

CENTER COMMENTS

COMMENTS FROM THE CENTER FOR BIOSECURITY OF UPMC ON DRAFT GUIDANCES FOR PANDEMIC INFLUENZA PLANNING

ON MAY 23, 2008, THE U.S. Department of Health and Human Services (HHS) proposed and requested public comment on 3 draft guidances for pandemic influenza planning (73 FR 31690-91): (1) Interim Guidance on the Use and Purchase of Facemasks and Respirators by Individuals and Families for Pandemic Influenza Preparedness; (2) Proposed Guidance on Antiviral Drug Use during an Influenza Pandemic; and (3) Proposed Considerations for Antiviral Drug Stockpiling by Employers in Preparation for an Influenza Pandemic. The documents are part of a series of HHS guidances to assist government agencies, businesses, community organizations, and the public in preparing for a pandemic. The Center for Biosecurity of UPMC reviewed the proposed draft guidances and submitted to HHS the following analyses of the antiviral use and employer stockpiling guidances as its official comments.

COMMENTS ON “PROPOSED GUIDANCE ON ANTIVIRAL DRUG USE DURING AN INFLUENZA PANDEMIC”

Overview

The Center for Biosecurity of the University of Pittsburgh Medical Center (UPMC) agrees with the basic medical and scientific premise of the *Proposed Guidance on Antiviral Drug Use during an Influenza Pandemic*: that antiviral drugs could mitigate the effects of an influenza pandemic if the circulating pandemic strain is susceptible to the medicine and if access to the drugs is timely and uniform.¹ We also support the proposed overall tiered strategy for use of these medicines (ie, the top priority for use of public stockpiles is for containment and suppression of initial outbreaks and

for *treatment*, with *prophylaxis* only if the stockpile is sufficiently large).

However, while we applaud the U.S. Department of Health and Human Services’ (HHS) effort to address difficult antiviral use issues, it is our view that: (1) it is unrealistic to expect the private sector to purchase sufficient supplies of antivirals for prophylaxis; (2) serious consequences may arise if the private sector does not stockpile recommended quantities of antivirals; (3) much of the perceived benefit outlined in the guidance is based on an optimistic set of assumptions that have large margins of error, including susceptibility of the influenza strain to the stockpiled antivirals; and (4) planning should better address issues associated with providing antivirals to workers and populations in “closed settings,” such as prisons, jails, and long-term care facilities.

Specific Issues

1. It is unrealistic to expect the private sector to create sufficient stockpiles of antiviral prophylaxis, and there is no reason to expect that the private sector will unilaterally accept this burden, especially with unsubsidized antiviral pricing. It is especially worrisome that segments of critical infrastructure are covered under voluntary participation by the private sector.

The proposed guidance notes that the “total number of antiviral drug regimens needed to fully implement the working group recommendations substantially exceeds current public sector stockpiling targets . . . [and that] . . . [i]mplementing prophylactic antiviral drug strategies . . . will require the establishment of stockpiles in the private sector.”¹ However, it is unrealistic to expect the private sec-

tor to create sufficient stockpiles of antiviral prophylaxis for healthcare and emergency service workers and for outbreak control for individuals in closed settings and people who are severely immunocompromised, who will need, respectively, an estimated 103 million, 5 million, and 2 million regimens. There is also no reason to expect that the private sector will unilaterally accept this burden and at prices that are not subsidized.

In addition, reliance on the private sector to purchase the antivirals necessary to implement the proposed policies is untenable given the number of “barriers to establishing such stockpiles” that were identified in the guidance. Barriers include the cost of antivirals, shelf-life maintenance, regulatory and logistical challenges, potential liability, and concerns that private sector stockpiles could be appropriated by the government in an emergency. These barriers preclude the full implementation of the proposed policies and are especially worrisome because segments of critical infrastructure would need to rely on voluntary participation by the private sector.

The document also states that “the public and private sectors should coordinate use of antiviral stockpiles so that available drug supplies most efficiently contribute to achieving national pandemic response goals.”¹ We concur with the principle that pandemic influenza preparedness is a “shared responsibility.” However, we would encourage language that assigns the federal government the responsibility of convening meetings with the private sector to establish a mechanism for facilitating such collaboration.

2. If the private sector fails to stockpile sufficient quantities of antivirals, serious consequences, including high rates of absenteeism among healthcare workers, might ensue.

We disagree that the creation and maintenance of antiviral stockpiles for such a critical public health event should be a shared responsibility, as this approach may lead to serious gaps in the availability of antivirals and other unintended consequences. For example, if healthcare workers are not offered antiviral prophylaxis by their employers in a pandemic, it is expected that many of those employees will not show up for work, which will add significant strain to what would already be an overburdened healthcare system. Although the proposed guidance notes that public sector stockpiles can be used for prophylaxis if supplies are sufficient, the conditions under which a determination would be made to shift policy are unclear given that public sector stockpiling targets are insufficient to meet prophylaxis requirements.

Serious consideration should be given to how public sector stockpiles will be used in the event that private sector stockpiles do not materialize or are insufficient to meet demand for prophylaxis. In addition, how will these recom-

mendations change if public sector stockpiling targets are not reached? As of November 2007, only 18 states had purchased their full allocation of antivirals at federally subsidized prices to meet public sector stockpiling targets, while 25 states had made partial purchases and 7 states had not made any purchases.²

The federal government should instead request and encourage the private sector to develop and support other important policies that would assist in pandemic mitigation. For example, the private sector could advocate and make it possible for the workforce to comply with the principles of social distancing, provide workforce education, and assist with the distribution of medical countermeasures.

3. Much of the perceived benefit of the proposed guidance centers around an optimistic set of assumptions that have large margins of error, including the influenza strain’s susceptibility to the stockpiled antivirals and community mitigation strategies significantly lowering the attack rate.

The proposed guidance assumes that using antiviral drugs to treat and prevent infection will be an important component of a pandemic influenza response. However, this will be the case only if the circulating strain is susceptible to the stockpiled antivirals. This fact should be acknowledged in the guidance, because it changes the cost-benefit ratio of antiviral stockpiling. In addition, while it is assumed in the guidance that community mitigation strategies will lower the attack rate by 50%, the government should also delineate the circumstances under which the proposed guidance for antiviral use would not make sense.

The document further mentions the intention to use antiviral medications from the Strategic National Stockpile (SNS) at U.S. borders to “reduce the risk of infected persons entering the United States early in an influenza pandemic as part of a risk-based border.”¹ The proposed guidance should explain how this strategy will be implemented, outline the quantity of antiviral regimens that have been allocated for this use, and provide an estimate of reduced risk based on this approach.

4. Planning should address in greater detail the issues associated with providing antiviral medications to staff and populations in “closed settings,” such as prisons, jails, and long-term care facilities.

The recommendation for postexposure prophylaxis (PEP) of people living in “closed settings,” such as prisons and jails, is included among the proposed recommendations for the use of antiviral drugs in private sector stockpiles. However, because these populations are under the jurisdiction of federal, state, or local correctional authorities, providing antiviral medications to these populations may actually be the responsibility of public sector stockpiles. As of June 30,

2007, approximately 2.3 million inmates were in custody in the U.S. Of these, 196,804 were located in federal prisons, 1,321,731 in state prisons, and 780,581 in local jails.³ Of the federal prisoners, 166,425 were held in federal facilities, 22,354 in privately operated facilities, and 8,025 in community correction centers. The issue of who has the responsibility to provide antiviral medications to these individuals and whether the drugs should be allocated from public or private stockpiles should be clarified, and recommendations should then be adjusted accordingly.

The estimated number of people held in prisons or jails in the U.S. also does not include juveniles housed in residential placement. In 2003, which is the latest year for which we could find data, 96,665 juveniles were held in residential placement in the U.S., including 37,335 in state facilities, 28,875 in local facilities, 30,321 in private facilities, and 124 in tribal facilities.⁴ This population should be included to better estimate the number of antiviral regimens needed for stockpiling.

In addition, the assumption that there will be “one exposure per person . . . for outbreaks in closed and high-risk settings”¹ seems overly optimistic. It is likely that in “closed settings,” particularly prisons and jails because of “crowding and a limited ability to apply other measures to reduce transmission,”¹ more than one exposure per person will occur during a pandemic. Accordingly, the estimated need of one antiviral regimen per person is an underestimate. Given that it is impossible to estimate how many exposures per person will likely occur during a pandemic in closed and high-risk settings, consideration should be given to recommending pre-exposure prophylaxis to these populations instead of postexposure prophylaxis.

Furthermore, the estimated 500,000 correctional officers and 800,000 healthcare providers in long-term care facilities^{5,6} should also be considered for inclusion in the group of individuals for whom pre-exposure prophylaxis is recommended. It is important to reduce potential absenteeism among these workers, who are at an increased risk for exposure, due to fear of being infected while at work.

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REFERENCES

1. U.S. Department of Health and Human Services (HHS). *Proposed Guidance on Antiviral Drug Use during an Influenza Pandemic*. 2008. <http://aspe.hhs.gov/panflu/antiviraluse.pdf>. Accessed June 16, 2008.
2. Trust for America's Health. *Ready or Not 2007*. December 18, 2007. <http://healthyamericans.org/reports/bioterror07/BioTerrorReport2007.pdf>. Accessed June 16, 2008.
3. Sabol WJ, Couture H. *Prison Inmates at Midyear 2007* (NCJ 221944). Washington, DC: U.S. Department of Justice; June

2008. <http://www.ojp.usdoj.gov/bjs/pub/pdf/pim07.pdf>. Accessed June 11, 2008.

4. *OJJDP Statistical Briefing Book*. March 27, 2006. <http://ojjdp.ncjrs.gov/ojstatbb/corrections/qa08201.asp?qa-Date=2003>. Accessed June 11, 2008.
5. Correctional Officers. Washington, DC: U.S. Department of Labor, Bureau of Labor Statistics; December 18, 2007. <http://www.bls.gov/oco/ocos156.htm>. Accessed June 11, 2008.
6. Federal Interagency Working Group. *Draft Guidance on Allocating and Targeting Pandemic Influenza Vaccine*. October 17, 2007. <http://www.pandemicflu.gov/vaccine/prioritization.pdf>. Accessed June 11, 2008.

COMMENTS ON “PROPOSED CONSIDERATIONS FOR ANTIVIRAL DRUG STOCKPILING BY EMPLOYERS IN PREPARATION FOR AN INFLUENZA PANDEMIC”

Overview

The Center for Biosecurity of the University of Pittsburgh Medical Center (UPMC) applauds the effort by the U.S. Department of Health and Human Services (HHS) to clarify federal roles and expectations regarding the stockpiling of antivirals during an influenza pandemic. We fully support public-private collaboration to address public health threats and agree that “our best chances of protecting health and maintaining community functioning during a pandemic rely on a coordinated response between public sector and private sector partners.”¹ We also recognize the importance of stockpiling medical countermeasures to prepare for public health emergencies, and we believe that the draft guidance is an appropriate first step in highlighting the many operational, legal, and ethical questions pertaining to the creation of private sector stockpiles.

However, it is our view that employer stockpiling, which will impose significant costs and implementation burdens on employers that choose to purchase the medicines, is not a viable strategy to ensure that the U.S. has the necessary supplies of antivirals for prophylaxis during a pandemic. In addition, the proposed considerations to encourage employer antiviral stockpiling do not offer sufficient guidance or incentives for employers to purchase the medicines and may actually discourage them from stockpiling. It is unrealistic to expect the private sector to create sufficient antiviral stockpiles or to unilaterally accept this burden, and it is especially troubling that segments of critical infrastructure are covered under the private sector's voluntary participation. If the private sector does not stockpile sufficient supplies of antivirals, serious consequences, including higher than necessary absenteeism rates among healthcare providers during a pandemic, will likely result.

If this strategy is advanced, it is our view that several issues must first be addressed to ensure that employer antiviral stockpiling and dispensing activities are fairly, safely, and legally executed and that antiviral stockpiling is a feasible and appealing pandemic influenza planning strategy for employers. Individual employers should not be encouraged to stockpile antivirals until they are: (1) given the option to participate in a program to extend the shelf-life of the medicine; (2) assured that their stockpiles will not be taken or seized by the government to supplement deficiencies in public antiviral caches in the event of a pandemic, unless such an approach is mutually agreed upon; (3) provided with a detailed assessment of the legal and regulatory issues that they could face with stockpiling and dispensing antiviral drugs; and (4) provided with guidance for how, when, and to whom to distribute antivirals that is consistent with the best available medical and public health recommendations.

Specific Issues

1. Employers will likely be discouraged from stockpiling antivirals due to the limited shelf-life of the medicines and lack of available options for rotation or extending the shelf-life, such as through the federal Shelf-Life Extension Program (SLEP).

The proposed considerations do not take into account that the recommended antivirals for employer stockpiles—oseltamivir (Tamiflu[®]) and zanamivir (Relenza[®])—have a shelf-life of 5 years from the date of manufacture. In addition, pharmacy dispensing laws in states often significantly shorten that time frame by giving an expiration date of 6 months to 1 year after dispensing the medicine to a patient.¹ The expiration date of oseltamivir capsules was reportedly extended recently from 5 to 7 years, but it appears that the 7-year dating does not apply to commercial product (eg, sold via commercial wholesalers or dispensed by pharmacists to individuals).²

Rotation does not appear to be an option for employer antiviral stockpiles, as the practice is not permitted for antivirals in the Strategic National Stockpile (SNS) and state stockpiles.² While Roche, the maker of oseltamivir, recently announced the introduction of a program to facilitate employer stockpiling by reserving, storing, and rotating the medicine, the plan does not appear to provide a rotation option for those employers that purchase the antivirals outright from the company.³ A similar plan does not currently appear to be available for zanamivir. Federal antiviral stockpiles are permitted to participate in the Shelf-Life Extension Program (SLEP), a program administered jointly by the U.S. Food and Drug Administration (FDA) and the Department of Defense (DoD) that extends the shelf-life of the medicines. However, employer, local, and state antiviral

stockpiles are not permitted to participate in the program and do not have access to other options to extend the shelf-life of their stockpile investment.

Allowing employer stockpiles to participate in SLEP or a similar program would likely provide businesses with a greater financial incentive to invest in antivirals. SLEP participation results in significant cost savings for the federal government. For example, one government report stated that “for every dollar spent on the SLEP testing of items the taxpayer has avoided the expenditure of 94 dollars for new, replacement materiel.”⁴ Given that employers will probably be paying more for antiviral regimens than the government does and that large amounts of stockpiled antivirals will have to be discarded if a pandemic does not occur during the shelf-life period, it is even more critical that the investments in employer stockpiles are maximized.

Expanding SLEP to nonfederal antiviral stockpiles has previously been considered at the national level. For example, the issue was considered in the 2006 *National Strategy for Pandemic Influenza Implementation Plan*⁵ but was determined, without a rationale provided, not to be feasible at the time.⁶ In April 2008, the Institute of Medicine’s (IOM) Committee on Implementation of Antiviral Medication Strategies for an Influenza Pandemic recommended that SLEP be expanded to include other public and private sector entities that are stockpiling antivirals for use in an influenza pandemic.² The Committee also suggested that HHS develop a process to use the knowledge acquired by the FDA in the operation of SLEP to facilitate the use of properly stored, recently expired medications that exist in supplies outside of SLEP in the event these medications are needed in a shortage.²

The proposed considerations acknowledge that the shelf-life issue is a barrier to employer stockpiling and that “[s]everal Federal initiatives have been launched in an effort to reduce these barriers.”¹ However, information about these initiatives, including what the possible solutions might be and when employers can expect to be informed about them, is not included in the guidance and should be provided to employers.

We fully support and encourage continued efforts at HHS to share information about SLEP and to find solutions for employer stockpiles, as well as state and local antiviral stockpiles, to participate in SLEP or a similar program. Encouraging employers to consider purchasing antivirals without providing them with the same or a similar option that federal antiviral stockpiles have to extend the shelf-life of their investment is a critical barrier to employer stockpiling.

2. Without assurances that government will not take possession of privately held antivirals in response to a pandemic, little incentive exists for employers to invest the necessary effort and funds to purchase and stockpile an-

antivirals or to share stockpile plans and information with state and local officials.

We agree with HHS that employers should communicate and coordinate their pandemic plans with relevant state and local health officials to better protect lives and preserve community function, and we applaud HHS for acknowledging in the proposed considerations the difficult issue of governments taking, or seizing, employer stockpiles to effectively respond to a pandemic. We also recognize that state leaders and health officials have significant powers, especially during times of emergency, and that these powers, when used appropriately, can have a significant and positive impact on the public's health.

However, the considerations note that while the "Federal government . . . discourages the potential appropriation of privately held stockpiles of antiviral medications by governmental authorities . . . [it] acknowledges the responsibility of a State to coordinate all assets within its jurisdiction and within its legal authorities to effectively respond to emergencies such as a pandemic."¹ This approach will likely discourage many employers from electing to make the significant investments in stockpiling antivirals in the first place, because they are not given sufficient reassurance or incentive to invest in medicines that could later be taken by the government to compensate for shortages in government stockpiles. The proposed considerations also do not provide information about possible penalties or sanctions for non-compliance by employers or about what compensation would be provided for the cost of antivirals and the time and effort spent on stockpiling if the government takes their medicines for public use.

For those employers that choose to assume the risk that their medicine could be taken and that purchase antivirals, what incentive is there for them to share and coordinate antiviral and pandemic influenza plans with state and local government officials? To encourage public-private information sharing and collaboration around pandemic planning and response, HHS should consider assuring employers that their stockpiles will not be taken for public use. If that is not a feasible option, then HHS, at a minimum, should consider developing, in close collaboration with employers, mechanisms (eg, legal agreements or protocols) that would better inform employers about possible takings by outlining the specific scenarios under which a taking might occur, the likelihood of a taking, the process by which the antivirals could be taken, and possible compensation plans if stockpiles are taken by government.

3. A more detailed assessment of the specific legal and regulatory issues that may be associated with employer antiviral purchasing, storage, and dispensing is required to enable employers to make better informed decisions about

stockpiling the drugs and to ensure that all employers are acting on the same information.

The proposed considerations briefly mention that various legal and regulatory issues may arise with employer antiviral stockpiling and that employer purchasing and stockpiling of antivirals "must comply with applicable Federal and State laws and regulations."¹ However, because of the complexity of such legal and regulatory issues, the federal government should provide employers with significantly more detailed information about the specific laws and regulations with which employers who choose to stockpile should be concerned. For example, stating that "Federal laws may also be implicated" is not sufficient.¹ Instead, HHS should consider assessing in detail *which* federal laws may be implicated and the likelihood of such laws being enforced during an influenza pandemic. The guidance should also address how compliance with and enforcement of the laws and regulations may change if a public health emergency is declared.

To further encourage and support employer stockpiling, HHS should also provide employers with more detailed guidance on the complex "ethical, logistical, and economic issues that will be encountered in ordering, storing, securing, and dispensing prescription medications" than outlined in the proposed considerations.¹ For example, what are some of the specific storage and logistical challenges that employers might confront in stockpiling?

4. Before issuing directive guidance, HHS needs to provide the private sector with a concept of operations plan for the use of antivirals during a pandemic that takes into account both the potential side effects of wide-scale antiviral use and the likely shortage of medical care and consultation during a pandemic.

We agree with HHS's statement that "[i]f antivirals are taken with less or no medical supervision, they also may be used incorrectly reducing their effectiveness and potentially contributing to the emergence of drug resistant viruses."¹ However, we feel that this concern is not limited to pre-pandemic dispensing of antivirals, as indicated in the HHS guidance. Such concern may be an issue for private sector distribution of antivirals during a pandemic when access to medical professionals may be limited. It is unclear how the private sector, absent a sufficient occupational health staff to oversee antiviral dispensing, will know when to distribute antivirals and to whom without intensive consultation with medical professionals. Specifically, we are concerned that without more specific guidance for the use of private sector antiviral stockpiles:

- *Difficulties in diagnosing pandemic influenza will lead to wide use of antivirals.* During a pandemic, it will be

difficult to rapidly differentiate between actual cases of influenza and people who are sick with other diseases, so antivirals will be distributed widely. Practically, unless effective rapid diagnostic tests for pandemic influenza are available, antivirals will be given out to many people who prove not to have pandemic influenza.

- *Influenza viruses may develop a resistance to antiviral medications.* Experience shows that it is possible that resistance may develop more frequently during times of wide-scale use, which could limit the effectiveness of the medicine for treatment.

Therefore, HHS should consider issuing more detailed guidance to ensure that overuse of antiviral medications, which both increases the potential for resistant strains to emerge and places undue burden on the healthcare sector, is minimized and that limited antiviral stockpiles are sufficiently effective for treatment.

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REFERENCES

1. U.S. Department of Health and Human Services. *Proposed Considerations for Antiviral Drug Stockpiling by Employers in Preparation for an Influenza Pandemic*. Washington, DC: HHS; 2008. <http://aspe.hhs.gov/panflu/stockpiling.html>.
2. Committee on Implementation of Antiviral Medication Strategies for an Influenza Pandemic, Institute of Medicine (IOM). *Antivirals for Pandemic Influenza: Guidance on Developing a Distribution and Dispensing Program*. Washington, DC: National Academies Press; 2008.
3. Roche introduces program to facilitate corporate pandemic stockpiling of Tamiflu® [news release]. Roche U.S.A. June 26, 2008. <http://www.rocheusa.com/newsroom/current/2008/pr2008062601.html>. Accessed June 27, 2008.
4. Extending the Shelf Life of Critical “War Reserves” Medical Materiel Using the FDA/DOD Shelf Life Extension Program. March 2005. https://slep.dmsbfda.army.mil/slep/slep_info_paper_mar2005.doc. Accessed July 29, 2008.
5. Homeland Security Council. *National Strategy for Pandemic Influenza Implementation Plan*. May 2006. http://www.whitehouse.gov/homeland/nspi_implementation.pdf.
6. *National Strategy for Pandemic Influenza Implementation Plan: Summary of Progress*. December 2006. <http://www.pandemicflu.gov/plan/federal/strateryimplementationplan.html>.