

drug, by subtracting patients who lack the genetic markers that predict a good response. Such research is a classic “public good” in the economic sense: absent government support (or state-imposed obligation), it will tend to be undersupplied by market actors. And without the needed follow-up science, racial categories are at heightened risk of being reified as biologic.

Second, race is a very crude marker — ill-defined, indeed undefined. Again, A-HeFT is illustrative. Its investigators included patients who were self-identified as black. They thus delimited “blackness” in social and cultural fashion, poorly connected to underlying population genetics. People with one or a few (or even no) black ancestors who nevertheless experience themselves as black — or are stamped by others around them as black — are A-HeFT blacks. The probability of shared, clinically relevant genetics, connected to race, is diminished accordingly. The genetic heterogeneity of African peoples further reduces this probability. Our species is of African origin, and the African continent’s current population has had more time than its past emigrant groups to accumulate genetic variations. Other American racial categories are similarly heterogeneous and ill-defined. Latino descent encompasses multiple ethnic backgrounds from three continents; Asian origin represents a similar mix.

Third, group differences in pathophysiology and responses to treatment are not necessarily genetic. This fact is both obvious and often lost in the research literature on race-based therapeutics. A miasma of psychosocial, economic, cultural, environmental, and other determinants affects human physiology in ways that are poorly understood. There is evidence, for example, that social isolation,

active versus passive coping styles, and confidence versus doubt about being able to handle life’s challenges influence both cardiodynamic and hemodynamic responses.⁵ To the extent that effects of this sort are not randomly distributed among racial groups, they play a role in racially disparate responses to treatment. We have hardly begun to elucidate these mechanisms. Focus on race as a genetic placeholder risks discouraging us from trying.

We need not shy away from the potential benefits of race-conscious therapeutics, but we should manage its downside risks. Greater awareness among physicians and the public that race is at best a placeholder for other predispositions, and not a biologic verity, would be a first step. Beyond such awareness, companies — such as NitroMed — that stand to gain from taking account of race could commit a substantial portion of their profits to research on genetic, psychosocial, and other mechanisms that might underlie racial gaps in clinical response.

From the Georgetown University Law Center, Washington, D.C., and the Bloomberg School of Public Health, Johns Hopkins University, Baltimore.

1. Kahn J. How a drug becomes “ethnic”: law, commerce, and the production of racial categories in medicine. *Yale J Health Policy Law Ethics* 2004;4:1-46.
2. Cohn JN, Archibald DG, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991;325:303-10.
3. Carson P, Ziesche S, Johnson G, Cohn JN. Racial differences in response to therapy for heart failure: analysis of the vasodilator-heart failure trials. *J Card Fail* 1999;5:178-87.
4. Lifton RJ. *The Nazi doctors: medical killing and the psychology of genocide*. New York: Basic Books, 1986.
5. Cacioppo JT, Hawley LC. Social isolation and health, with an emphasis on underlying mechanisms. *Perspect Biol Med* 2003; 46:Suppl:S39-S52.

Weathering the Influenza Vaccine Crisis

John Treanor, M.D.

Contamination problems in their British manufacturing facility at Speke, Liverpool, recently forced the Chiron Corporation of San Francisco, one of only two companies licensed to provide inactivated

influenza vaccine in the United States, to withdraw their vaccine (Fluvirin) from the market. Currently, it appears that about 54 million doses of inactivated vaccine (Fluzone) will be available from the remain-

ing manufacturer, Aventis, with another 1.1 million doses of intranasal live influenza vaccine (FluMist) available from MedImmune for use in healthy people 5 to 49 years of age. This represents about half the amount of vaccine expected for the 2004 vaccination campaign — enough to vaccinate approximately one third of the persons to whom the vaccine is usually targeted. Unsettling reports of price gouging by suppliers are already beginning to circulate in the public media.

Glitches can crop up in the manufacturing of any pharmaceutical product, and public health officials have long been aware of the vulnerability of the vaccine supply chain, which often relies on only one or two manufacturers for critical products. Influenza vaccine is especially vulnerable to interruptions in supply, because of the unique features of influenza-vaccine production. Unlike any other vaccine, influenza vaccine must be reformulated to keep pace with antigenic changes in the hemagglutinin and neuraminidase proteins of influenza viruses — essentially necessitating the manufacture of a brand new product from scratch every year. The process is a long one, beginning with the identification of new antigenic variants in the autumn of the previous year and the selection of the strains for inclusion in the vaccine, and proceeding to the generation of appropriate reference reagents, the production and purification of the vaccine antigens, and packaging and distribution, all within a period of six to eight months (see Figure).¹ In addition, the vaccine is produced in embryonated hens' eggs and requires the sometimes laborious adaptation of an appropriate seed virus for high-yield growth in this substrate in order to allow efficient production. Problems are compounded when there is a simultaneous change in more than one of the three included influenza strains.

Efforts are under way to determine whether additional supplies of vaccine might be obtained from a variety of sources, including Canada, but planning must proceed under the assumption that the amount of available vaccine will be limited. Therefore, the Centers for Disease Control and Prevention has prudently recommended that the vaccine be targeted to those persons who are most likely to have complications of influenza, including severe illness, hospitalization, or death (see Table). In addition, it is important to continue efforts to vaccinate health

care workers who provide direct, hands-on care to patients — a critical strategy for limiting the nosocomial spread of influenza. Although it will be extremely difficult to prioritize among the subgroups listed in the recommendations, the risk of influenza-related hospitalization increases linearly with age after 50 years,² and the rate of hospitalization among women in the first two trimesters of pregnancy is somewhat lower than that among persons older than 65 years. It should be noted that only the Aventis vaccine was licensed for use in young children, so that the loss of the Chiron vaccine may not have much effect on the effort to vaccinate this group.

The available vaccine should be used as efficiently as possible. Live vaccine (FluMist) is licensed for intranasal use in healthy adults and could be used in health care workers in order to save the doses of inactivated vaccine for high-risk patients. In one recent study,³ the serum antibody responses of healthy young adults to the administration of a half-dose of vaccine were very close to those after a full dose. This is a strategy that could be considered for use in healthy adults, but the available data are restricted to a single year. In addition, no data in high-risk populations are available, and there are no data on efficacy. Given the urgent need for more vaccine, additional studies of vaccine doses that are less than full-strength should be explored. Antiviral agents, such as the adamantanes amantadine and rimantadine and the newer neuraminidase inhibitors zanamivir and oseltamivir, are also available for both prevention and treatment of influenza,⁴ though supplies of these drugs are also limited.

What is likely to be the effect of reduced vaccination coverage on the morbidity and mortality related to influenza in the United States this year? Our current use of influenza vaccine is designed primarily to reduce morbidity and mortality and probably has little effect on the transmission of influenza or the overall number of cases. Since the vaccine is clearly effective at reducing the rates of influenza-associated hospitalization and death, reductions in vaccine coverage could be anticipated to result in corresponding increases in the rates of these events. However, this observation is made in the context of the poor job we do of immunizing high-risk patients even when there is no apparent shortage of influenza vaccine. On the basis of the

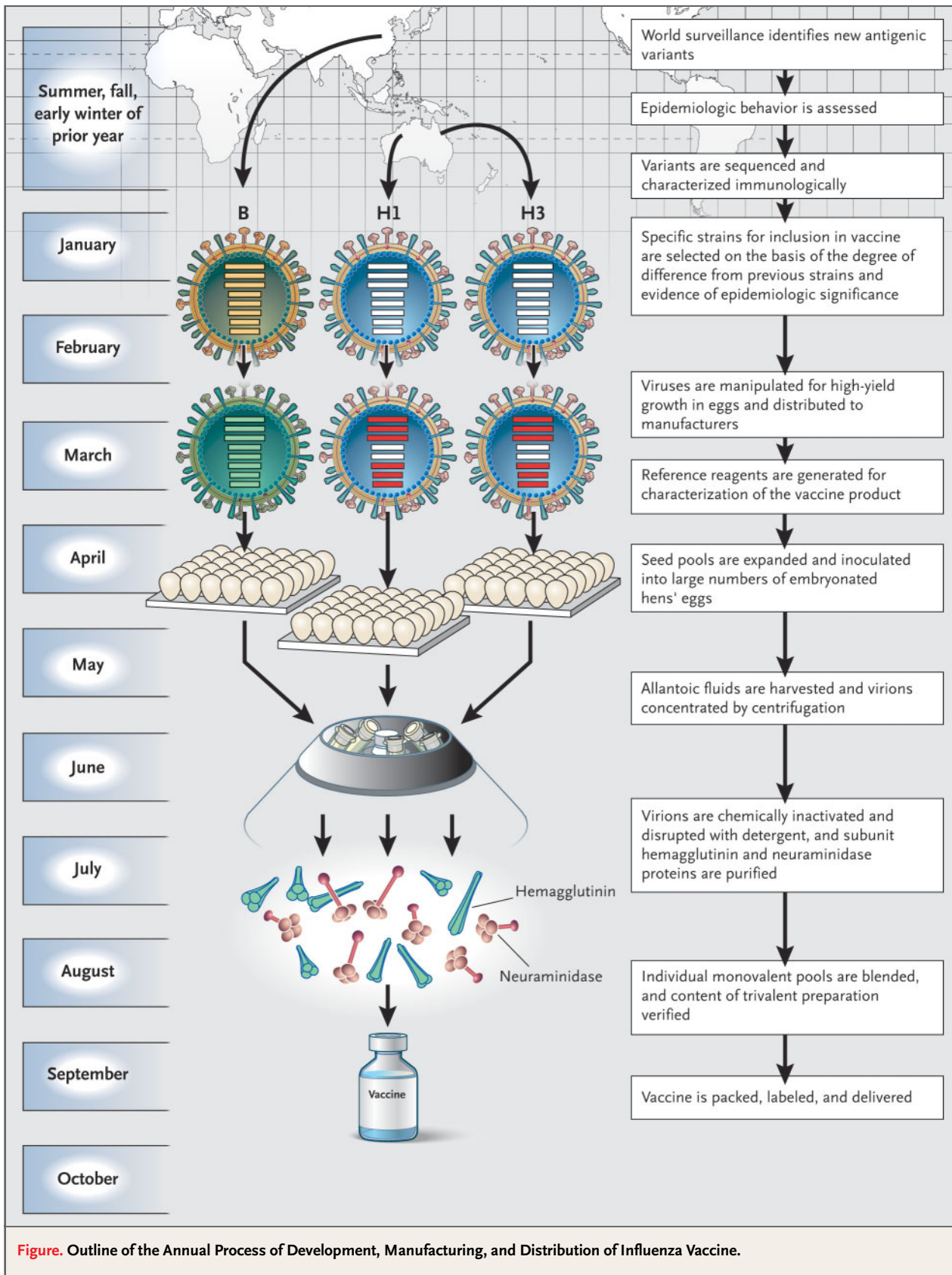


Figure. Outline of the Annual Process of Development, Manufacturing, and Distribution of Influenza Vaccine.

Table. Interim Vaccine Recommendations, 2004.**Priority groups for vaccination**

All children 6 to 23 months of age
 Adults 65 years of age or older
 Persons 2 to 64 years of age with chronic medical conditions
 All women who will be pregnant during influenza season
 Residents of nursing homes and long-term care facilities
 Health care workers involved in direct patient care*
 Out-of-home caregivers and household contacts of children younger than 6 months of age*

Nonpriority groups

Persons who are not included in one of the priority groups described above should be informed about the vaccine supply situation and asked to forgo or defer vaccination. This includes some groups for whom vaccine was recommended in 2003, such as healthy adults 50 to 64 years of age and household contacts of high-risk persons other than children younger than 6 months of age.

* Since live vaccine is licensed for use only in healthy persons 5 to 49 years of age, it should be used primarily for the vaccination of healthy persons in that age group who are health care workers or household contacts of infants younger than 6 months of age.

most recent National Health Interview Survey, only 43 million doses of vaccine would be required in 2004 to immunize the high-priority groups at the same rates reported for the 2002–2003 season.⁵

The magnitude of the effect will also depend on the severity of this year's influenza season. Influenza epidemics are notoriously difficult to predict, but experience has shown that the worst seasons are typically those in which an antigenically drifted influenza A virus of the so-called H3 hemagglutinin subtype predominates.² Last year's epidemic, caused mainly by viruses resembling A/Fujian/411/2002 (H3N2), was an example of this phenomenon. To date, no important new H3 virus has been detected through surveillance, so if we are lucky, the impact of the vaccine shortage may be mitigated by a relatively mild influenza season.

Regardless of how we fare with this year's influ-

enza epidemic, it is clear that we need to substantially expand our options for dealing with the threat posed by influenza. The continued development of influenza vaccines grown in mammalian cell culture rather than embryonated hens' eggs will increase the flexibility of the manufacturing process. Use of protein expression systems, such as recombinant baculovirus, for production of the influenza hemagglutinin and neuraminidase as vaccine antigens may shorten the time required between the identification of new strains and the production of the new vaccine. It might even be possible some day to use conserved viral proteins to make vaccines that do not need to be updated every year. In the meantime, however, we should take sensible steps to encourage more manufacturers to make influenza vaccines and to facilitate the licensure and marketing of more such vaccines in the United States, as well as in other countries. At a time when vast resources are being funneled into the development of vaccines against agents that might hypothetically be used by terrorists, we must find ways to protect our citizens against a virus that predictably — each and every year — causes major morbidity and mortality.

This article was published at www.nejm.org on October 18, 2004.

From the Infectious Diseases Unit, University of Rochester Medical Center, Rochester, N.Y.

Dr. Treanor reports having received consulting fees from Powderject.

1. Wood JM. Standardization of inactivated influenza vaccine. In: Nicholson KG, Webster RG, Hay AJ, eds. *Textbook of Influenza*. London: Blackwell Science, 1998:333-45.
2. Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the United States. *JAMA* 2004;292:1333-40.
3. Treanor J, Keitel W, Belshe R, et al. Evaluation of a single dose of half strength inactivated influenza vaccine in healthy adults. *Vaccine* 2002;20:1099-105.
4. Gubareva LV, Kaiser L, Hayden FG. Influenza virus neuraminidase inhibitors. *Lancet* 2000;355:827-35.
5. Interim estimates of populations targeted for influenza vaccination from 2002 National Health Interview Survey data and estimates for 2004 based on influenza vaccine shortage priority groups. Atlanta: Centers for Disease Control and Prevention, 2004. (Accessed October 21, 2004, at <http://www.cdc.gov/flu/professionals/vaccination/pdf/targetpopchart.pdf>.)