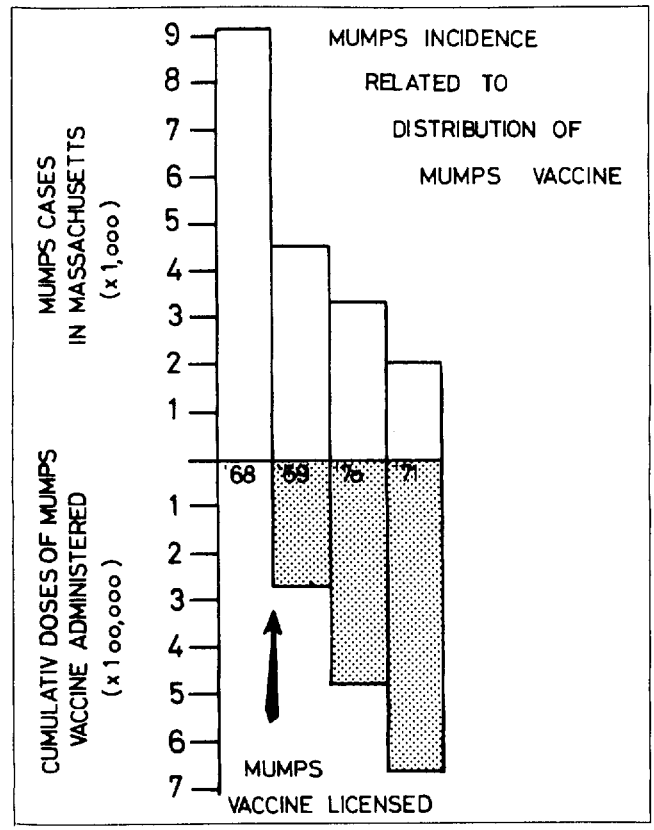
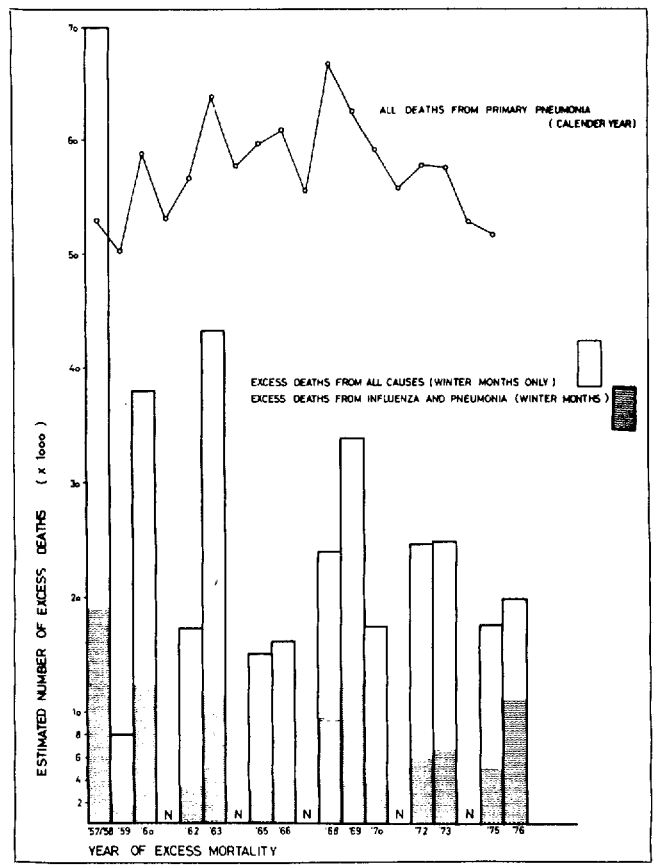



*Fig. 5. Effect of influenza on the number of deaths ascribed to other causes* [11].



The group with single or double doses of 400 CCA of the split vaccine had little or no immunologic memory for the haemagglutinin antigen and behaved "much like the placebo controls" after challenge [4].

One of the main reasons for the development of split vaccines was the reactogenicity of the original unpurified whole virus vaccines. Of course, with today's density-gradient purified vaccines this is no longer of great concern. The side reactions may be local (redness, swelling, enduration, pain) and systemic (malaise, fever, headache). *Fig. 9* summarizes the reaction rates observed with the two types of vaccine [52, 19]. Obviously, reactions increased with the amount of antigen in a dose. Of the twelve vaccines compared, eleven had produced a "systemic" reaction grade of less than "1" (this grading system attributes "1" to 1 ° temperature rise above normal and/or to mild systemic reactions, in a scale of 0–3). The twelvth contained 800 CCA of whole virus per dose. Local reactions remained insignificant and varied only little from vaccine to vaccine [19]. In all, only two allergic reactions were reported [52].

In *Fig. 10* we have assorted according to their antigenic efficacy all vaccine and dosage forms which were employed in the population 6-months to 18-years old. The most potent split vaccine (800 CCA) produced a conversion rate just barely above 40 %. If we want to immunize at least 50 % we must give 100–200 CCA units of a whole virus vaccine. *Fig. 11* gives the same information for those 17- to 24-years old. The only split vaccine with conversion rates greater than 35 % was one containing 800 CCA of antigen. Clearly, there are slightly greater reactions with the whole virus vaccines, but are these reactions indeed so important compared with the much greater antigenicity of these vaccines? Sufficient antigenicity to immunize with one dose is of particular importance in the face of a rising epidemic where one must be able to produce vaccine quickly, deliver it efficiently, and immunize with the first dose especially those who are not primed by some prior antigenic experience. Unfortunately, not even the most effective influenza vaccine will guarantee a

*Fig. 6. Conversion rates in susceptible vaccinees given one dose of vaccine* [52, 71].

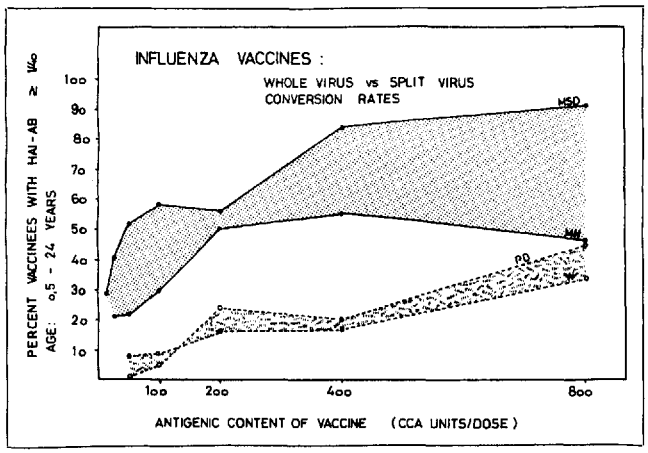



*Fig. 7. Antibody levels in susceptible vaccinees given one dose of vaccine* [52, 71].

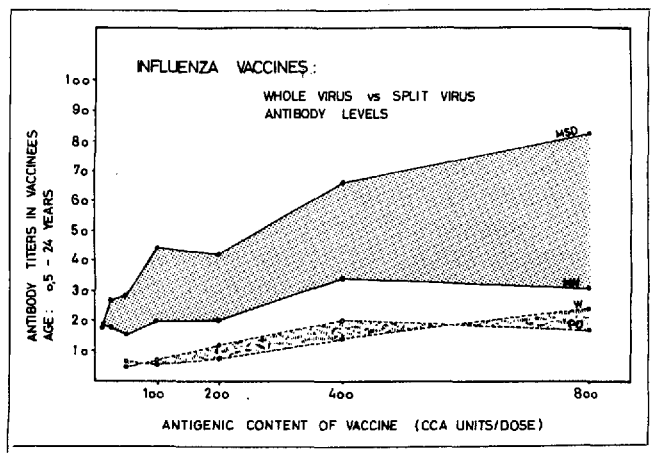



*Fig. 8. Protective effects of influenza vaccines in mice* [22].

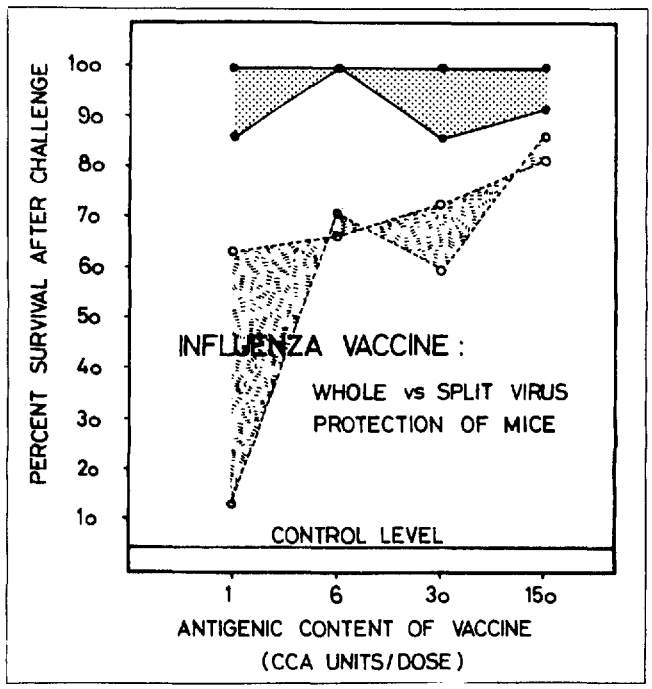
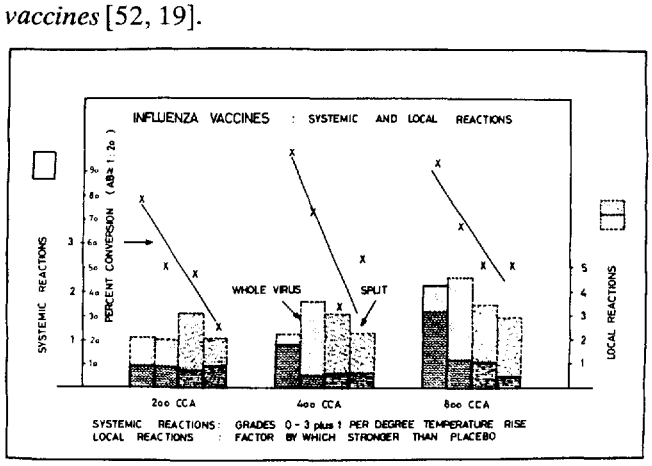



*Fig. 9. Reaction rates in susceptible vaccinees after one dose of vaccine in relation to conversion rates with those vaccines* [52, 19].



response in everyone vaccinated with one dose, but at least the chance that this should happen is considerably greater with the more potent vaccines.
During the course of this immunization campaign an increased incidence of Guillain-Barré syndrome cases was noticed in A/New Jersey vaccinees and ascribed to the use of vaccine. The incidence was approximately 1:100,000. At a 5–10 % rate of fatality or permanent damage after Guillain-Barré this suggests the possibility of one permanent injury or death among one to two million vaccinations [13, 48]. The exact correlation of Guillain-Barré incidence with influenza vaccine use is not clear, although it has been reported that attack rates in vaccinated individuals were 7.5 times that in nonvaccinated ones [5]. Incidence reports in nonvaccinated individuals are a function of severity of the disease and one's own decision to see a physician. Close self-observation of those vaccinated in a public widely sensitized to this problem, on the other hand, may have produced an overreporting of even the mildest cases that otherwise might have gone undetected. It is also known that virus infections in general may be occasionally involved in the etiology of this syndrome. One should therefore look at the incidence of Guillain-Barré after an acute infection with wild influenza which will set, as is known, a much greater antigenic stimulus than any vaccine could.

**Comment**

We have seen that vaccine use results in the reduction of infectious disease incidence. Smallpox is a pertinent example. Moreover, the occurrence of poliomyelitis in populations which do not permit vaccination is striking evidence for the need to vaccinate [70].
Why then only limited effects of vaccination against influenza? First, we do not vaccinate–except for selected segments of the population. Then, when we do vaccinate, we do not appreciate the differences between the antigenic potentials of available vaccines and the importance of antigenicity for an effective and lasting immune response. Moreover, not all influenza-like illness is caused by influenza virus [54] although, by inference [59, 60, 61], one can say that at least 50 % are due to the virus. Obviously, one can not expect to protect the other 50 % even with effective influenza virus vaccines. Finally, we must consider the vaccinee and the preparedness of his immune response system to react to the vaccine antigen. If unprepared ("unprimed") it may not respond to a split virus vaccine and if primed it may first produce an anamnestic response to the priming antigen before it does to the vaccine antigen proper [26, 23]. Obviously, our immunoprophylactic expectations must be directed at influenzavirus induced or -accelerated illnesses and deaths, and can be fulfilled only if antigenic vaccines are employed as extensively as other virus vaccines.
To express the magnitude of influenza in monetary terms, *Kavet* [34] has analyzed the costs involved *(Table 7)* and came up with estimates of 3.1 billion dollars for the 1962–3 epidemic in the US (27 million cases with nearly 32 million lost workdays), 1.7 billions for the 1965–6 epidemic (22 million cases, 20 million lost workdays), and 3.9 billion for the 1968–9 epidemic (51 million cases, 66 million workdays lost). Certainly sufficient justification for instituting the US National Influenza Immunization Program at a cost of 135 millions, and certainly enough reason for public health authorities to think again about influenza.
Here and there, industry has recognized the importance of lost productivity and has instituted yearly immunization plans. The Swiss Federal Government has a voluntary program for public service employees of vaccination with whole virus vaccines. In those vaccinated, absences due to influenza-like illness were reduced by one half and absences due to less well-defined "short duration illness" by one quarter to one third [59–61]. Since, obviously, not all influenza-like illnesses are due to influenza virus, we must assume that the direct effectiveness of these vaccines against true influenza was even greater than expressed by the given percent protection over all influenza-like illness. We can moreover conclude that at least 25–30 % of ill-defined short-term diseases were due to influenza virus and thus preventable.
As mentioned above, our present efforts against influenza are too little, too late, and often with inadequate means. A more positive approach would be to vaccinate regularly with antigenic vaccines not only those at risk, but to lay as broad and as durable a base of immunological preparedness as possible. In many influenza epidemics attack rates are higher in the young [26, 40, 33, 29]. This may be due to the fact that they have had fewer antigenic experiences than the older population and that they are concentrated in kindergardens, schools, universities, and scout camps, and more likely to be infected. Thus, a logical approach to prevent the initial infection and to break the chain of dissemination would be to vaccinate in addition to those at high risk, the population at large and, in particular, schoolchildren, thereby also protecting their high-risk contacts. This has worked well, as we have seen, with many others infectious diseases, and there is no good reason why this strategy should not be tried.

The reasons for not doing wide scale immunization campaigns are apathy to influenza and the assumption of poor antigenicity and high reactogenicity of the available vaccines, as well as short duration of vaccine-induced immunity, antigen variability and short supply of the required antigenic components. One should be able to deal with public apathy by appropriate education of what influenza vaccines can and can not do and by the development of an understanding for the toll influenza takes each year. The objection of poor antigenicity of influenza vaccines and short duration of immunity is more the result of a lack of understanding for the available vaccines and their antigenic capabilities. Reports of the reactogenicity of influenza vaccines are often colored from the occasional incident and, of

course, from historical evidence with first generation nonpurified vaccines.

As to antigen variability and short supply of vaccines, they are less of a problem for whole virus vaccines with their greater stimulative power: less antigen is needed, a broader range of antigenic variants is covered, and antibody persists longer and at higher levels.

In this context one must also question the eagerness of changing vaccines with every minor change in antigenicity. *Davenport* [18] has suggested that we were overreacting in our efforts to be up to date with the latest influenza variant. Three different vaccines had to be made in the decade between 1957 and 1967 without any evidence that the latest vaccine substitute was any better or more specific then the previous two. Lately the replacement of the broadly antigenic Port Chalmers variant of the $H_3N_2$ prototype of influenza A by a variety of later variants with narrower specificities [11] has little practical or scientific basis. Instead of having to wait for yearly new WHO decisions, discarding millions of doses of "old" vaccine, and having to tool up for the new vaccine, manufacturers could be producing the vaccine quantities necessary for a generalized broad-scale public health immunization program.

This concept is finding new interest with the increasing likelihood that the antigenic variability of influenza virus may be finite *(Table 8)*. Then, one could see a vaccine assorted as needed with senior antigens of the available major influenza subtypes to be given year round to the general population, providing a relatively broad base of immunity to influenza viruses.

*Fig. 10. Antigenic efficacy of influenza vaccines given once [71].*

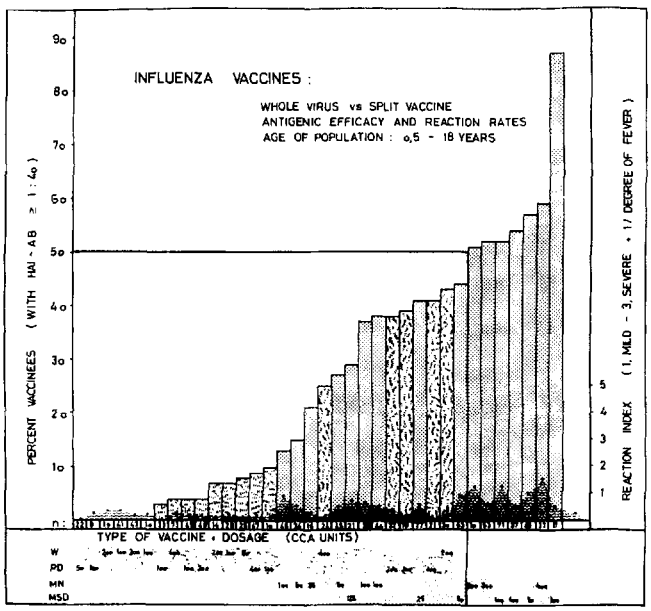



*Fig. 11. Antigenic efficacy of influenza vaccines given once* [52].

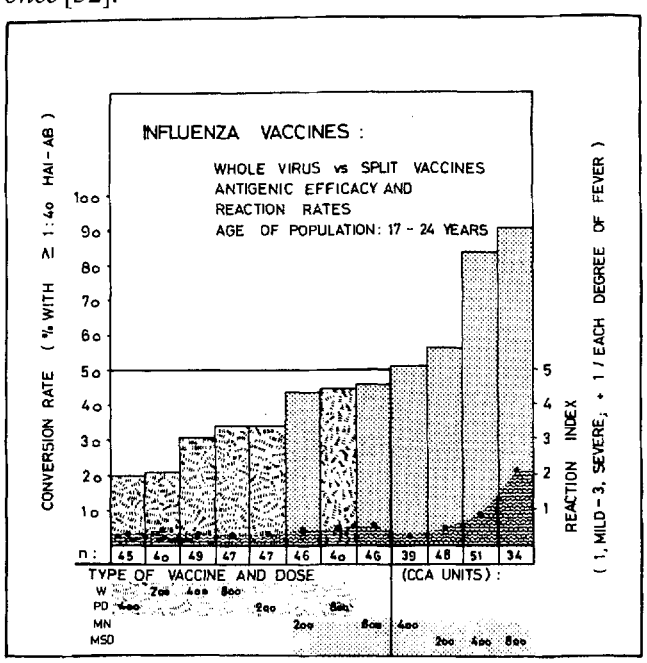



*Table 7. Economic impact of influenza in the United States* [34]

| Epidemic | Cases reported | Work days lost | Total excess deaths | Cost[1] |
|---|---|---|---|---|
| 1962–3 | 27,140,000 | 31,750,000 | 48,901 | 3148 |
| 1965–6 | 21,748,000 | 20,608,000 | 20,621 | 1681 |
| 1968–9 | 51,155,000 | 66,210,000 | 27,495 | 3880 |

[1] Cost (millions US$), include direct (medical) an indirect (productivity) cost estimates (based on costs in 1968)

*Kavet, J.*, Am. J. Publ. Health *67*, 1063–70 (1977).

*Table 8. Recycling of influenza HA antigen subtypes* [36]

| Subtype | Year of prevalence | | |
|---|---|---|---|
| HswN1 | | 1918 | (1976)[1] |
| HoN1 | | 1929 | |
| H1N1 | | 1946 | 1977 |
| H2N2 | –1889 | 1957 | |
| H3N2 | 1889– | 1968 | |

( )[1] Remained localized to New Jersey incident

*Masurel, N.*, and *Marine, W. M.*, Am. J. Epidem. *97, 44–49 (1973).*

**Summary**

One of the most important and most lasting benefits of medicine to human health and health expenditure is the controlled immunological interruption of the vicious cycle of infectious disease such as smallpox, poliomyelitis, yellow fever, measles. Smallpox, with globally more than 2.5 million cases ten years ago, is gone. The incidence of infectious diseases with available immunoprophylaxis has been reduced by 90 % over the past two decades, while the incidence of diseases without vaccine has nearly tripled.

By contrast, influenza, a disease against which there have been vaccines in existence for many years, demands more deaths than any other infectious disease. Reasons for this failure of influenza immunoprophylaxis are discussed and suggested to include: indiscriminate use of available vaccines of which some types are much less antigenic than others, the disappointment that influenza virus vaccines will not protect against influenza-like illnesses caused by noninfluenza

virus pathogens and the concomitant indiscriminate rejection of all influenza vaccines as being of doubtful value; superficial vaccination policies which aim at narrow populations, leaving those most likely to spread the virus the full potential to do so; the unjustified fear of side reactions following vaccination which are considerably less severe than the disease this vaccination is attempting to prevent.

**Zusammenfassung**

**Impfung gegen Viruskrankheiten**

Einer der wichtigsten und dauerndsten Gewinne der Medizin für die menschliche Gesundheit und die damit verbundenen Ausgaben war die immunologische Unterbrechung der Verbreitung infektiöser Krankheiten, wie Pocken, Kinderlähmung, Gelbfieber, Masern. Die Pockenkrankheit, noch vor zehn Jahren mit etwa 2,5 Millionen Kranken weltweit, existiert heute nicht mehr. Das Vorkommen infektiöser Krankheiten, für die Impfstoffe verfügbar sind, ging im Laufe der vergangenen Jahrzehnte um 90 % zurück, während jenes infektiöser Krankheiten ohne mögliche Immunprophylaxe sich nahezu verdreifachte.

Demgegenüber verlangt die influenzavirusverursachte Grippe heute soviel Todesfälle wie eh und je, und zwar mehr als jede andere Infektionskrankheit. Die Ursachen für das Versagen der Immunprophylaxe für Influenza werden diskutiert und angedeutet: die wahllose Anwendung vorhandener Influenzaimpfstoffe, von denen einige Arten viel weniger antigen sind als andere, die enttäuschende Beobachtung, dass die Immunisierung mit Influenzavirusimpfstoff nicht gegen grippeartige Erkrankungen anderer Ursachen schützen kann und die damit verbundene Verwerfung aller Influenzavirusimpfstoffe als ungenügend; beschränkte Impfpolitik, die nur auf eng begrenzte Personenkreise zielt und dabei die Bevölkerung, welche für die Verbreitung des Virus verantwortlich ist, ausser acht lässt; die ungerechtfertigte Angst vor Impfreaktionen, die sicherlich weniger schwerwiegend sind als die Krankheit, welcher die Impfung vorzubeugen sucht.

**Résumé**

**La vaccination contre les maladies virales**

L'un des bénéfices les plus importants et plus continus de la médecine en faveur de la santé de l'humanité et des dépenses en connexion était l'interruption immunologique du cercle vicieux de maladies infectieuses telles que variole, poliomyélite, fièvre jaune, rougeole. La variole, globalement avec 2,5 millions de malades il y a dix ans, n'existe plus aujourd'hui. La fréquence de maladies infectieuses contre lesquelles on a des vaccins à disposition, a été réduite de 90 % au cours des dernières décennies, tandis que la fréquence de maladies infectieuses sans vaccin correspondant a presque triplé.

Par contre, la grippe causée par le virus d'influenza exige toujours beaucoup plus de morts que toute autre maladie infectieuse. Les causes de cette défaillance de la prophylaxie immunologique contre la grippe sont discutées: l'usage au hasard de vaccins anti-influenza disponibles, dont quelques-uns sont beaucoup moins antigéniques que d'autres, le fait que l'immunisation avec le vaccin anti-influenza ne peut pas protéger contre des maladies grippales d'autre origine et par conséquente le rejet de tous vaccins antigrippaux comme insuffisants; une politique de vaccination superficielle qui ne vise qu'une catégorie de personnes limitée et qui néglige en même temps la population responsable de la dissémination du virus; la peur injustifiée de réactions vaccinales certinament moins graves que la maladie que cette vaccination cherche à prévenir.

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