Influenza Vaccine: Review of Effectiveness of the U.S. Immunization Program, and Policy Considerations

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ABSTRACT

A number of studies have reported that influenza vaccine (IV) administration has been less than optimally effective in certain subpopulations. This study examines yearly influenza death rate, yearly influenza case rate, and yearly rate of hospitalizations with influenza as the first-listed discharge diagnosis. By these measures, the yearly U.S. mass influenza vaccination campaign has been ineffective in preventing influenza in vaccine recipients. The use of antiviral drugs to treat influenza, in light of the potential for an influenza pandemic, needs further consideration.

Background

Vaccines are one of the great public-health triumphs of the 20th century.[1]

Vaccination began in the late 18th Century with Dr. Edward Jenner's inoculation of people with the much less deadly cowpox virus to protect against deadly smallpox because he noticed that milkmaids, who had had cowpox, did not contract smallpox.[2] The widespread use of vaccines to prevent infectious disease is based on the long-known observation that, for many infectious diseases, people who recover from having an infectious disease develop a long-term immunity against that disease.[3]

Influenza is inherently different from the common vaccine-preventable diseases. An individual who recovers from influenza usually does not acquire resistance to other strains of influenza virus. Through genetic drift, the immunological determinants change, enabling the virus to escape the adaptive immunological defenses of the host. Every few years, this produces a significant change called a genetic shift.[4]

The influenza vaccine program is the first that seeks to offer population-wide protection against a disease that undergoes such rapid antigenic changes. It therefore differs from other vaccine programs in many significant ways. First, because it takes many months to produce sufficient vaccine to protect a large population, an educated guess has to be made as to which strain(s) of influenza will be endemic in the following influenza season. This guess must be made well before there is an outbreak of cases of influenza. Second, influenza vaccine has to be made and administered without specific efficacy testing, which, in other viral vaccines, includes some double-blind field trials against the wild-type disease. Third, there is no time to fully test each newly made influenza vaccine for its safety, especially with respect to its long-term rarer side effects.

The Centers for Disease Control and Prevention (CDC) has recommended the administration of influenza vaccine during the 2006-2007 influenza season to the following persons:[5]

- children aged 6 to 59 months;
- women who will be pregnant during the influenza season;
- persons aged $\geq$ 50 years;
- children and adolescents (aged 6 months to 18 years) who are receiving long-term aspirin therapy and, therefore, might be at risk for experiencing Reyes syndrome after influenza infection;
- adults and children who have chronic disorders of the pulmonary or cardiovascular systems, including asthma (hypertension is not considered a high-risk condition);
- adults and children who have required regular medical follow-up or hospitalization during the preceding year because of chronic metabolic conditions (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunodeficiency (including immunodeficiency caused by medication or human immunodeficiency virus);
- adults and children who have any condition (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions, or that can increase the risk for aspiration;
- residents of nursing homes and other chronic-care facilities that house persons of any age who have chronic medical conditions;
- persons who live with or care for persons at high risk for influenza-related complications, including healthy household contacts and caregivers of children aged 0 to 59 months;
- healthcare workers;
- any person who wishes to reduce the likelihood of becoming ill with influenza or transmitting influenza to others should they become infected.

Simonsen et al. from the National Institute of Allergy and Infectious Disease have recently studied influenza-related mortality in the U.S. over the past three decades.[6] They found that the influenza mortality rate in the over-65 age group has increased despite a concurrent jump in vaccination rates in that group from 15% in 1980 to 65% in 2001. The Simonson article used mathematical models to correct for the effects of aging of the population as well as for the variations in the virulence of the influenza strains prevalent in the population. Even with these corrections, the authors concluded that the mortality-reduction benefits of influenza vaccination may be substantially less than previously thought.

The mortality reduction found in several observational studies, which compare cohorts of vaccinated and unvaccinated people, reflects systematic bias, in the opinion of Simonsen et al. The unvaccinated groups had a disproportionate number of very ill people. People in fragile health right before the influenza season, suggested Simonsen et al., are more likely to die and less likely to

Table 1. Raw Data Employed for Analysis in the Present Study

Year	Estimated United States Population*	Total Net Number of Influenza Vaccine Doses Distributed†	Influenza Vaccine Percent Population Coverage [IVPPC]	Influenza Death Rate‡ (per 100,000 persons) [Total Number]	Influenza Case Rate‡ (per 100 persons) [Total Number]	Influenza First-Listed Hospital Discharge Rate‡ (per 10,000 persons) [Total Number]
1979§	225,055,487	18,270,794	8.1	0.3 [604]	-	-
1980	227,224,681	12,425,890	5.5	-	-	-
1981	229,465,714	19,829,170	8.6	1.3 [3,006]	-	-
1982	231,664,458	16,959,690	7.3	-	33 [74,925,000]	-
1983	233,791,994	17,877,970	7.6	0.6 [1,431]	38 [87,299,000]	-
1984	235,824,902	19,179,060	8.1	-	45 [103,440,000]	-
1985	237,923,795	20,700,761	8.7	0.9 [2,054]	40 [94,409,000]	-
1990	249,464,396	27,076,206	11	-	43 [106,807,000]	1.8 [44,000]
1991	252,153,092	32,809,662	13	0.4 [1,137]	52 [129,583,000]	1.0 [26,000]
1992	255,029,699	40,352,367	16	-	43 [107,309,000]	0.5 [13,000]
1993	257,782,608	42,980,814	17	0.4 [1,044]	52 [132,633,000]	1 [25,000]
1994	260,327,021	60,084,728	23	-	35 [90,447,000]	1.2 [31,000]
1995	262,803,276	36,512,538	14	0.2 [606]	41 [108,009,000]	0.7 [19,000]
1996	265,228,572	38,915,520	15	0.3 [745]	36 [95,049,000]	0.8 [21,000]
1997	267,783,607	40,996,883	15	0.3 [720]	-	0.7 [19,000]
1998	270,248,003	48,080,122	18	0.6 [1,724]	-	1.3 [34,000]
1999**	272,690,813	60,468,427	22	0.6 [1,665]	-	1.4 [37,000]
2000	281,421,906	65,582,650	23	0.6 [1,765]	-	1.4 [39,000]
			Mean ± SD	0.5 ± 0.3 [1,269 ± 786]	38 ± 13 [94 ± 3.4 million]	1 ± 0.5 [25,667 ± 12,323]

* U.S. Census Bureau
† Biologic Surveillance Summaries of the Centers for Disease Control and Prevention
‡ National Center for Health Statistics
§ Estimates for 1979 through 1998 use International Classification of Diseases, 9th Revision (ICD-9) coding
** Estimates for 1999 through 2000 use International Classification of Disease, 10th Revision (ICD-10) coding

receive the vaccine. Additionally, Kristen Nichols, an epidemiologist with the Veterans Administration in Minnesota, noted that measuring influenza deaths by looking at the "excess mortality" that occurs during a given influenza season is inappropriate because other respiratory illnesses that circulate during the same season can also cause death. Blood tests are rarely done to confirm that ailing persons actually had influenza.[7]

Maeda et al. conducted a prospective trial of healthy infants and young children (6-24 months old) who had received inactivated influenza vaccine before influenza seasons.[8] Age-matched children were randomly assigned as the control. These children were followed up from January to April in each year (2000, 2001, and 2002). Influenza attack rates were not significantly different in the two groups.

Because a number of previous epidemiological studies have raised doubts about the effectiveness of influenza vaccines, large-scale population data need to be reviewed to assess the effectiveness of the mass influenza vaccine campaign in the United States. The present study examines the period from 1979 through 2000.

Materials and Methods

An ecologic method was used. The total number of doses of influenza vaccine distributed/administered each year was determined from the Biological Surveillance Summaries of the CDC for the periods 1979 through 1985, and 1990 through 2000 (CDC, personal communication 2002). In order to estimate influenza vaccine coverage rates in the United States, the U.S. Census Bureau estimates were used for the population of the United States from 1979 through 1985, and 1990 through 2000.[9] Based upon these measurements, the influenza vaccine percent population coverage (IVPPC) was determined for each year examined in this study ([Yearly Total Net Number of Influenza Vaccine Doses Distributed / Yearly Estimated United States Population] x 100 = IVPPC).

The effectiveness of influenza vaccine administration in the United States was studied by evaluating the IVPPC in comparison to three outcomes: (1) yearly influenza death rate (1979, 1981,

Table 2. Number of Influenza Deaths per Year in Children

Year	<1 year-old	1–4 years-old	5–14 years-old
1979	9	8	8
1981	13	8	12
1983	6	8	3
1985	7	6	7
1987	8	6	1
1989	12	8	14
1991	16	15	11
1993	10	14	13
1995	7	7	7
1996	15	3	8
1997	12	10	13
1998	6	3	14
1999	13	12	11
2000	9	10	11
2001	7	6	12
Mean ± SD	10.0 ± 3.2	8.3 ± 3.5	9.7 ± 3.7
Median	9.0	8.0	11.0

Source: National Center for Health Statistics

1983, 1985, 1991, 1993, and 1995 through 2000); (2) yearly influenza case rate (1982 through 1996); and yearly rate of hospitalization with influenza as the first-listed discharge diagnosis (1990 through 2000). The data for these measures were obtained from the National Center for Health Statistics.[10] Table 1 presents a complete summary of the raw data employed. Our sources did not provide data for the years that are not included in our analysis.

The Simple Linear Regression statistical test from StatsDirect (Version 2.4.1) statistical package was utilized for data analysis. The null hypothesis employed in this study was that the IVPPC should have no effect on the measures of effectiveness; in other words, the slope of the line should not be different from zero. In this analysis, the equation of the regression line, the slope of the regression line, the correlation coefficient (r), and the regression coefficient (R^2) value were determined for each statistical test performed. *P*-values and 95% Confidence Intervals (CI) were determined, and a double-sided *P*-value of < 0.05 was considered statistically significant.

Results

From the data shown in Table 1, the mean number of influenza deaths per year in the years studied was 1,269 ± 786 or 5.0 ± 3.3 deaths per hundred thousand, with a median of 1,284 and a range of 604 to 3,006. The mean number of cases of influenza per year was 94 million ± 3.4 million with a median of 100 million and a range of 75 million to 133 million, and the case rate was 37.6% ± 13.2%. The mean number of hospitalizations with a first-listed discharge diagnosis of influenza was 25,667 ± 12,323, with a median of 26,000 and a range of 13,000 to 44,000, and the influenza hospitalization rate of 9.8 ± 4.8 per ten thousand.

From data shown in Table 2, the mean annual number of deaths for children under the age of 1 year was 10.0 ± 3.2, with a median of 9.0 and a range of 6 to 16. The mean annual number of deaths for children from the age of 1to 4 years was 8.3 ± 3.5, with a median of 8.0 and a range of 3 to 15. The mean annual number of deaths for children from the age of 5 to 14 years was 9.7 ± 3.7, with a median of 11.0 and a range of 1 to 14.

In Figures 1 through 3, the IVPPC was plotted on the same time axis as each of the three outcomes measures. Figure 1 displays the

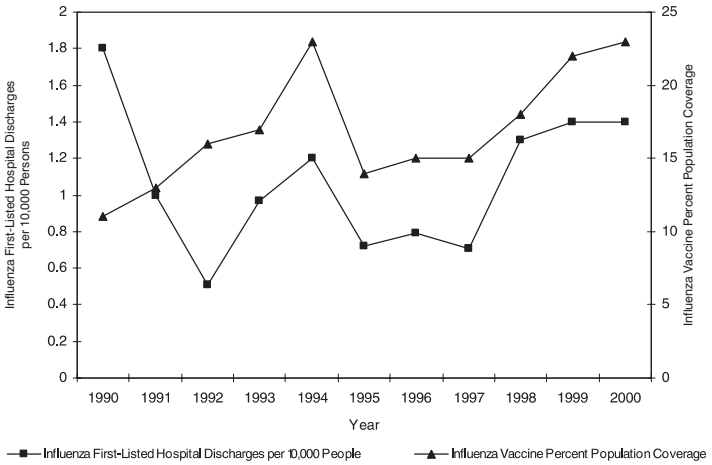

Figure 1. Yearly Rate per 10,000 Persons of Influenza First-listed Hospital Discharge Diagnoses in Comparison to the Influenza Vaccine Population

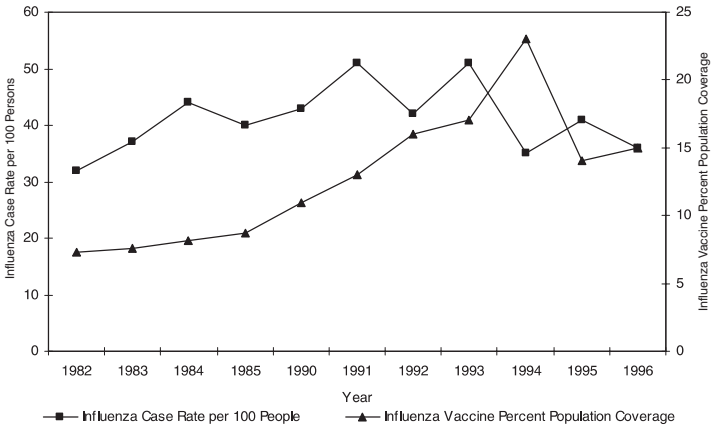

Figure 2. Yearly Rate per 100 Persons of Influenza Cases in Comparison to the Influenza Vaccine Population Percent Coverage

rate per 10,000 persons of influenza as first-listed hospital discharge diagnosis. A linear regression of this rate as the dependent variable with the IVPPC as the independent variable gives the following regression line equation**:**

Influenza as first-listed hospital discharge diagnosis (per 10,000 persons) = 0.021 IVPPC + 0.72.

The regression-line correlation coefficient was 0.22 (95% correlation-coefficient CI = -0.44 to 0.72, $R^2 = 0.048$, $P = 0.52$).

In Figure 2, the rate per 100 persons of influenza cases is displayed over time. The regression line equation for this rate versus IVPCC is:

Case Rate (per 100 people) = 0.010 IVPPC + 40.

The regression correlation coefficient for the regression line was 0.08 (95% correlation-coefficient CI = -0.55 to 0.65, $R^2 = 0.006$, $P = 0.82$).

Figure 3 plots the rate of influenza deaths per 100,000 persons, along with the IVPCC. The regression line equation is:

Death rate (per 100,000 persons) = -0.015 IVPPC + 0.75.

The regression line correlation was -0.25 (95% correlation-coefficient CI = -0.72 to 0.38, $R^2 = 0.062$, $P = 0.43$).

Discussion

Between 1979 and 2000, influenza vaccine was shown to have little or no effectiveness over the U.S. population for preventing

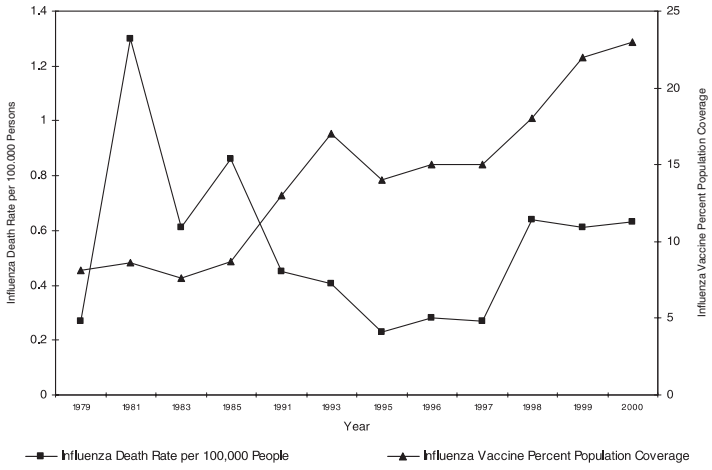

Figure 3. Yearly Rate per 100,000 Persons of Influenza Deaths in Comparison to the Influenza Vaccine Population Percent Coverage

influenza cases, deaths, or hospital admissions. Influenza vaccination was correlated with a decreased number of deaths, but this correlation (of approximately 6.2%) was not statistically significant. For the other two measures, there were nonsignificant correlations between increasing influenza vaccination coverage and increasing numbers of influenza cases (0.6%) and influenza hospital discharge diagnoses (4.8%).

Influenza case rates and death rates are significantly influenced by the virulence and transmissibility of the viral strains prevailing during the influenza season. The efficacy of the vaccine is of course dependent in large part on the accuracy of the antigenic matching. Our methodology is not capable of sorting out these effects but only of assessing the overall gross impact of the U.S. immunization program as implemented.

The results of the present study appear to be similar to those obtained by the CDC in a recent analysis of the population efficacy of the 2003-2004 influenza vaccine.[11] The CDC determined that immunization with the 2003-2004 influenza vaccine offered negligible population protection against developing influenza-like illnesses, and that in some of their methods of analysis there were results, which, though not significant at the 95% confidence level, indicated that influenza vaccination was associated with an increased risk of developing influenza-like illnesses.

Our results also appear to be similar to those observed by Demicheli et al. in their meta-analysis of published studies to assess the effectiveness of influenza vaccines in preventing cases of influenza in healthy adults.[12] These researchers determined that the yearly recommended influenza vaccines had low effectiveness against clinical influenza cases, and minimally reduced lost work time. Demicheli et al. concluded that universal immunization of healthy adults with influenza vaccine is not supported.

The poor effectiveness shown by the present study is particularly troubling in view of the cost of the influenza vaccine program. If it were recommended that every person be vaccinated annually against influenza, full implementation would require giving approximately 300 million doses annually in the United States. At $25 per dose, this would cost $7.5 billion per year for the vaccine alone.

To this must be added the cost of administration. Since the summer of 2005, influenza vaccine for both adults and children has been covered under the no-fault National Vaccine Injury Compensation Program (NVICP), which is administered by the United States Claims Court.[13] By statute (42 U.S.C. 300aa-25), each patient receiving an influenza vaccine must be seen in a medical setting in order to: (a) create a medical record or update existing visit records; (b) discuss and document the informed consent issues involved; (c) administer the vaccine; (d) record the lot number, expiration date, and manufacturer of the vaccine in the medical record; (e) follow up and report any adverse reactions to the Vaccine Adverse Event Reporting System (VAERS); and (f) record the follow-up information in a medical record. These requirements seem to preclude administration of influenza vaccine in non-medical settings such as in department stores, supermarkets, parking lots, etc., as has often been the practice with influenza vaccine in the past. A modest charge of $50 for the required visit would increase the cost of each dose of vaccine to $75 per person or $22.5 billion for the whole population.

Just considering children, the annual cost of two 0.25 mL doses of the influenza vaccine to the approximately 4 million eligible children under one year of age would be around $600 million. Even if the influenza vaccines were almost 100% effective in preventing deaths for these children, which certainly does not seem to be the case, the cost of preventing the average of 10 deaths per year in children under 1 year of age would be about $60 million per death prevented. When viewed in this way, the real cost of gaining an unsubstantiated benefit from the influenza vaccine in this age group is very high. Moreover, the annual cost to the NVICP of paying compensation for adverse effects would probably increase these estimates substantially, as a number of studies have reported an association between influenza vaccine administration and adverse reactions such as Guillain-Barre syndrome,[14-17] Bell's palsy,[18,19] and systemic vasculitis.[20-22]

Under the current recommendations, a person born today would receive two influenza vaccines in the first year of life and could receive one influenza vaccination every year for the rest of his life. Assuming an average life span of about 75 years, compliant persons would receive around 75 influenza vaccines in a lifetime. No data exist on the safety of receiving a large number of doses of vaccine. Although the influenza viruses change rapidly over the years, they still share many epitopes with each other. The potential risks of receiving so many similar vaccinations include but are not limited to allergic, anaphylactic, hyperimmune, and dysimmune reactions.[23,24]

Another problem with annual influenza vaccinations is that a large proportion of available vaccines currently contain 25 µg of mercury from thimerosal per 0.5 mL dose. Thimerosal is a highly toxic, ethyl-mercury containing compound, which has been found to pose a significant risk to some vaccine recipients.[25-27] The public's awareness of this risk is shown by the passage of statutes that will soon ban the use of thimerosal at other than "trace" levels and/or completely in the states of Iowa, California, Missouri, Illinois, Delaware, New York, and Washington. The presence of thimerosal at preservative levels in influenza vaccine is one of the main reasons for public support of this legislation. Its passage may impede the distribution of influenza vaccines.

An additional reason for caution is the infectiousness of live-virus influenza vaccines, for example, FluMist (MedImmune

Vaccines, Gaithersburg, Md.), a live cold-adapted trivalent nasally administered vaccine, which is currently being recommended for individuals aged 5–49. The probability of acquiring a transmitted vaccine virus following close contact with a single FluMist inoculee is estimated to be 2.4% (95% CI: 0.13-4.6).[32] Vaccine recipients are advised to avoid close contact with immunocompromised individuals for at least 21 days. Persons with conditions such as human immunodeficiency virus infection (HIV), malignancy, leukemia, or lymphoma, and patients who are receiving systemic corticosteroids, alkylating drugs, antimetabolites, radiation, or other immunosuppressive therapies may be placed at significant risk. Other individuals who should avoid contact with a FluMist inoculee include, but are not limited to, pregnant women or adults and children with chronic cardiovascular or pulmonary disorders, including asthma; metabolic diseases, including diabetes; renal dysfunction; or hemoglobinopathies. The widespread use of FluMist would place a significant part of the population at risk, raising serious concerns about the wisdom and ethics of recommending FluMist for use in the general population.

In addition to transmissibility, a live virus vaccine poses the risk that vaccine strains could recombine or re-assort genes in the event that an inoculee contracts a second viral infection, potentially producing a "super virus."

Antiviral Drugs

Given the limited vaccine efficacy and potential adverse effects of mass immunization with influenza vaccine, the role of antiviral drugs needs to be evaluated.

Oseltamavir phosphate (Tamiflu, Roche Laboratories, Nutley, N.J.) has a high degree of efficacy against all known strains of influenza A and B. If taken prophylactically, it has been shown to prevent confirmed influenza in 90% of cases. It has also been shown to significantly shorten the duration and severity of disease in those who take it soon after developing influenza symptoms, as well as to reduce the transmission of the disease to others.[33-5] Zanamivir (Relenza, GlaxoSmithKline, Research Triangle Park, N.C.) given by inhalation has also been shown to be highly efficacious in preventing and treating influenza A and B.[33,36] Amantadine[37] and rimantadine,[38,39] both older anti-influenza drugs, are both efficacious against influenza A, but they tend to have more side effects, and resistance to these drugs by influenza strain is increasing significantly.[39]

Importantly, the risk of unintended side effects from antiviral drugs is only borne by those who choose to take them either because of exposure or illness. In contrast, the risk of unintended side effects in the influenza vaccine program is borne by a much larger fraction of the population: all those who are vaccinated, plus the bystanders who come in contact with live-virus recipients.

The estimated average prescription cost of protecting the entire U.S. population today with Tamiflu would be no more than $65 per treatment course of drug plus $50 per diagnostic office visit x 300 million people x 0.376, the average fraction of the U.S. population that contracts influenza per year, or not more than $13 billion, on average, per year. Additionally, the number of patients treated could be adjusted downward in a given year if that year's influenza strain turns out to be mild. Obviously, this type of adjustment cannot be done with the influenza vaccine program because all of the patients would need to be vaccinated before it is possible to see how virulent the season's influenza strains actually are.

Ferguson et al. have used a computer simulation to demonstrate the potential effectiveness of a targeted mass prophylactic use of antiviral drugs reinforced by interventions to reduce population contact rates, such as social distance measures, in eliminating a nascent pandemic of H5N1 influenza A in Southeast Asia.[40] Might a similar strategy be even more effective in stopping annual influenza outbreaks in the U.S.? Such a strategy could well be far more efficacious and far less costly than the currently used influenza program.

Antiviral resistance represents a currently unquantifiable challenge to a prophylaxis-based containment strategy. However, current evidence indicates that fitness deficits in Tamiflu-resistant strains mean that their transmissibility is limited.[41,42] The strategy described by Ferguson et al. is estimated to require only 3 million treatment courses of Tamiflu to stop an impending epidemic. If this strategy is successful, the cost of protecting the U.S. population could be reduced to 3 million treatment courses x $65 per treatment course or about $195 million per year.

Conclusions

The annual risk of influenza is substantial, affecting, on average, about 37.6% of the population annually. However, these millions of influenza cases annually translate into an average of about 1,300 deaths in the U.S., not the often-quoted inflated number of 36,000 influenza deaths per year.[43]

The current influenza vaccine program seems to be ineffective, and the U.S. should consider replacing it with a program based primarily on antiviral medications. Research is needed to develop more and better antivirals, especially agents to which influenza viruses do not readily develop resistance.

If the influenza vaccine program is to continue, improved vaccines, which are not potentially infectious, are needed. It will be necessary to develop and license an effective vaccine that confers significant immunity to a wide variety of strains so that vaccine does not have to be given every year.

Vaccine recipients need to be informed of the limitations and risks of the vaccine and of the alternatives to vaccination. In particular, they need to know of the possibility that repeated vaccinations may increase the risk of adverse effects.

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