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Cristina V. Beato, M.D.
Acting Assistant Secretary for Health
Director, National Vaccine Program
Department of Health and Human Services
200 Independence Avenue, SW, Rm. 716G
Washington, DC 20201

RE: NVAC – June 7-8, 2005 Meeting and
NVAC/ACIP – July 19, 2005 Joint Committee Meeting

Dear Dr. Beato:

As you know, last year's unexpected shortage of influenza vaccine and this year's urgent need to develop and implement a pandemic influenza plan have made for a remarkable twelve months for many branches of the Department of Health and Human Services. At your request, the National Vaccine Advisory Committee (NVAC) has been reviewing and advising on issues related to vaccine shortages and pandemic influenza. I am sorry you were unable to attend the recent regular meeting of the National Vaccine Advisory Committee (NVAC) in June and the special July 19th joint committee meeting of NVAC and the Advisory Committee of Immunization Practices (ACIP). This letter will update you on our progress.

Day 1 of our regular June meeting opened with a review by Jeanne Santoli of NIP of lessons learned from this past influenza season. Ray Strikas then reviewed current preparations for the season ahead and summarized the proceedings of this year's National Influenza Summit. These baseline presentations initiate an NVAC activity of annual evaluation of the influenza immunization program.

Alan Hinman then updated NVAC on activities of the Pandemic Influenza Working Group during meetings held on April 19-20 and June 15-16. The Working Group has been divided into two subgroups to facilitate more rapid progress. The Antiviral Subgroup has been working to develop a set of

recommendations for stockpiling, distribution and use of antiviral drugs in the event of an influenza pandemic. The Vaccine Subgroup, a joint subgroup with the Advisory Committee on Immunization Practices, has been developing a set of recommendations addressing the use of influenza vaccine in the event of a pandemic.

Additional presentations to NVAC included Jerome Klein's review of the proceedings and recommendations from the *2nd NVAC Workshop on Strengthening the Supply of Vaccine in the U.S.* and Sarah Landry's review of the Department's Pandemic Influenza Communications, Public Engagement, and Outreach activities. Dr. Klein noted that many of the supply workshop recommendations would become oversight tasks of the newly formed NVAC Subcommittee on Vaccine Development and Supply. Sarah Landry's presentation summarized the work being done by the PITFORCE Communications Group, an HHS cross-agency group to develop a pandemic influenza communications strategy, and by the Pandemic Flu Vaccination Priorities Public Engagement Pilot Project.

As you'll recall, we have changed the NVAC subcommittee structure to accommodate new challenges and changing priorities in vaccine and immunization policy. The new subcommittees (Vaccine Development and Supply, Communications and Public Engagement, and Vaccine Safety) had their first meetings on June 7th. They discussed their new charges and began setting new agendas. The Subcommittees have all continued their organizational conversations via conference call and are expected to report back to the NVAC in September.

The Subcommittee on Immunization Coverage discussed issues arising during a recent CDC and NVPO sponsored meeting, *Strengthening the Delivery of New Vaccines for Adolescents: A National Stakeholders' Meeting.* They determined the need for a Working Group on Adolescent Immunization to comprehensively address the complicated issues surrounding setting program goals, approaches to effectively and efficiently delivering vaccines, financing immunization; and enhancing demand.

The second day of the June NVAC meeting opened with summaries of the Subcommittee meetings. These were followed by a presentation about the NVPO's Unmet Needs Program, a summary of a report recently published by the Institute of Medicine entitled "Vaccine Safety Research, Data Access, and Public Trust, and a summary of the aforementioned meeting on adolescent immunization. In preparation for the next fiscal year's unmet needs funding, Ben Schwartz provided an overview of the previous two year's priorities and funding and requested volunteers from the Committee to participate in the determination of priority categories and the review of proposals. Dr. Debra Lappin, a member of the IOM Committee on the Review of NIP's Research

Procedures and Data Sharing Program, gave an overview of the committee's findings and recommendations, published earlier this year in which they recommend the NIP develop, with the input of key stakeholders, an annual Vaccine Safety Datalink research plan and that the NVAC develop a subcommittee to review the NIP's annual plan.

Last, but not least, the June NVAC meeting concluded with valuable agency and committee updates presented by: NIP/ACIP (Dr. Larry Pickering - CDC), ACCV/DVIC (Dr. Geoff Evans - HRSA), FDA/VRBPAC (Dr. Norman Baylor – FDA/CBER), NVPO (Dr. Bruce Gellin), and NIH/NIAID (Dr. George Curlin).

On July 19th, the ACIP and the NVAC held concurrent committee meetings to make recommendations regarding prioritization for the use of vaccines in the event of a pandemic influenza. The NVAC unanimously voted to recommend the priority structure depicted in the following table, with the understanding that, as a pandemic event unfolds, it may be determined that an alternate structure may be more effective. The ACIP voted independently of NVAC for the same prioritization structure. The ACIP's recommendations will be submitted to the Director of the Centers for Disease Control and Prevention.

NVAC Recommended Pandemic Influenza Vaccine Priority Groups

Element and Tier	Personnel (1,000's)	Cumulative total (1,000's)
1A. Health care workers involved in direct patient contact & essential support	9,000	9,000
Vaccine and antivirals manufacturing personnel	40	9,040
1B. Highest risk group	25,840	34,880
1C. Household contacts children <6 months, the severely immunocompromised, and pregnant women	10,700	45,580
1D. Key government leaders & critical public health pandemic responders	151	45,731
2A. Rest of high risk	59,100	104,831
2B. Most CI and other PH emergency responders	8,500	113,331
3. Other key government health decision makers & mortuary services	500	113,831
4. Healthy 2-64 years not in other groups	179,260	293,091

The ACIP having adjourned its meeting, the NVAC continued in session to develop recommendations on the purchase of vaccines during a pandemic. After careful review of the options, the Committee unanimously recommended the Federal purchase of all vaccine during a pandemic. The Committee also recommended that the distribution of vaccine occur through systems established by state, local, and Federal agencies in advance of a pandemic event.

Again, after review of options and with the understanding that these recommendations may need to be revisited during a pandemic event due to unanticipated responses to both vaccine and antivirals and developing epidemiology of the particular influenza virus that may cause a pandemic event, the Committee voted to recommend the following antiviral drug use and prioritization strategies:

1. Sufficient antiviral drugs should be maintained in stockpiles to support a robust pandemic response because of the key role that antiviral drugs can play in reducing health impacts of an influenza pandemic, particularly early in the pandemic when vaccines may be unavailable. Stockpiling is essential because the available supply of neuraminidase inhibitors in the pipeline and ongoing production will not contribute substantial quantities of drug to an antiviral response.
    a. A stockpile that includes about 133 million treatment courses would provide sufficient antiviral drugs to treat all who are infected and support prophylaxis of health care workers and the highest risk population groups (see priority groups and strategies, below). About 40 million courses is considered to be the minimum stockpile size that would support the most critical pandemic response needs.
    b. Within this wide range, stockpiles that exceed the minimum would be advantageous for several reasons:
        i. The primary pandemic response goal of reducing severe morbidity and mortality would be best achieved with sufficient antiviral drugs to treat all who are infected and to provide prophylaxis to several key occupational and patient groups;
        ii. Greatest equity and public acceptance would be achieved with sufficient antiviral drugs to treat all those who are infected;
        iii. In a more severe pandemic, prophylaxis beyond what is projected may be required to avoid absenteeism among health care workers and other pandemic responders due to fear of becoming infected;
        iv. Groups at greatest risk for severe morbidity and mortality have differed among past pandemics and may be larger than predicted;
        v. Optimal treatment may require a higher dose or longer course of therapy than for annual influenza based on results of an animal model of H5N1 infection, so that the actual number of courses available would be less than projected; and
        vi. Some antiviral drugs may be used for treatment and for prophylaxis of contacts associated with the first cases of

pandemic influenza introduced into the U.S. Depending on the intervention strategy, substantial quantities of antiviral drugs could be used attempting to slow the spread of disease.

2. Oseltamivir should be the primary antiviral drug stockpiled. Zanamivir also should be included because it is effective against many oseltamivir resistant strains; supporting ongoing production of both agents increases protection against supply disruptions; and, given the limited availability of oseltamivir before the end of 2006, purchase of zanamivir could accelerate preparedness. Because zanamivir is delivered by inhalation and achieves lower systemic concentrations, its use may be preferable during pregnancy. Risks and benefits should be considered. Adamantanes, beyond the 5 million courses of rimantadine currently in the SNS, should not be stockpiled due to the likelihood of antiviral resistance.

3. Proposed target groups, in priority order, and drug use strategies are shown in the Table. The number of groups targeted would depend on the size of the available stockpile. Although small additional quantities of oseltamivir may be obtained from the supply chain at the time of a pandemic, this quantity would be limited making it unlikely that additional groups could be targeted. Additional information on target group definitions and the rationale for their inclusion is included in the Annex.

Target Group	Approximate population (in millions)	Strategy	# Courses (in millions)	
			For target group	Cumulative
Patients admitted to hospital*	10.0	T	8.0	8.0
HCWs and EMS providers with direct patient contact	9.2	T	2.4	10.4
Highest risk outpatients	2.5	T	0.7	11.1
Pandemic health responders, public safety & key government decision makers	3.3	T	0.9	12.0
Increased risk outpatients	85.5	T	22.4	34.4
Outbreak response**	NA	PEP	2.0	36.4
HCWs in ER, ICU, EMS, and dialysis settings	1.2	P	4.8	41.2
Pandemic societal responders & other HCWs	10.2	T	2.7	43.9
Other outpatients	180	T	47.3	91.2
Highest risk outpatients	2.5	P	10.0	101.2
Other HCWs with direct patient contact	8.0	P	32.0	133.2

Notes on priority group recommendations:

*No studies have assessed the impacts of antiviral treatment for patients admitted to hospital where complications already may be present and the interval from illness onset to therapy is likely to be longer. Additional data should be collected from annual influenza and early in a pandemic to determine whether this represents an effective use of resources when available antiviral drug supply is limited.

**Outbreak response includes post-exposure prophylaxis in nursing homes and other closed settings where risk of transmission and severe outcomes of infection are high.

4. Use of antiviral drugs from the U.S. stockpile is recommended to support an international effort to contain an outbreak caused by a novel influenza strain, potentially preventing a pandemic, if the following conditions are met: 1) International guidelines and protocols are developed and accepted describing the intervention strategy and when it would be implemented; 2) Field exercises in countries where an initial outbreak may occur suggest an ability to effectively implement containment; and 3) Other industrialized countries with antiviral stockpiles also contribute to this effort.

5. Critical research should be conducted to support development and implementation of optimal recommendations for pandemic influenza antiviral drug use. Studies that should be supported include:
    a. Impact of treatment at hospital admission on morbidity outcomes, including length of hospital stay.
    b. Optimal treatment dose and schedule in a ferret model with H5N1 and other influenza strains with pandemic potential.
    c. Sensitivity of rapid diagnostic tests for H5N1 and other influenza strains with pandemic potential using nasal and throat swab specimens.
    d. Safety and pharmacokinetics of oseltamivir among infants <1 year old.
    e. Investigation of the impact of other drugs (antiviral and other classes such as statins) on influenza.

6. Additional work with public and private sector groups should be done to further hone definitions of target groups and their estimated population sizes, and to provide further guidance on antiviral drug distribution and dispensing.

As you can see, the past two months have posed particularly significant challenges to NVAC, the NVPO and other USPHS support staff. Thanks to hard work by all, it has been possible to gather and digest the information necessary to offer advice in a timely fashion in this area of national import.

Feel free to contact me with any questions or concerns you may have in regard to our last NVAC meetings. The next NVAC meeting is scheduled for September 27-28, 2005. We hope you will be able to join us.

Sincerely yours,

Charles M. Helms

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cc: Bruce Gellin, M.D., M.P.H.
NVAC members