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From: PSC gquinnan USUHS.MIL
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To: OS NBSB; Pavia, Andrew
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Hamburg, Margaret A. (FDA); hamburg1, Margaret; Dretchen, Kenneth; Robert
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John; Fauci, Anthony (NIH/NIAID) [E]; MacVittie, Thomas; Berkelman, Ruth;
Scannon, Patrick
Subject: Letter to Dr. Pavia

Dr. Pavia and NBSB Staff:

The attached letter is submitted by Bob Belshe and myself for your consideration and that of the NBSB at the meeting scheduled for July 17, 2009.

Best Regards,

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July 10, 2009

Dear Dr. Pavia:

It was a privilege to participate in the *H1N1 Countermeasures Strategy and Decision Making Forum* hosted by the Pandemic Influenza Working Group of the National Biodefense Science Board on June 18-19, 2009, and we extend our gratitude for being invited to participate.

We wish to take this opportunity to convey to you in writing some of the opinions we expressed at that meeting that we believe should be seriously considered in the course of development of the national strategy for evaluation and use of influenza vaccines incorporating the novel H1N1 antigen. Further, we suggest that the Board consider making recommendations on the following specific points:

1. Should vaccine containing novel H1N1 antigens be distributed and used before completion of extensive immunogenicity studies?

The concern underlying this question is that it is likely that the first wave of epidemic influenza will occur early in the season, perhaps even early in September, as indicated by the continued occurrence of outbreaks of influenza into this summer and past history of influenza pandemics. Ideally, immunogenicity studies would be completed before use of the novel vaccine antigens in licensed vaccines. However, the balancing issue in this case is that the time required to complete such studies is likely to result in unacceptable delay in availability of vaccine. It is conceivable that a one dose immunogenicity study could be conducted, and still allow the vaccines to be distributed in Mid August. However, considering that it is already mid July and there are apparently no specific plans in place for such a study, it seems unlikely that immunogenicity data will be available on a timely basis to make a data driven decision by early August. If that is true, the only alternative to delayed release would be to release vaccines in the absence of new immunogenicity data.

In fact, there is extensive evidence that vaccines containing the novel H1N1 antigens should be highly immunogenic. There is extensive population-wide immunity to H1N1 antigens in the United States and worldwide as a result of the continued circulation of H1N1 viruses between 1918 and 1957 and again from 1977 to the present. This immunity is, of course, not fully apparent in the results of hemagglutination inhibition testing of sera from the general population, but will certainly be reflected in the responses induced when vaccine is administered. The evidence that supports this expectation includes the dramatic responses obtained in national clinical trials of influenza A/New Jersey/1976 and A/USSR/1977 in those same years. Some of this data was presented by Dr. Treanor at your meeting. It is notable that just as the A/New

Jersey strain was antigenically distinct from the strains that circulated before 1957, the current novel H1N1 strains are similarly distinct from recently circulating H1N1 strains. Consider additionally that H1N1 viruses have been actively circulating in all age groups for the past 30 years, conferring extensive priming to the general population, not just those alive before 1957. It is highly likely that individuals who have been repeatedly exposed to H1N1 viruses in the past will respond well to vaccines containing the novel H1N1 antigens.

Available data provides strong assurance that "standard" doses of current vaccines containing the novel H1N1 antigens will induce adequate antibody responses that confer protection to a degree similar to annual influenza vaccines. For inactivated influenza vaccines, the dose that has been used in recent years is 15 micrograms, which was an amount of antigen adequate for induction of antibodies against the A/New Jersey virus in a high proportion of vaccine recipients. Similarly, standard doses of live attenuated vaccine are very likely to suffice. It should not be necessary to await the completion of immunogenicity studies to begin formulation and distribution of vaccines. If clinical trials demonstrate subsequently that certain individuals will benefit from receipt of second doses of vaccine, recommendations can be appropriately modified.

2. Should the vaccine be targeted to all Americans, or mainly to those at highest risk of infections and complications of infections?

Based on the presentation given by Dr. Robinson, the amount of inactivated vaccine that is expected to be available in September is an amount sufficient to vaccinate a substantial proportion of the groups traditionally considered at high risk of complications from influenza and critical service providers. Additional doses will be available on a monthly basis thereafter that can be made available for other members of those groups.

The epidemiology of this virus to date suggests that most of the infections that occur will be in children. Targeting vaccine for use in children may significantly impact morbidity and mortality in that age group and reduce disease burden in the general population. Since there will not be sufficient inactivated vaccine in September to vaccinate a high proportion of children and others who should be targeted, emphasis on the use of live attenuated vaccine (single dose rather than two doses of inactivated vaccine) in children should be considered. It was stated at your meeting that availability of syringes for packaging of the live attenuated vaccine was a limiting factor with respect to the number and time of availability of doses to be released. It should be noted that the vaccine can be easily administered as drops, and there is ample evidence of safety and effectiveness when administered by this route. The manufacturer and FDA may be willing to consider amending procedures to permit formulation of the vaccine to be administered as drops, in order to increase the number of children who could benefit from receipt of this vaccine.

A vaccination program that attempts to deliver vaccine to all Americans will probably conflict with the delivery of vaccines to those groups who need it most; even more so if it is necessary to depend primarily on inactivated vaccine for immunization of children. One approach that has been proposed to address the issue that supply may not be sufficient to meet demand is to add adjuvant to vaccines and use them under Emergency Use Authorization. It is likely that the adjuvant planned will be dose sparing for some or all of the inactivated vaccines licensed in the United States. However, to the extent that the use of adjuvanted vaccines requires the

completion of immunogenicity studies before distribution of vaccines, their release will probably not be timely with respect to epidemicity in the early fall. It appears to us that the approach that is most likely to result in vaccines being available in the optimum time frame is the use of vaccines that can be released in an expedited fashion on the basis of amendments to existing licenses.

3. What approval or release mechanisms should be used to expedite availability of vaccines?

The availability of tens of millions of doses of inactivated and attenuated vaccines in August, September, October, and November hang in the balance, based on the approach adopted to address this problem. The options to be considered are approval of vaccines through license amendments, approval through new Biologics License Applications (BLAs), and release under Emergency Use Authorization (EUA). In our view, the introduction of a new H1N1 strain into vaccine production is a minor change in manufacturing which should easily lend itself to approval by amendments to existing licenses. A requirement for submission of new BLAs for documentation of the strain change is likely to introduce enormous uncertainty into the approval process and time line. Since approval of license amendments can occur rapidly, there should be no need for use of EUA for release of standard vaccines incorporating the novel H1N1 antigens. Invoking the EUA as soon as possible should facilitate release of products dependent upon process changes that would not be suitable for approval as license amendments. For example, the use of live attenuated vaccine administered by dropper may be more efficiently addressed using EUA. New licenses will undoubtedly be needed if adjuvanted vaccines are to be distributed as licensed products. Use of the EUA authority could enormously accelerate release of adjuvanted vaccines.

Based on these considerations and the concepts discussed above, we propose the following strategy for release of vaccines containing the novel H1N1 antigens. Standard vaccines should be released through the license amendment approval mechanism as early as possible, formulated in 15 µg doses for inactivated vaccines and in standard doses for attenuated vaccine. These vaccines should be distributed so as to reach the largest possible number of individuals in groups identified above. Clinical trials of immunogenicity of standard and adjuvanted vaccines should proceed as rapidly as possible, so that data may be taken into account as the season proceeds. If studies demonstrate that second immunizations are needed for certain groups, recommendations should be made to that effect. If the adjuvant is proven to be dose sparing, and the severity of the epidemic is seen to be so great that the use of adjuvanted vaccine in a massive immunization campaign is needed, the nation should be prepared to proceed expeditiously in that direction.

As stated above, we present only our personal opinions based on our experiences related to influenza vaccination. However, we do believe there is ample evidence to support them, and that consideration of these opinions should help inform policy making.

Thank you for your efforts to contribute to leadership on this important issue.

Best regards,



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