A. Introduction

The antiviral armamentarium for chemoprophylaxis and treatment of influenza includes two main classes of antiviral agents, the adamantanes (amantadine and rimantadine) and the neuraminidase inhibitors (zanamivir and oseltamivir), however, the Centers for Disease Control and Prevention (CDC) recommended against the use of the adamantanes for treatment or prophylaxis during the 2005-06 influenza season because of resistance. This interim recommendation remains in effect until susceptibility can be re-established. The adamantanes have activity against only influenza A, while the neuraminidase inhibitors have activity against both influenza A and B. Recent evidence indicates that amantadine has no, or only limited, activity against the H5N1 avian influenza A strains circulating in Asia. While the adamantanes are much less expensive and in greater supply compared to the neuraminidase inhibitors, current evidence suggests that the neuraminidase inhibitor oseltamivir is the best antiviral to stockpile for chemoprophylaxis and treatment during the next influenza pandemic. However, both adamantanes and neuraminidase inhibitors may play a role in chemoprophylaxis and treatment depending on the following factors:

- Susceptibility of the pandemic influenza strain to currently available antiviral medications
- Prophylactic and therapeutic efficacy of the respective antiviral agents against the strain
- Number of doses of the respective antiviral agents available via the public and private sectors
- Size of the target populations recommended to receive chemoprophylaxis or treatment
- Cost and reimbursement

The main goals of chemoprophylaxis and treatment are to reduce the human influenza infection rate and to reduce human morbidity and mortality associated with the pandemic strain. Reduction of the infection rate via chemoprophylaxis should be the last preventive option and should follow implementation of other recommended or indicated preventive efforts (e.g., restrictions on travel and communal events, isolation of ill persons, quarantine of exposed persons, implementation of infection control measures such as the use of masks and diligent hand washing, and vaccination).

If sufficient stockpiles of antivirals exist at the time the pandemic reaches the United States, chemoprophylaxis efforts in North Carolina should prioritize those persons deemed at high risk of exposure and indispensable to carrying out public health, clinical and public safety-related functions during the early stages of the pandemic while vaccine is being produced and vaccination clinics are being established and placed in operation.

If there are insufficient stockpiles of antiviral agents for chemoprophylaxis, treatment should be directed toward those same groups and also target groups at increased risk of morbidity and mortality, as prioritized by the CDC. Antiviral drug priority group recommendations have been drafted by the National Vaccine Advisory Committee (NVAC) and are outlined in the US DHHS Pandemic Influenza Plan, released in November 2005. (These priority groups are also listed in Appendix D-1).

The early epidemiology of disease associated with the next pandemic strain may identify high risk groups that are somewhat different from those identified during the prior pandemics and outbreaks due to novel influenza viruses. However, our knowledge of seasonal influenza indicates that infants and children 6 to 23 months, adults over age 65, and adults and children with malignancy, cardiopulmonary disease (such as asthma and other chronic lung diseases, congenital heart disease, congestive heart failure) and chronic renal disease (including those with renal failure on dialysis) are those primarily at risk for increased morbidity and mortality.

These historical data have guided the NVAC recommendations for specific target populations for antiviral treatment and prophylaxis during an influenza pandemic. State and local level estimates of specific target populations may be obtained by accessing state and county-specific demographic data (i.e., age distribution of the population available through the State Center for Health Statistics or the State Demographics unit) and determining (from published references or other sources) the estimated prevalence of asthma, chronic cardiac,
pulmonary or renal disease, malignancy, and other illnesses or conditions of concern in children, adults, or the general population. Appendix D-1 can be used as a template to estimate the number of people in certain priority groups as outlined in the US DHHS Pandemic Influenza Plan.

B. Interpandemic Phases 1 and 2

1. The NC Division of Public Health will provide technical assistance to local health departments for planning and policy development to include:
   - Notification of CDC’s assessment of high-risk populations (for morbidity and mortality) and recommended priority groups for chemoprophylaxis and treatment
   - Sharing of CDC’s guidelines and recommendations for chemoprophylaxis and treatment, including criteria for identification and prioritization of specific priority groups.
   - Assistance in the calculation and review of county-specific priority groups that are considered high-risk.
   - Assistance in the calculation and review of county-specific priority groups necessary to ensure immunization of the public, maintenance of health care capacity and quality, and maintenance of public health and safety.
   - Assistance in the calculation and review of county-specific antiviral doses required for chemoprophylaxis or treatment of identified priority groups.
   - Education and training on the receipt, handling, transport, storage, security, and tracking of antiviral medications.
   - Review and assessment of county plans for receipt, handling, transport, storage, security, and tracking.
   - Review and assessment of county delivery/distribution plans for antivirals to hospitals, private health care providers, clinics and other points of care.
   - Review and assessment of distribution plans for antivirals to tribal authorities and bordering counties and states (mutual aid agreements).

2. Review the current NC DHHS Distribution Plan for the Strategic National Stockpile and update it as necessary for receipt and distribution of influenza antivirals. (Appendix D-2 is an abridged version of the current SNS Plan for North Carolina).

3. Develop an antiviral distribution plan for counties based on CDC guidelines and recommendations for antiviral chemoprophylaxis and treatment, number of doses of antivirals allocated or available to NC, and county-specific priority group calculations.

4. Review, and modify as necessary, existing legal framework for distribution/dispensing of antivirals as determined necessary by the State Health Director or other designee. This framework should include provisions for the use of standing orders (by the State Health Director or other designee) for chemoprophylaxis and/or treatment with licensed antivirals, as well as unlicensed antivirals under FDA’s IND protocol or HHS’s Emergency Use Authorization procedures.

5. Review, and modify as necessary, state workers compensation laws to determine applicability to health care workers, public or civil service workers, and other essential workers who take antivirals for chemoprophylaxis or treatment.

6. Consider the indications and feasibility of procurement and maintenance (including availability of antivirals, shelf-life/expiration date issues, etc.) of local or state stockpiles of antiviral drugs versus establishment of institutional stockpiles in health care facilities versus emergency purchase from private sector distributors. Develop plans accordingly.

C. Pandemic Alert Phase 3

1. The General Communicable Disease Control branch (GCDC) will maintain weekly electronic and/or phone contact with CDC, WHO and other organizations as necessary for updates on the epidemiology of emerging or re-emerging strains and antiviral efficacy against the strains.

2. Obtain from CDC the most current recommendations on daily dosage and duration of therapy of antivirals for treatment and chemoprophylaxis. Provide this guidance to hospitals, health care providers, local health departments and other key stakeholders.
3. Enhance education and training at the state and local levels. Perform exercises with hospitals and health care providers at the local level that simulate receipt and distribution of antivirals so that roles and responsibilities are well understood. The medical community and public should be knowledgeable on the following topics:
   a) the role of antivirals in responding to pandemic influenza,
   b) the need to prioritize the use of limited supplies of antivirals for treatment and chemoprophylaxis,
   c) rationale for identified priority groups
   d) importance of appropriate use to minimize the development of drug resistance.
4. Refine and revise antiviral distribution plan based on current stockpile situation as well as any updates to priority group recommendations
5. Purchase available antivirals from US DHHS contract for state stockpile

D. Pandemic Alert Phases 4 and 5

1. GCDC will maintain weekly or twice weekly electronic and/or phone contact with CDC, WHO and other organizations as necessary for updates on the epidemiology of the pandemic strain, antiviral efficacy against the strain and vaccine development timetable.
2. Review updated geographic distribution of outbreaks with pandemic potential and determine, as best as possible, the estimated arrival date (or window) of the pandemic to the United States and North Carolina.
3. Review the county-specific priority group data, amending the list if analysis of early epidemiologic and morbidity and mortality data suggest other high-risk groups
4. Coordinate with the Immunization Branch to assess preparedness and response capacity for vaccination of priority groups and the general public once vaccine is available.
5. Determine the available supplies of indicated antiviral medication(s) in the public (federal SNS, state and any local stockpiles) and private sectors.
6. Review and update antiviral distribution plan to address preparedness at the state and local level for receipt, transport, storage, security, tracking, and delivery/distribution of antivirals.
7. Review and update pandemic influenza antiviral chemoprophylaxis and treatment plan based on information obtained from 1 through 6 above.
8. Coordinate updated antiviral chemoprophylaxis and treatment plan with Immunization, GCDC and DHHS Public Affairs. Develop and distribute educational materials to appropriate state agencies, local health departments, hospitals, private health care providers and the public.

E. Pandemic Phase 6 (without cases occurring in the United States)

1. GCDC will maintain twice weekly or daily electronic and/or phone contact with CDC, WHO and other organizations as necessary for updates on the epidemiology of the pandemic strain, antiviral efficacy against the strain and vaccine development timetable.
2. Review updated geographic distribution of outbreaks with pandemic potential and determine, as best as possible, the estimated arrival date (or window) of the pandemic to the United States and North Carolina.
3. Provide technical assistance to local health departments to ensure readiness for receipt, transport, storage, security, tracking and delivery/distribution of antivirals.
4. Request, according to federal guidelines and the protocol set forth in the current NC DHHS Plan for Requesting, Receiving and Distributing the Strategic National Stockpile, antiviral medication delivery to North Carolina via the SNS; this will most likely be via Vendor Managed Inventory (VMI).
5. Communicate with local health departments the expected delivery date(s).
6. Obtain from CDC updated guidance and recommendations on the use of antivirals in the following scenarios:
   a) sporadic reporting,
   b) limited transmission, and
   c) widespread transmission

**F. Pandemic Phase 6 (with cases occurring in the United States)**

1. GCDC will maintain daily electronic and/or phone contact with CDC, WHO and other organizations as necessary for updates on the epidemiology of the pandemic strain, antiviral efficacy against the strain and vaccine development timetable.
2. Review updated geographic distribution of outbreaks with pandemic potential and determine, as best as possible, the estimated arrival date (or window) of the pandemic to North Carolina.
3. Assure delivery/distribution of antivirals to counties based on the most current federal (HHS/CDC) and state guidelines.
4. Assist local health departments in the redistribution of antiviral medications as needed and available.
5. Review available epidemiologic and clinical data on the efficacy of chemoprophylaxis and treatment. Increase surveillance for resistance to antivirals associated with treatment or chemoprophylaxis. Encourage hospitals and health care providers to obtain specimens from patients who develop severe disease while receiving treatment or chemoprophylaxis.
6. Encourage health care providers to report adverse reactions (via FDA’s MedWatch or other adverse event reporting system). Review available safety data from CDC and FDA (i.e. type and frequency of any reported adverse reactions and epidemiologic evidence for causal association) and communicate relevant information to hospitals, health care providers and the public.
7. Update antiviral plan accordingly based on efficacy and safety issues in 3 and 4 above.

**G. Second or Subsequent Waves**

1. If available and epidemiologic and clinical data indicate antiviral medications were efficacious in reducing infection and/or reducing morbidity and mortality, re-order antiviral medications utilizing experience gained from the initial wave.
2. Redistribute antivirals according to plan and experience gained from the first wave.

**H. Postpandemic Period**

1. Determine total amounts of antivirals ordered, shipped, administered and wasted (if possible).
2. Determine type and frequency of any reported adverse reactions and review epidemiologic evidence for causal association.
4. Update antiviral plan accordingly based on 2 and 3 above.