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DHB

MEMORANDUM FOR: ELLEN P. EMBREY, DEPUTY ASSISTANT SECRETARY OF DEFENSE (FHP&R), PERFORMING THE DUTIES OF THE ASSISTANT SECRETARY OF DEFENSE FOR HEALTH AFFAIRS

SUBJECT: Recommendations Pertaining to Pandemic Influenza Preparedness and Response

1. References:

a. Department of Defense (DoD), Weekly Global Surveillance Summary – Novel Influenza A/H1N1, 28 July 2009.

b. Centers for Disease Control and Prevention (CDC), Novel H1N1 Flu Situation Update, 24 July 2009 1400 ET.

c. California Department of Public Health: Health and Human Services Agency, Pandemic (H1N1) 2009 Health Alert Update for Healthcare Providers and Clinicians, 22 July 2009.

d. CDC, Intensive-Care Patients with Severe Novel Influenza A (H1N1) Virus Infection – Michigan, June 2009, Morbidity and Mortality Weekly Report (Dispatch) 10 July 2009;58:1-4.

e. DoD, Pandemic Influenza: Clinical and Public Health Guidelines for the Military Health System Swine-Origin Influenza A (H1N1) Virus, June 2009.

f. DoD, Weekly Global Surveillance Summary – Novel Influenza A/H1N1, 12 June 2009.

g. World Health Organization, Summary Report of a High-Level Consultation: New Influenza A (H1N1), 18 May 2009.

h. Memorandum, (Performing the Duties of) Under Secretary of Defense (Personnel and Readiness), Public Health Emergency Management of the 2009 H1N1 Flu, 11 May 2009.

i. CDC, Weekly Influenza Surveillance Report Prepared by the Influenza Division for 2008-2009 Influenza Season Week 18 Ending 9 May 2009.

j. Memorandum, LCDR Thomas Luke and CDR Timothy Burgess, Department of Defense (DoD) Vaccine Efforts: Naval Medical Research Center (NMRC)/VICAL H1N1 Influenza DNA-Vaxfectin Vaccine, 6 May 2009.

k. Memorandum, LCDR Thomas Luke and CDR Timothy Burgess, DoD Vaccine Efforts: NMRC Prime-Boost and Intradermal Delivery of Seasonal Influenza Vaccine for Improved Activity Against Swine-Origin H1N1 Influenza, 6 May 2009.

l. Memorandum, DHB, Convalescent Plasma Therapy, 14 May 2008.

m. U.S. Department of Health and Human Services and U.S. Department of Homeland Security Guidance on Allocating and Targeting Pandemic Influenza Vaccine, 2008.

n. Memorandum, DHB Select Subcommittee on Pandemic Influenza Preparedness, Pandemic Influenza Preparedness Recommendations, 27 July 2007.

o. Memorandum, DHB, Recommendations on Southern Hemisphere Influenza Vaccine for U.S. Forces, 25 September 2007.

p. Office of the Assistant Secretary of Defense for Homeland Defense, DoD Implementation Plan for Pandemic Influenza, August 2006.

q. Memorandum, Armed Forces Epidemiological Board (AFEB) Select Subcommittee on Pandemic Influenza Preparedness, Recommendations for the Use of Pandemic Influenza Vaccine, 18 July 2006.

r. Memorandum, AFEB Select Subcommittee on Pandemic Influenza Preparedness, DoD Pandemic Influenza Preparedness Recommendations, 18 July 2006.

s. Memorandum, AFEB Select Subcommittee on Pandemic Influenza Preparedness, Recommendations Regarding the Use of Masks During an Influenza Pandemic, 17 July 2006.

t. Memorandum, AFEB Select Subcommittee on Pandemic Influenza Preparedness, The Role of Children in the Epidemiology of Influenza, 17 July 2006.

u. Memorandum, AFEB Select Subcommittee on Pandemic Influenza Preparedness, Pandemic Influenza Scenarios, 15 July 2006.

v. Memorandum, Assistant Secretary of Defense for Health Affairs (ASD (HA)) AFEB Select Subcommittee on Pandemic Influenza, 1 December 2005.

2. At the request of Dr. Winkenwerder in a memorandum dated 1 December 2005, the Select Subcommittee on Pandemic Influenza Response and Preparedness was established in order to advise the Surgeons General and Assistant Secretary of Defense for Health Affairs on matters related to Department of Defense (DoD) pandemic influenza preparedness and response. The charge of the Subcommittee included but was not limited to providing recommendations for optimizing influenza surveillance processes and preparations for a pandemic. The Select Subcommittee on Pandemic Influenza Response and Preparedness

was renamed the Pandemic Influenza Preparedness Subpanel following the transition of the Armed Forces Epidemiological Board to the Defense Health Board (DHB).

3. In response to the recent confirmed and probable case reports of novel influenza A/H1N1 infection, the Subpanel held a preparatory session by teleconference on 29 April 2009 and a meeting on 8 May 2009. During these sessions, the Subpanel reviewed and discussed information regarding the Department's planning and response to these case reports and in response to a potential escalation in outbreak severity. Representatives from the following entities provided briefs, comments, and background information: the Centers for Disease Control and Prevention (CDC); the DoD Global Emerging Infections Surveillance and Response System (DoD-GEIS); the Department of Health and Human Services (DHHS); the Preventive Medicine Office of the Assistant Secretary of Defense for Health Affairs (Force Health Protection and Readiness); the Naval Medical Research Center; and the DoD Joint Staff J4 Health Services.

BACKGROUND

4. A novel strain of influenza A/H1N1 first detected in April 2009, has demonstrated efficient person-to-person transmission, resulting in the declaration of a pandemic by the WHO, and 43,771 confirmed and probable cases and 302 mortalities in 50 states, the District of Columbia, the U.S. Virgin Islands, American Samoa, Guam, and Puerto Rico, as of 23 July 2009.

5. There have been 3,849 confirmed cases among Armed Forces beneficiaries between 17 April and 28 July 2009, of which 593 new cases were reported during the week prior to 28 July 2009. Among Service members stationed in Kuwait, the logistics base for operations in Iraq, 68 cases were confirmed by 12 June 2009. However, no validated cases from either Iraq or Afghanistan have been reported at this time, although probable theater cases exist.

6. Although overall influenza incidence appears to be decreasing nationwide, novel outbreaks are occurring in a few areas in the U.S. and throughout the world, some experiencing a high concentration of cases.

7. While the current severity of this novel H1N1 pandemic appears to be mild, its projected severity, as measured by morbidity and mortality in comparison with other influenza strains, is currently unknown. Whether this influenza virus will undergo mutations that would enhance its infectivity or increase its virulence also remains unknown.

8. The Director-General of the World Health Organization elevated the status of the novel influenza A/H1N1 outbreak to that of an influenza pandemic on 11 June 2009. The majority of cases appear to be mild in severity worldwide; however, severe illness, hospitalization, and death have occurred, particularly among individuals under 60 years of age. The majority of the morbidity and mortality within the U.S. has occurred among immunocompromised individuals or those with pre-existing medical conditions. Among

U.S. Armed Forces beneficiaries, the preponderance of cases to date is among individuals below 30 years of age.

FINDINGS

9. Novel influenza A/H1N1 is resistant to adamantane antivirals (amantadine and rimantadine). To date, the virus has undergone minor mutation but remains susceptible to the neuraminidase inhibitors oseltamivir and zanamivir. Eight (8) cases of oseltamivir-resistant H1N1 have been reported to CDC, and appear to be isolated cases.

10. Baseline antiviral stockpiles equivalent to 30% of the population at risk (PAR) and personal protective equipment (PPE) are in place at each military treatment facility (MTF), both within and outside the continental U.S., and appear adequate at this time.

11. The CDC has developed and provided a polymerase chain reaction (PCR) diagnostic kit for the rapid detection of novel influenza A/H1N1 to health departments in all states, the District of Columbia, and Puerto Rico, as well as internationally.

12. Collaborative efforts pursued by the DoD-GEIS, CDC, Food and Drug Administration (FDA) and the Joint Program Executive Office for Chemical and Biological Defense (JPEO CBD) to integrate the CDC's 2009 novel influenza A/H1N1 PCR assay with an existing identification and diagnostic platform enabled the prompt dissemination of the diagnostic kit to public health laboratories.

13. The Armed Forces Health Surveillance Center (AFHSC) operates the Defense Medical Surveillance System (DMSS), of which the Electronic Surveillance System for Early Notification of Community-based Epidemics is a component. DoD influenza surveillance capabilities encompass a broad spectrum of critical elements necessary for an appropriate and timely response in the event of a pandemic, including monitoring probable and confirmed influenza cases, secondary bacterial infections, severe acute respiratory infections, influenza treatments, and laboratory requests for diagnosis.

14. Previously, the Subpanel has considered information and issued recommendations regarding the potential contribution of convalescent plasma as treatment for serious complications of pandemic influenza, adenovirus, or other pathogen(s) for which inadequate or insufficient therapies exist. The DoD has the ability to produce large volumes of convalescent plasma in its MTF FDA-licensed Blood Collection Centers from military members and beneficiaries who have recovered from H1N1 or who have received vaccine given their early priority in the National Pandemic Plan. The convalescent plasma could be used to treat serious cases of influenza-pneumonia or Acute Respiratory Distress Syndrome in the military and civilian population. Potential collaborations between the Naval Medical Research Center, the Armed Services Blood Office, NIH, and other government and civilian researchers have been developed; however, lack of funding has prevented meaningful progress on the development of this capability.

15. The Naval Medical Research Center is investigating various vaccine approaches, including DNA vaccine technology as well as prime-boost and intradermal delivery of seasonal influenza vaccine for improving immune responses against novel influenza A/H1N1.

CONCLUSIONS

16. Since the evolving threat of novel influenza A/H1N1 is currently unpredictable, the Subpanel will monitor events on a continual basis and issue recommendations reflecting the evolving evidence and understanding regarding its activity. As such, the relevancy of the Subpanel's recommendations should be regarded within the temporal context in which they are issued.

17. Specific pandemic influenza vaccine recommendations will be provided in the near future as data become available. Recently (29 July 2009) the Advisory Committee on Immunization Practices released recommendations regarding vaccine administration priorities.

18. The following recommendations are intended to update or complement rather than supplant those previously issued by the Subpanel.

19. The Subpanel would like to commend the Department's efforts to date and is thankful for the opportunity to continue to assist the DoD in its response efforts to the threat of pandemic influenza. In particular, the Subpanel recognizes the significant collaborative efforts between AFHSC and the Military Vaccine Agency (MILVAX) regarding vaccine surveillance and research, as well as other instrumental alliances between various DoD and other federal agencies to include the DoD-GEIS, DHHS, JPEO CBD, and the CDC, for deploying rapid and effective epidemiologic surveillance and detection capabilities, and for the efficient and transparent dissemination of information. Such partnerships will establish a vital precedent for the development of synergistic approaches that would optimize the level of the Department's preparedness and response to novel and rapid influenza outbreaks.

20. In particular, the United States Air Force Academy medical staff should be commended for ably and rapidly handling a recent large outbreak of over 180 cases of H1N1 among cadets. Flawless implementation of recommendations previously provided resulted in termination of the outbreak within 10 days, and the absence of any serious or hospitalized cases.

RECOMMENDATIONS

21. Based on these findings, the Subpanel provides the following recommendations to the Department:

a. Current CDC guidance should be followed for antiviral use. However, an exception should exist for situations in which deployed forces, situations where large numbers of service members are congregated (such as recruit training or Service Academies),

or national security may be compromised if the CDC guidance were to contraindicate the prophylactic administration of antivirals to a larger U.S. population. In these circumstances, the Subpanel advises that appropriately defined DoD sub-populations receive antiviral prophylaxis as needed to mitigate any potential or immediate threat of infection. It is critical that the special requirements of deployed military personnel, particularly shipboard, Special Operations Forces, and trainee and Service academy populations, be recognized to ensure the optimal protection of the Armed Forces and the continuation of the DoD's national security mission.

b. **Particular consideration should be given to the management of populations with specific needs, including obese and pediatric patients with confirmed or suspected H1N1 infection; appropriate oseltamivir dose adjustments should be determined for these patients. Children are at high-risk for acquiring complications resulting from H1N1 infection, and have significantly influenced the epidemiology of novel influenza A/H1N1.**

c. **Given recent expert concerns, the Subpanel notes the risks inherent in a single-drug approach for the treatment of influenza. Since viruses with a ribonucleic acid (RNA) genetic composition have relatively high mutation rates, such therapies may significantly contribute to the development of viral drug resistance. While no recommendation currently exists for an alternative approach to monodrug treatment, this may change in the foreseeable future, and may significantly change DoD antiviral stockpiling requirements.**

d. **The Subpanel commends the Department's approach toward replenishing antiviral supplies and optimizing the sustainability of other influenza incidence containment strategies.**

e. **The DoD is well-positioned to provide leadership in instituting epidemiologic investigations during this critical period when timely data are needed to review the efficacy of antiviral agents, transmission dynamics of disease in close quarters (such as U.S. Navy vessels and DoD Service academies), as well as the clinical spectrum of disease. The Panel encourages DoD to actively fund and disseminate such research efforts.**

f. **Active surveillance should be heightened to allow for the enhanced detection of any modification in case severity, count, and epidemiology, as well as antiviral sensitivity. In addition, surveillance should be expanded in Mexico and Central America. Since the addition of new DoD-GEIS collection sites is not feasible at the present time due to insufficient funding, and because of the existent need for the sustainment of the current influenza surveillance infrastructure, the identification of additional resources for focused Southern Hemisphere and equatorial surveillance should be a priority. The Subpanel is concerned that requesting DoD-GEIS be "cost-neutral" at this time will compromise the agency's ability to detect different**

emerging strains elsewhere. Their value in this regard was well demonstrated with their role in being the first to identify this H1N1 variant through not one, but two of their partners' laboratories.

g. Interagency interactions and Departmental cooperation with U.S. Northern Command (NORTHCOM), Canadian Command, and Mexican Command are encouraged for the appropriate monitoring of 2009 novel influenza A/H1N1 cases.

h. Given concerns about the illness becoming more widespread this Summer or Fall, diagnostic capabilities for novel Influenza A/H1N1 should be expanded to include more sites where possible, while ensuring continued or expanded throughput capacities.

i. The development and adherence to an algorithm that clearly defines influenza testing procedures is encouraged. Potential testing issues in Fall 2009 should be considered, including confusion that may arise between the identification of typical seasonal influenza outbreaks, novel Influenza A/H1N1, or other novel viral strains.

j. Approval of alternative diagnostic platforms should be accelerated so the DoD could be better positioned to diagnose H1N1 and so the level of preparation may be enhanced in the event of resurgence in Fall 2009. The Subpanel encourages the addition of FDA approved capabilities when possible, and supports efforts that promote such capacities, as clinical diagnostic testing conducted under an "Emergency Use Authorization" (EUA) provision is temporary and does not offer long-term benefit for the DoD.

k. The establishment of an internal DoD team for respiratory disease virus research is advised in order to strengthen the Department's ability to conduct mission-essential clinical research and vaccine trials. This would help reinstate DoD's long-standing role and credibility as a major stakeholder in providing needed expertise, especially through collaborative efforts with the DHHS and CDC, for the examination of matters pertaining to pandemic influenza preparedness and response. Long-term funding would be required to meet this need.

l. The Subpanel deems the DoD is well positioned to conduct efficient clinical trials of candidate vaccines, and encourages cooperative research agreements with vaccine manufacturers. DoD directly benefits from such trials by gaining early experience in the use of candidate vaccines and early evidence of efficacy in DoD populations. Collaborations between the National Institutes of Health (NIH) and Biomedical Advanced Research and Development Authority (BARDA)-funded pharmaceutical companies should be established for clinical trial research of candidate vaccines. The DoD Infectious Diseases Clinical Research Program (IDCRP) offered through the Uniformed Services University of the Health Sciences (USUHS) and supported by the NIH, includes the participation of all three Services. This network could be utilized to carry out a clinical research agenda.

m. The Subpanel would like to reiterate the DHB recommendation issued May 2008 which encourages the consideration of convalescent plasma therapy as a component of the national pandemic influenza preparedness plan, and as a significant addition to pre-existing treatment regimens. As such, it would serve as a potential mitigation strategy for challenges that may arise from antiviral drug resistance, rapid viral mutation, and limited vaccine production capabilities. If the virus undergoes mutation that results in a marked increase in virulence, the Department may consider an Investigational New Drug (IND) approach for the acquisition and administration of intravenous convalescent plasma. Funding will be necessary. The pursuit of such research with the NIH is encouraged. Given the large number of H1N1 cases this year, a plentiful pool of potential donors exists; potential donors should be identified from the confirmed cases within the military in the event of a clinically severe pandemic.

n. The DoD plan regarding the prioritization and capacity for pneumococcal vaccine administration should be reviewed, taking into consideration the differences in and potential logistical challenges of implementing a one- or two-dose H1N1 influenza vaccine schedule , as well as the potential impact such schedules may have on electronic record keeping. Data suggest the use of a polysaccharide vaccine as the primary pneumococcal vaccine may diminish future attempts to boost immune responses through either a polysaccharide or a conjugate vaccine. The Subpanel cautions against the use of polysaccharide vaccine if possible, as the adult clinical trials for the conjugate vaccine are currently in Phase III.

o. Cross-neutralizing antibody seroepidemiology studies should be considered as a research approach for candidate vaccines. Such investigations may significantly benefit from the resources made available through the DoD Serum Repository.

p. Due to the importance of force readiness and national security, the DoD should be involved in the decision-making process regarding vaccine production, schedules, and potential rationing.

q. Given the likelihood that novel H1N1 vaccine will be available and administered this Fall, active vaccine safety surveillance capabilities should be ensured, including the establishment of appropriate reporting mechanisms and a database, as well as electronic data transfer capabilities to ensure reporting systems are sufficiently robust. Uniformity and consistency in reporting across the Services should be established and sustained. The Subpanel would like to emphasize its recommendation of October 2007 that states a thorough collection of follow-up safety and immunogenicity data should be conducted on all individuals receiving a vaccine.

r. Given that a vaccine will be manufactured, it should not be administered absent a credible threat or a high index of concern. The Subpanel would like to review and

comment on any plans for force-wide novel H1N1 influenza vaccine recommendations.

s. Strategies should be identified that would enhance the long-term sustainment of surge capacity management, including appropriate coordination between various entities, as well as the availability of essential resources in the event a more virulent second wave of influenza outbreak occurs. Manufacturer capacity limitations for vaccine production should be considered as these plans are developed.

t. Communication approaches for providers at all levels, Active Duty personnel, Armed Forces beneficiaries, and retirees should be evaluated on a regular basis to ensure their effectiveness and whether they appropriately meet the education needs of those populations.

22. The above recommendations were unanimously approved.

FOR THE DEFENSE HEALTH BOARD:

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