Landry, Sarah

From: Andrew Noymer [andrew@demog.berkeley.edu]
Sent: Friday, August 27,20041 :47 PM
To: NVPO
Subject: Draft report comment

PDR_1918_f1u.pdf
(78 KB)

Dear Colleague,

I have just finished reading your excellent and important draft report on pandemic influenza. I would like to point out some published research that is relevant to your report.

Evidence strongly suggests that many who died in 1918 were infected with tuberculosis. Tuberculosis death rates plummeted after 1918, which can be explained by the fact that many TB sufferers died of the flu and therefore were not around to die later, nor to pass the TB bacillus to others. Fortunately, in 2004 tuberculosis prevalence is much lower than in 1918, which bodes well for our potential susceptibility to a would-be repeat of 1918.

This research was published in a peer-reviewed demography journal. A copy is attached (PDF format). In the event that the attachment becomes separated from this email, the stable URL for the document is: http://demog.berkeley.edu/-Eandrew/1918/PDR_1918_flu.pdf

This is, emphatically, not to criticize the need to prepare for a potentially-catastrophic pandemic. Your report is timely and necessary. Rather, it is to point out that some demographic research supports a note of cautious optimism that, all things being equal, a repeat of 1918 would have less lethality today in the USA (though, regrettably, this statement does not hold for the many developing nations where TB is still a major problem) .

Thank you very much.

Best,
Andrew Noymer

Landry, Sarah

From: Andrew Noymer [andrew@demog.berkeley.edu]
Sent: Friday, August 27,20041 :53 PM
To: NVPO
Subject: URL correction

The correct stable URL for the Tuberculosis-1918 connection is:

http://demog.berkeley.edu/-andrew/1918/PDR_1918_flu.pdf

The previous one had a typo.

On Fri, 27 Aug 2004, Andrew Noymer wrote:

> Dear Colleague,
>
> I have just finished reading your excellent and important draft
> report on pandemic influenza. I would like to point out some
> published research that is relevant to your report.
>
> Evidence strongly suggests that many who died in 1918 were infected
> with tuberculosis. Tuberculosis death rates plummeted after 1918,
> which can be explained by the fact that many TB sufferers died of the
> flu and therefore were not around to die later, nor to pass the TB
> bacillus to others. Fortunately, in 2004 tuberculosis prevalence is
> much lower than in 1918, which bodes well for our potential
> susceptibility to a would-be repeat of 1918.
>
> This research was published in a peer-reviewed demography journal.
> A copy is attached (PDF format). In the event that the attachment
> becomes separated from this email, the stable URL for the document is:
> http://demog.berkeley.edu/-Eandrew/1918/PDR_1918_flu.pdf
>
> This is, emphatically, not to criticize the need to prepare for a
> potentially-catastrophic pandemic. Your report is timely and
> necessary. Rather, it is to point out that some demographic research
> supports a note of cautious optimism that, all things being equal, a
> repeat of 1918 would have less lethality today in the USA (though,
> regrettably, this statement does not hold for the many developing
> nations where TB is still a major problem) .
>
> Thank you very much.
>
> Best,
> Andrew Noymer
>
>
>

The 1918 Influenza Epidemic's Effects on Sex Differentials in Mortality in the United States

ANDREW NOYMER
MICHEL GARENNE

THE 1918 INFLUENZA epidemic was a major demographic event in the United States and worldwide. It is notable for its virulence (over 20 million deaths worldwide, approximately half a million in the United States); its maleness (a difference between male and female age-standardized death rates of 174 per 100,000[1]); and its W-shaped mortality age profile (death rates having a mode in the 25-34-year age group, strange for influenza, which usually has a U-shaped profile). This study presents a new finding from reexamination of published statistics on death: the 1918 influenza had a strong and fairly long-lasting effect on differential mortality by sex, diminishing the earlier female advantage. The mechanism we posit is a selection effect, whereby those with tuberculosis (TB) in 1918 were more likely than others to die of influenza. This outcome affected males more than females because TB morbidity was disproportionately male. The reduction of the pool of male TB cases lowered the male TB death rate in the years following 1918, and brought males' life expectancy closer to the longer female life expectancy.

Before going into detail about our reexamination, we briefly review some of the salient features of the 1918 influenza epidemic, which, in spite of its enormity, has not been a major focus of studies by demographers.

Background of the 1918 influenza pandemic

Influenza is caused by a virus, a member of the family Orthomyxoviridae. The genome of the influenza virus consists of eight single strands of RNA.

Formation of new flu strains can occur when a host cell is infected by two existing viral strains. For this reason, there are many strains of influenza virus, which explains why, in the practice of modern medicine, new vaccines, based on surveillance of early cases, are recommended before each flu season. Four aspects that set the 1918 epidemic apart from other flu epidemics are the sheer magnitude of the epidemic, the high mortality rate, the aforementioned unusual W-shaped age profile of deaths, and recent molecular discoveries about the 1918 strain.

The first noteworthy aspect of the 1918 epidemic was how many people were affected. Crosby (1989) cites estimates that one-quarter of the American population had clinically recognizable cases of flu during the epidemic. The epidemic was truly global. leaving no continent untouched, and it spread very rapidly. The geographic origin of the epidemic is still debated, with viable North American and European hypotheses (Pyle 1986; Oxford et al. 1999). The "Spanish" attribution of the epidemic, common in the literature, is thought to be a result of the fact that the press in neutral Spain was not censored during World War I, and therefore some early printed reports of the flu originated from Spain. The epidemic began in spring 1918 and much of its impact was experienced during that calendar year. But the epidemic also persisted into 1919 (albeit less so in the United States), when it was most severe in the southern hemisphere, and also dogged the representatives at the Paris peace conference. By 1920, the epidemic's world tour was over; some cases but few fatalities were reported in 1921 in New Caledonia (in the southwest Pacific) after the island was released from maritime quarantine (Crosby 1989: 234).

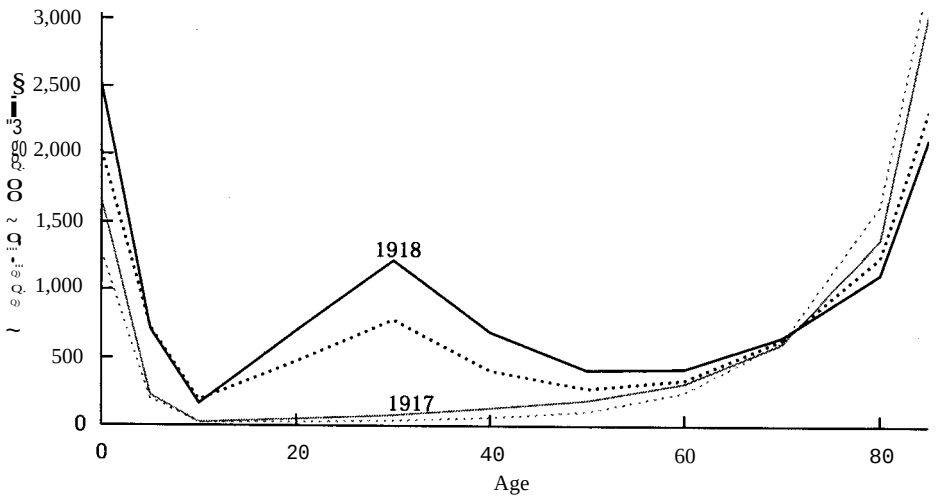
The next noteworthy aspect of the 1918 influenza epidemic is the exceptionally high mortality associated with it. Crosby (1989) estimates that it took the lives of 550,000 Americans, a figure that he deems conservative. The estimated population of the United States on 1 July 1918 was some 103 million (Linder and Grove 1943), so approximately 0.5 percent of the US population died as a result of the epidemic. Worldwide, the death toll is generally put at 20 million. Given the rudimentary state of vital registration in most of what was then the colonized world, this is a rough estimate. Kingsley Davis (1951: 237) calculated that in colonial India alone there were some 18.5 million influenza deaths during 1918-19, and in one of his scenarios the total is 31 million. Thus, the worldwide death total could easily have been in the neighborhood of 40 million. Before the 1918 epidemic, one has to go back to the black death (bubonic plague) of 1346 to find a similarly devastating epidemic. Since 1918, only the AIDS epidemic comes close in terms of global mortality, but, when taking the time frames into account, AIDS has a slow burn compared to the explosion of the 1918 influenza epidemic.

The mortality of the 1918 epidemic was exceptional not only quantitatively, but qualitatively as well. The W-shape of the mortality age profile

is the most peculiar aspect of 1918 flu epidemic. Normally, influenza kills only the very young and the very old. For adults, flu means a bad case of cold and usually some time in bed, but rarely death from secondary pneumonia. Figure 1 presents death rates for influenza and pneumonia combined (except pneumonia of the newborn) by age and sex for 1917 and 1918 in the United States. In 1917 (the bottom two curves in the figure), death rates are high at the very youngest ages, drop to near zero later in childhood, then show a gradual increase throughout younger adulthood and a steeper increase above age 60. As in the age pattern of mortality for all causes combined, this is the classic U-shaped mortality pattern by age. In 1918, the pattern is radically different: we have a W-shape. At the youngest ages, influenza death rates in 1918 are about the same as in 1917. At the oldest ages, influenza death rates in 1918 are less than in 1917. In contrast, the middle ages, the age groups 15-24, 25-34, and 35-44, show a drastic departure from the norm. The death rates have a local maximum at these ages, such that adults in the prime of their lives experienced death rates from influenza comparable to those experienced by the elderly. Note also in Figure 1 that the male death rates in 1918 far exceed the female death rates among adults. Among the elderly in both years, there is a slight female excess death rate. Among children and adults, there is a slight male excess death rate in 1917. But in 1918, males were at a much greater disadvantage in terms of flu mortality.

The search for the cause of the 1918 influenza epidemic originally centered on bacteria, specifically Pfeiffer's bacillus *(HaemophiJus influenzae).* It

FIGURE 1 Age-specific death rates for influenza and pneumonia combined, males (solid) and females (dotted), 1917 and 1918



SOURCE: US Department of Health. Education, and Welfare 1956.

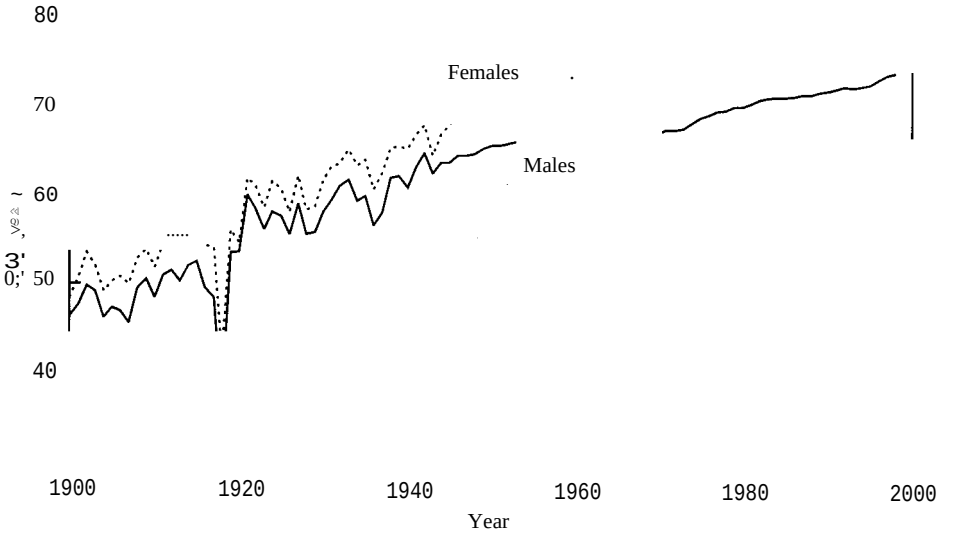
was in his research on the putative etiologic agent of the 1918 flu that Alexander Fleming made his serendipitous discovery in 1929 of the antibiotic properties of *Penicillium.* In 1933, it was finally determined that influenza is caused by a virus. Recently, with the advent of techniques permitting creation of laboratory samples of genetic code from the most minute traces of virus (through polymerase chain reaction, or PCR), molecular biologists have taken a renewed interest in the 1918 epidemic. Reid et al. (1999,2000) report genetic characterization of the 1918 virus from human bodies preserved in Alaskan permafrost and from autopsy tissue samples embedded in paraffin. These studies show that of all the mammalian flu strains, the 1918 strain is closest to the avian strains of influenza virus; the 1918 virus is also related to swine strains. The general zoonotic nature of influenza (Le., its transmissibility from animals to humans) appears to have played a particular role in the exceptional 1918 epidemic. Frustratingly, these findings have not answered the question why the 1918 virus was so virulent, nor do they offer an explanation for the unusual age profile of deaths.

Changes in life expectancy

Life expectancy at birth, $e(0)$, is a summary of mortality at a given time. It is the mean length of life that would be experienced by a birth cohort subject to the mortality rates of the reference period through the cohort's entire life span. The 1918 influenza epidemic affected life expectancy at birth in the United States, with the measure for each sex dropping by 11.8 years from 1917 to 1918.[2] There was no lasting effect on $e(0)$ values, however, as survivorship for both sexes rebounded quickly; indeed, $e(0)$ for both sexes was greater in 1919 than in 1917.[3] We now examine changes in the sex difference in $e(0)$ before and after 1918. (On the merits of looking at absolute differences rather than ratios, see Sheps 1958 and 1959 and Keyfitz 1985: 60-62.)

To provide a broad perspective on the impact ofthe 1918 flu epidemic, Figure 2 presents the evolution of life expectancy at birth, by sex, for 1900 to 1998. Figure 3 presents the evolution of the age-standardized death rate (ASDR), by sex, for the same years. The ASDR measures the crude death rate (deaths per 100,000 population) calculated by applying observed age-specific rates to the US standard population.[4] Changes in $e(0)$ need not track very closely changes in the ASDR.[5] Figure 4 presents the absolute differences between male and female $e(0)$ and ASDR for the same years. The results in Figure 4 are striking: by either measure, the 1918 influenza epidemic had a major impact on male-female differences in mortality. After 1918, the female mortality advantage in $e(0)$ fell from 5.6 years to one year (the drop is the same whether comparing 1919 to 1917 or 1918); in ASDR the female advantage fell from over 350 per 100,000 to below 100. Females would not regain their pre-epidemic mortality advantage over males until

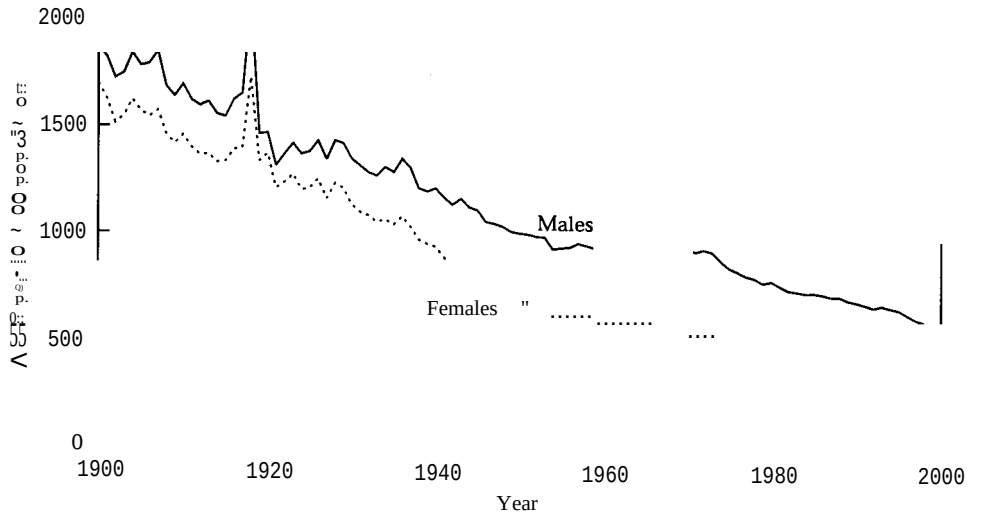
FIGURE 2 Expectation ofHfe at birth. e(O). males and females. 1900-98



SOURCES: Grove and Hetzel 1968; Murphy 2000.

the mid-1930s. or. if the reference point is the female advantage registered in 1917 and 1918. until the 1950s. The literature on sex differentials in mortality does not discuss this finding (see, for example, Retherford 1975; Preston 1976: 120-162, 1977; Berin. Stolnitz. and Tenenbein 1989).

FIGURE 3 Age-standardized death rate, ASDR (all causes). males and females. 1900-98



SOURCES: Grove and Hetzel 1968; Murphy 2000.

FIGURE 4 Sex difference in expectation of life at birth, e(O)(left scale, female minus male), and sex difference in age-standardized death rate, ASDR (right scale, male minus female), 1900-98

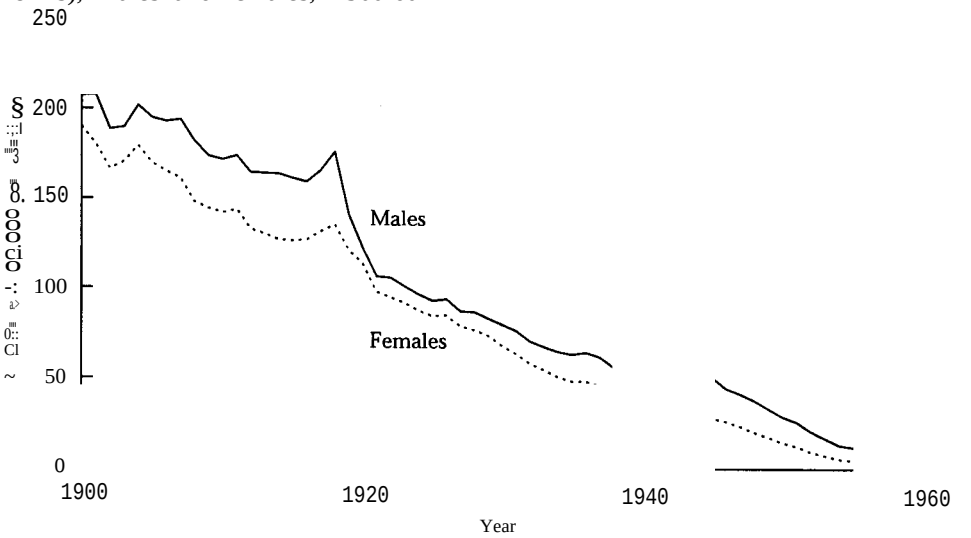
SOURCE: Calculated from data in Figures 2 and 3.

To understand better the origin of these changes, we examined death rates by age and sex for 30 causes, representing around 80 percent of all registered deaths in the United States. The age-standardized death rate is useful here, because the ASDR for all causes is the sum of all cause-specific ASDRs.

The key role of tuberculosis

Figure 5 presents the age-standardized death rate for tuberculosis (all forms), by sex, for the United States, 1900-60; and Figure 6 presents the male-female absolute difference in ASDR for TB for the same time period. Two aspects of Figure 5 are already well known: TB death rates fell precipitously in the first half of the twentieth century; and males have higher TB death rates. (Note also that the 1918 epidemic interrupted the downward trend, causing a temporary upsurge in TB death rates.) When plotted by sex, the rates reveal a third major feature that has not previously been discussed in the literature: just after 1918, TB death rates experience their steepest decline of the century, and this decline is much more pronounced for males than for females. In 1921, the male ASDR for TB exceeded the female ASDR by only 8.6 per 100,000 (compared with a difference of 40.7 in 1918).

FIGURE 5 Age-standardized death rate, ASDR, for tuberculosis (all forms), males and females, 1900-60



SOURCES: US Department of Health, Education, and Welfare 1956: Grove and Hetzel 1968.

Table 1 presents key data in numerical form, to complement the graphs. The raw data in the table are age-standardized death rates for males and females for several causes for the pre-epidemic year of 1917, for the epidemic year, and for 1921, when female mortality advantage began to re-

FIGURE 6 Sex difference in age-standardized death rate, ASDR, tuberculosis (all forms), 1900-60

SOURCE: Calculated from data in Figure 5.

TABLE 1 Age-standardized death rate per 100,000 population, males and females, selected causes

	1917		1918		1921		~ 1917-1921	
	Raw	Smoothed	Raw	Smoothed	Raw	Smoothed	Raw	Smoothed
All causes								
M	1,650	1,540	2,085	1,504	1,318	1,432	-332	-107
F	1,398	1,398	1,727	1,393	1,213	1,264	-185	-134
M-F	252	214	358	173	105	111	-147	-103
Influenza and pneumonia[a]								
M	193	207	672	235	108	154	-85	-53
F	156	184	498	216	96	144	-60	-39
M-F	38	21	174	18	12	12	-26	-9
Violence[b]								
M	167	162	161	156	134	133	-32	-29
F	56	51	52	51	50	50	-6	-2
M-F	111	111	109	105	85	84	-26	-27
Modified all causes[c]								
M	1,290	1,283	1,252	1,248	1,076	1,091	-215	-192
F	1,186	1,184	1,177	1.171	1,067	1,067	-119	-117
M-F	104	92	75	67	8	25	-95	-67
TBd								
M	166	163	176	156	107	110	-59	-53
F	132	128	136	127	98	101	-34	-26
M-F	34	34	41	30	9	9	-25	-25
Nephritis[e]								
M	137	133	125	125	105	112	-32	-21
F	110	103	101	101	96	99	-14	-4
M-F	27	27	25	24	10	13	-18	-14
Stroke[f]								
M	126	123	120	120	114	118	-12	-4
F	125	123	123	123	121	123	-5	1
M-F	1	1	-3	-3	-7	-6	-7	-7
Heart disease[g]								
M	229	224	221	219	205	211	-24	-13
F	200	200	204	200	192	199	-8	-2
M-F	29	21	17	16	12	13	-16	-9
All other!'								
M	632	629	609	609	545	545	-87	-84
F	619	619	614	609	561	561	-59	-59
M-F	13	5	-5	-5	-16	-9	-29	-14

NOTES: Raw data are age-standardized death rates per 100.000 population. from US Department of Health, Education. and Welfare 1956. Smoothed data were obtained by smoothing the entire dataset with the "3RSSH, twice" smoother (Tukey 1977). The M - F (male minus female) smoothed values are the smoothed differences, not the differences of the smoothed values.

"Influenza and pneumonia combined. except pneumonia of newborn.

bMotor vehicle accidents. other accidents. suicide, and homicide.

CAlicauses. excluding violence and influenza and pneumonia (see text).

dTuberculosis. all forms.

eChronic nephritis (chronic and unspecified nephritis and other renal sclerosis).

(Stroke (vascular lesions affecting central nervous system).

!!J)iseasesof the heart (does not include rheumatic fever).

hModified all causes. additionally excluding the above four causes.

bound (as seen in Figure 4). The category "modified all causes" in Table 1 was calculated by subtracting violent causes and influenza and pneumonia from the data for all causes.[6] Violence is excluded to concentrate on biological causes of death, and influenza and pneumonia are excluded in order to measure the *indirect* after effects of the 1918 epidemic. Including influenza and pneumonia, the sex difference in mortality fell after 1918 in part because the flu epidemic vanished. Between 1917 and 1921. the smoothed male-female differential of modified all causes fell from 92 to 25 per 100,000, a drop of 67 (Table 1). Tuberculosis alone dropped by 25 per 100,000, or 37 percent of the overall drop between 1917 and 1921 in the differential in age-standardized death rates, more than any other cause.

Tuberculosis and influenza very likely interacted in 1918. Vital statistics cannot address this question well, because even if contributory causes are listed on the death certificate, a unique cause of death is recorded, a general problem that hinders cause-specific studies of death. Raymond Pearl (1919) published individual-level data on influenza-TB co-infection in 1918 (the uniqueness of the 1918 virus makes it important to have contemporary data). We have reanalyzed these data using logistic regression, and found that TB infection was a significant risk factor for contracting influenza.[7] This analysis was conducted among persons classified as having no other cases of influenza in the household, so it measures community-acquired influenza infection. The different rates of disease progression for the two pathogens minimize reverse causality. Pearl's dataset as published is not perfect: there are no controls for age, sex, or socioeconomic status, and the sampling frame is households with at least one case of tuberculosis (though data on all household members were collected). Only white households were surveyed. Despite these shortcomings, cautious use of Pearl's dataset is justified because it is the only source of contemporary micro data on TB and influenza that we have found after an extensive search.

We conjecture that many influenza deaths in 1918 took place among the tuberculous-persons with clinical disease or latent infection with *Mycobacterium tuberculosis.* That the 1918 influenza virus, known to be atypical, should interact pathologically with M *tuberculosis* seems likely.s Influenza and TB are not strongly linked in the medical literature, though there are some clinical references to interactions (e.g., Couch 1981). The age pattern of the 1918 flu means that TB and influenza overlapped much more than usual. Seemingly no one was invulnerable to the 1918 flu, and we know that TB prevalence was high in 1918, even among some ostensibly healthy individuals (if we include those in whom infection was latent). The influenza-tuberculosis interaction need not be a molecular phenomenon (Le., involving some direct interaction between the TB bacillus and the influenza virus). The secondary pneumonia that occurs as a complication of influenza infection could be exacerbated by active tuberculosis or by tubercu-

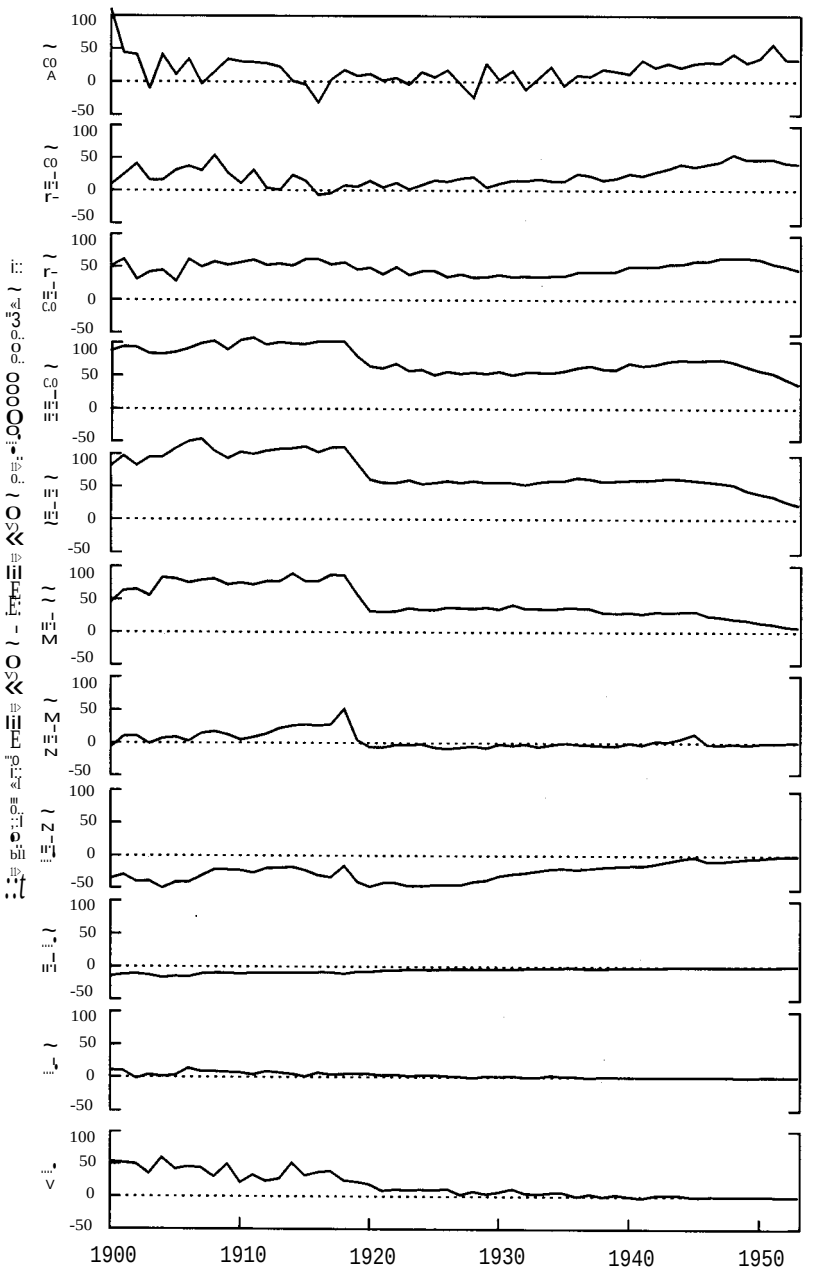
lar lesions in the case of latency. Virtually all influenza deaths involved the lungs, an important site of pathology for tuberculosis.

An influenza-tuberculosis nexus is consistent with what is known about the 1918 epidemic, including the high fatality rate and the W-shaped mortality age profile, and it helps explain the sex differentials we observe. The deadliness of the epidemic seems less extreme if we consider that many victims also had TB. Excess male flu mortality is consistent with the differential incidence of TB by sex. The fact that flu deaths had a mode in the 25-34 age group is also strongly indicative of a TB interaction; TB is a disease of adulthood, not of old age.[9] In the natural history of TB infection, progression to clinical disease may take place years after initial infection with the TB pathogen (Bloom and Murray 1992; Murray, Styblo, and Rouillon 1993). At any given time, there is a pool of active and latent TB cases from which future TB deaths are drawn. The diminution of this pool by a selective effect such as death from influenza will reduce the incidence of TB deaths in subsequent years.

The age-standardized death rate alone is a blunt measure; a sufficiently large rate change in any age group could alter the ASDR. The selection hypothesis predicts that the narrowing of post-1918 male-female differences in TB mortality is due to drops in male TB death rates at the ages especially affected by the flu epidemic. Figure 7 shows sex differentials in TB death rates, with each panel of the figure representing a successive age group. This collection of graphs can be seen as a "rough cut" of a Lexis surface. The panels, each drawn with the same scale to permit comparison, represent a third dimension, the other two dimensions being period (the horizontal axes) and death rate (the vertical axes). Thus, in Figure 7 we have information by age and calendar year; true cohort data would be preferable but are unavailable. The decline in the male-female difference in TB death rates occurs only in the age range 15-64 years. Among those 65 years and older and below 15 years, there is very little change in the sex differential in TB mortality; the most pronounced effects are at ages 25-54. For age groups 15-64, we see a sudden and sustained drop in the sex differential of TB mortality after 1918, because male rates drop faster than female ones. Females have higher TB death rates at ages 5-24. However, males' drop relative to females' is not limited to age groups where their death rate from TB exceeds females'. Interestingly, following 1918, in the 25-34-year age group, among whom influenza death rates show a peak, men and women experienced near parity in TB death rates, as if starting with a clean slate (Figure 7). Changes in TB death rates below age five years reflect recent transmission of the bacillus, and are not illustrative of the effects we consider. The effects we observe are not driven by race: nonwhites have much higher TB death rates than whites, but qualitatively there is no difference in the observed patterns.

There is a modest rise in males' excess TB mortality centered at 1945 (Figures 5 and 6). This effect is driven by changes in the 15-34-year age

FIGURE 7 Male minus female age-specific death rates, ASDR (per 100,000 population), for tuberculosis (all forms), 1900-53



NOTE: Each panel has identical scale.
SOURCE: US Department of Health. Education. and Welfare 1956.

groups (Figure 7), which is consistent with the selection effect, since the corresponding cohorts were largely untouched by the 1918 epidemic. If the "normal" pattern by sex is for men to ,have higher TB mortality rates, then the effect observed around 1945 could be seen as a temporary return to the status quo ante, after the effects of the 1918 epidemic had worn off and before TB death rates declined to very low levels.[10]

For two years after 1918, pulmonary tuberculosis as a percent of all TB deaths among males declined, from 86.6 percent to 85.2 percent. This is a relatively small decline, but the denominators are large: over 50,000 male TB deaths each year. Importantly, the general trend is toward pulmonary TB becoming more prominent, and the percentage of pulmonary TB among women did not decline after 1918. Because this decline is a short-term (two-year) phenomenon, it is more difficult to assess whether this is another consequence of the 1918 flu epidemic. There were three nonpulmonary TB forms for which male death rates increased but female rates did not: tubercular meningitis, Pott's disease (tuberculosis of the vertebral column), and tuberculosis of other organs. The increased importance of nonpulmonary TB for males but not for females suggests that the lungs as a shared site of pathology for TB and influenza may have played a role in the diseases' interaction. Specifically, if pulmonary tuberculosis made one more likely to die from influenza-induced pneumonia, then having nonpulmonary TB would be less of a risk factor for flu death; consequently, in the years after 1918, death rates for non pulmonary forms of TB as a proportion of all TB deaths would increase, even if this reverses the secular trend of pulmonary TB being increasingly important.

If the pre-1918 trends in male and female age-specific death rates from TB had continued through 1932, the death registration area of the United States would have observed 500,000 more TB deaths than it actually did. In this counterfactual analysis, we fitted a quadratic trend to age-specific TB death rates, 1900-17, for each age group above age five years. We projected these trends forward and calculated absolute numbers of deaths that would have resulted, which were then compared to the true death tallies. This exercise demonstrates that the magnitude of the post-1918 shift in the trend of TB death rates is not too large to have been caused by the 1918 influenza epidemic. ıı That is, it would be surprising if the magnitude of the ostensible selection effect (the number of influenza deaths) did not have some concordance with the consequences (the shift in the TB trend) .

Consider the above findings from the point of view of tuberculosis epidemiology as opposed to influenza epidemiology. The approximately 50,000 male TB deaths observed each year during the late 1910s correspond to approximately 300,000 male active TB cases in the United States at any given time (this estimate is based on data in Murray, Styblo, and Rouillon 1993: 238 and Lowell 1969: 17). Furthermore, the post-1918 reductions in

the number ofTB deaths. compared to extrapolation of the pre-1918 trend, do not need to be precisely accounted for by the toll of the 1918 influenza epidemic. This is because of the cumulative effect of the shrinking number of tuberculous persons in the population. Tuberculosis is spread by those who have tuberculosis, so the accounting work should be done in light of a declining. not fixed, population of tuberculous individuals. Given the fact that many men in this period must have gotten TB from other men, such as those in the workplace, the cumulative effect on TB mortality would have reinforced the selection effect. Thus, the cumulative effect is consistent with the hypothesis that the 1918 flu epidemic's excess male mortality was disproportionately among tuberculous males.[12]

From a biological perspective, the link between influenza and TB may include a third pathogen. Tuberculosis infection causes lung cavities to form. which become a breeding ground also for non- TB bacteria, including *Staphylococcus aureus.* This would have had the effect of priming tuberculous individuals for S. *aureus* superinfection in the event of co-infection with influenza. It is highly plausible that TB infection laid the ground for the massive secondary bacterial pneumonias that killed the victims of the flu in 1918.

The role of other causes of death

The role of nontuberculosis causes of death in the overall decline in the male-female mortality differential after 1918 is less clear. Throughout the first half of the twentieth century. infectious disease death rates fell toward zero for both sexes, and so there is necessarily a tendency for the sex differential in absolute terms to decline. At the same time, death rates for heart disease, a major determinant of the overall death rate, rose and became more masculine, so women did not lose their advantage in the longer term. It took until the 1930s for female mortality advantage to return to its pre-1918 level. As seen in Figure 4, females began regaining their pre-1918 mortality advantage in 1920. But it took over ten years to regain the level of advantage prevailing in the first decade of the century and well over 20 years to reach and surpass the advantage registered in 1917-18. The factor (or factors) that depressed females' mortality advantage post-1918 were not persistent. but represented a temporary shock.

The cause that accounts for the second-highest share in the decline of the male-female mortality differential between 1917 and 1921 (14 per 100,000 in Table 1. or 21 percent of the drop in the modified all causes category) is chronic nephritis, a notoriously inaccurate death code (Dublin and Kopf 1913; Preston 1976: 6). Even if coded correctly, there are multiple etiologies leading to death from this cause (including M. *tuberculosis).* Stroke accounts for 10 percent of the fall in that differential during the period (7 per 100,000 in Table 1), due to the peculiar fact that from 1918 to

1925 females had higher age-standardized death rates for stroke than males. After 1925, mortality from stroke among males again became higher than among females, as was the case prior to 1918.13 Heart disease accounts for 13 percent of the observed decline (9 per 100,000 in Table 1). This cause is concentrated in older ages, and both sexes experienced a temporary drop in death rates from heart disease, but the drop was greater among males than among females after 1918. It is plausible that 1918 flu deaths reduced subsequent heart disease deaths, again through a selection effect. The diminution of the magnitude of TB transmission after 1918 (observable, for example, in the drop in childhood TB death rates) may have had secondary effects also on other diseases. The posited key role of TB in reducing the post-1918 male-female mortality differential is strengthened when causes of death other than TB are also examined, because, unlike with TB, no clear pattern emerges from these causes of death.

We emphasize that the highly unusual mortality age pattern of the flu deaths in 1918 (Figure 1) not only corroborates the connection with tuberculosis, which, as noted above, was a disease of adulthood in 1918, but also rules out causal connections between flu deaths and most other causes of death. For example, stroke is overwhelmingly a cause of death among the elderly. It is highly unlikely that the 10 percent contribution of deaths from stroke to the drop in the total male-female differential of mortality between 1917 and 1921 is causally related to influenza, as those who died of flu in 1918 were not susceptible to stroke in the years immediately following the epidemic. The reverse is true with tuberculosis, where the middle of the W-shape of flu death rates (Figure 1) coincided with the peak ages ofTB death rates in the years following 1918.

Conclusion

Some of the huge losses of life resulting from the 1918 influenza epidemic were, in some sense, borrowed against future deaths from tuberculosis. Although males suffered more than females from the heightened death rates during the flu epidemic, males' life expectancy rebounded faster in the two years immediately after 1918. This is a selection effect, or what Hobcraft, Menken, and Preston (1982) called a "cohort inversion" effect. Stated succinctly, the robustness of a cohort in the face of death can increase over age and time (up to a point), because of a shift in the unobserved heterogeneity among mortality risk factors. In the present case, the selecting mechanism was sex-differential mortality resulting from the 1918 influenza epidemic, and the unobserved (at the time) shift in risk factors was a decreased prevalence of tuberculosis infection, also differentially affecting males and females.

These results have much to teach us. The details of the epidemiologic transition (Omran 1971) are sex specific. Epidemiologic shocks can have

long-term effects on mortality differentials by sex if they act as a selecting mechanism. A result of this kind has not previously been documented in the demographic literature. Our study does so for the United States; exploration of the effect elsewhere would be worthwhile. This requires accurate mortality data, detailed by age and sex and cause, from the period both before and after 1918. The non-belligerent European countries during World War I, as well as Canada, Japan, Australia, New Zealand, and South Africa, may provide fertile ground for further investigation.

If another pandemic of hyper-virulent influenza were to appear, it is possible that the United States, where since 1918 the prevalence of tuberculosis has been reduced dramatically, would not suffer as greatly as before. This is because some of the peculiar and intense middle-age mortality from influenza observed in 1918 appears to be related to prior tuberculosis infection. On the other hand, developing countries, where TB is still highly prevalent (Dye et al. 1999), would be vulnerable and very likely would subsequently experience appreciable changes in male-female mortality differentials.

Notes

The authors acknowledge the support of the Rockefeller Foundation, grant number HS-9810. David Bloom, Leo Goodman, Ulrich Mueller, Ndola Prata, George Rutherford, Ross Stolzenberg, and Kenneth Wachter provided useful comments.

1 The reference is to the male minus female difference in the age-standardized death rate for influenza and pneumonia combined (except pneumonia of the newborn). By comparison the difference was 38 per 100,000 in 1917 and 13 per 100,000 in 1919.

2 All data presented here come from published vital statistics volumes. See Grove and Hetzel (1968) and US Department of Health, Education, and Welfare (1956). Before 1932, mortality statistics refer to the death registration area, not the entire country; in 1918, about 77 percent of the population of the United States was included in the death registration area (Linder and Grove 1943: 998).

3 Overseas war deaths are excluded from both the numerator and denominator of vital rate calculations (Grove and Hetzel 1968: 50).

4 The US standard population is the enumerated population of 1940, both sexes, all races. It is given in Grove and Hetzel (1968: 37).

5 This was the case in the 1940s, for example. A change in age-specific mortality rates affects the life table population (from which $e(0)$ is calculated) at that and all subsequent ages, so $e(0)$ is more sensitive than the ASDR to young mortality, except in cases where the standard population is weighted toward young ages. In the 1940s in the United States, male death rates attributable to childhood diseases improved more than female death rates, with improvements in both sexes possibly resulting from the introduction of antibiotic drugs or from wartime food rationing, which is redistributive (Dreze and Sen 1989: 181). This change affected $e(0)$ more than it did the ASDR.

6 Violent causes are: motor vehicle accidents, other accidents, suicide, and homicide. Influenza and pneumonia are listed as a single cause and exclude pneumonia ofthe newborn.

7 Analyzing Pearl's table 1, with influenza infection as the dependent variable, the logit coefficient for TB was 0.79 (odds ratio 2.2), controlling for household size ($p<0.0005$). In other words, among those living in a household with at least one case of active tuberculosis, the odds of getting influenza (i.e., the probability of getting influenza divided by the probability of not getting influenza) were 2.2

times higher for actively tuberculous individuals, compared to nontuberculous individuals in the household. A random sample of households would be preferable to a sample in which each household has at least one known case ofTB. However, Pearl did not design the study from the ground up: he was trying to make use of some routine data collected about tuberculous persons.

8 The analysis of Pearl's dataset is consistent with an interaction inside the body between the two pathogens. However, there are alternative explanations for the risk factor demonstrated in that analysis, such as occupational exposure to many other people and thus the increased likelihood of having contracted TB in the past as well as contracting influenza in 1918. Tuberculosis kills slowly, and in spite of public health campaigns not all those infected would have stayed away from work.

9 This was particularly true in the period we consider. In 1905, 1908, 1910-12, and 1915-20, TB death rates peaked at ages 25-34. In 1906-07 and 1909, non-infant TB death rates peaked in the 25-34 age group; in 1913-14, TB death rates peaked in the 35-44 age group. And in 1921-34, TB death rates had a mode in the 25-34 age group. After 1934, reflecting the changing epidemiology and demography of TB, death rates shifted to a unimodal profIle, peaking at older ages.

10 One caveat is the possible effect on TB death rates of American involvement, 1941-45, in World War II. This is hard to assess. Overseas servicemen, as noted earlier, are not included in the vital statistics system of the United States, and TB deaths can take place years after infection.

11 The exact agreement of excess TB deaths in the analysis with the estimates ofthe number dead in the 1918 epidemic might be a coincidence, but it is interesting to note that the two figures have the same order of magnitude.

12 The observation by Drolet (1942: A47), that in rural areas of the United States the sex differential of TB mortality was smaller than in urbanized areas, also points to the importance of transmission in the workplace.

13 Although the reversal in sign of the male-female ASDR differential for stroke lasted from 1918 to 1925, male rates were barely above female rates for stroke in 1917, whereas in 1916 and before men had a consistently higher ASDR for stroke. Whatever happened to the male-female differential in stroke death rates began in 1917, not in the year ofthe influenza epidemic.

References

Berin, B. N., G. J. Stolnitz, and A. Tenebein. 1989. "Mortality trends of males and females over the ages," *Transactions of the Society of Actuaries* 41: 1-19.

Bloom, B. R. and C. J. 1. Murray. 1992. "Tuberculosis: Commentary on a reemergent killer," *Science* 257 (5073): 1055-1064.

Couch, R. B. 1981. "The effects of influenza on host defenses," *Journal of Infectious Diseases* 144(3): 284-291.

Crosby, A. 1989. *America's Forgotten Pandemic: The Influenza of* 1918. Cambridge: Cambridge University Press.

Davis, K. 1951. *The Population of India and Pakistan.* Princeton: Princeton University Press.

Dreze, J. and A. Sen. 1989. *Hunger and Public Action.* Oxford: Clarendon Press.

Drolet, G. J. 1942. "Epidemiology of tuberculosis," in B. Goldberg (ed.), *Clinical Tuberculosis.* Philadelphia: F. A. Davis, pp. A3-A70.

Dublin, 1. 1. and E. W. Kopf. 1913. "An experiment in the compilation of mortality statistics," *Publications of the American Statistical Association* 13: 639-647.

Dye, C. et al. 1999. "Global burden of tuberculosis: Estimated incidence, prevalence, and mortality by country," *Journal of the American Medical Association* 282 (7): 677-686.

Grove, R. D. and A. M. Hetzel. 1968. *Vital Statistics Rates in the United States, 1940-1960.* Washington, DC: National Center for Health Statistics.

Hobcraft, J., J. Menken, and S. Preston. 1982. "Age, period, and cohort effects in demography: A review," *Population Index* 48(1): 4-43.

Keyfitz, N. 1985. *Applied Mathematical Demography.* Second edition. New York: Springer-Verlag.

Linder, F. E. and R. D. Grove. 1943. *Vital Statistics Rates in the United States. 1900-1940.* Washington, DC: US Government Printing Office.

Lowell, A. M. 1969. "Tuberculosis morbidity and mortality and its control." in A. M. Lowell, 1. B. Edwards, and C. E. Palmer, *Tuberculosis.* Cambridge, MA: Harvard University Press, pp. 1-121.

Murphy, S. 1. 2000. "Deaths: Final data for 1998," *National Vital Statistics Reports* 48(11): 1-108.

Murray, C., K. Styblo, and A. Rouillon. 1993. "Tuberculosis," in D. T. Jamison et al. (eds.), *Disease Control Priorities in Developing Countries.* Oxford: Oxford University Press, pp. 233-259.

Omran, A. R. 1971. "The epidemiologic transition: A theory of the epidemiology of po pulation change," *Milbank Memorial Fund Quarterly* XLIX(4, part 1): 509-538.

Oxford, J. S. et al. 1999. "Who's that lady?" *Nature Medicine* 5(12): 1351-1352.

Pearl, R. 1919. "Preliminary note on the incidence of epidemic influenza among the actively tuberculous," *Publications of the American Statistical Association* 16 (128): 536-540.

Preston, S. H. 1976. *Mortality Patterns in National Populations: With Special Reference to Recorded Causes of Death.* New York: Academic Press.

---. 1977. "Mortality trends," *Annual Review of Sociology* 3: 163-178.

Pyle, G. F. 1986. *The Diffusion of Influenza: Patterns and Paradigms.* Totowa, NJ: Rowman & Littlefield.

Reid, A. H., T. G. Fanning, J. V. Hultin, and J. K. Taubenberger. 1999. "Origin and evolution of the 1918 'Spanish' influenza virus hemagglutinin gene," *Proceedings of the National Academy of Sciences of the USA* 96(4): 1651-1656.

Reid, A. H., T. G. Fanning, T. A. Janczewski, and J. K. Taubenberger. 2000. "Characterization of the 1918 'Spanish' influenza virus neuraminidase gene," *Proceedings of the National Academy of Sciences of the USA* 97(12): 6785-6790.

Retherford, R. D. 1975. *The Changing Sex Differential in Mortality.* Westport, CT: Greenwood Press.

Sheps, M. C. 1958. "Shall we count the living or the dead?" *New England Journal of Medicine* 259(25): 1210-1214.

---. 1959. "An examination of some methods of comparing several rates or proportions," *Biometrics* 15: 87-97.

Tukey, J. W. 1977. *Exploratory Data Analysis.* Reading, MA: Addison-Wesley.

US Department of Health, Education, and Welfare. 1956. "Death rates by age, race, and sex, United States, 1900-1953: Selected causes," *Vital Statistics-Special Reports,* Vol. 43. Washington, DC: National Office of Vital Statistics.

Landry, Sarah

From: Andrew Pekosz [pekosz@borcim.wustl.edu]

Sent: Monday, September 20,20043:49 **PM**

To: NVPO

Subject: comments on pandemic influenza preparedness and response plan

To whom it may concern,

As a faculty member at an urban medical school/hospital complex who is running a basic research program investigating influenza virus replication, I read with much interest the draft proposal "Pandemic Influenza Preparedness and Response Plan" submitted for public comment by the Department of Health and Human Services. Overall, I found the plan to be well written and easy to follow, with a concise logical presentation of the proposed goals. I do however have several concerns that I would like to express. I will use the section designation of the executive summary draft to help relay my comments.

C. Pandemic Plan Development Process

bullet 5 - The updating of the preparedness plan should be done twice yearly, and be mandatory. This will allow for modifications, updates and revisions to be made mandatory.

E. Key Pandemic Preparedness and Response Principles

bullet 1 - Large scale increases in local surveillance for influenza will require a massive funding effort, not to mention drastic increases in laboratory worker numbers, increases in overtime costs, protective gear for hospital and laboratory workers and allocation of space for increased diagnostics.

In addition, changes in sample acquisition, storage, handling and testing will most likely need to be implemented due to the risk of exposure even if the workers are on an anti-influenza prophylaxis or have been immunized. There will most likely be regional or national centers that will be providing more rigorous (ie sequencing) characterizations of virus isolates. Shipping companies will need to be made aware of the increased volume of dangerous cargo and be educated accordingly.

Procedures for virus isolation and distribution will need to be assessed. Will research labs have access to these strains from local sources or from a regional/national bank? Local access would be preferred and more simple but procedures for distributing the virus should be in place. Getting pandemic influenza virus isolates into the hands of capable, trained investigators will be critical in order to characterize the virulence and replication changes going on during the viruses initial passage in the human population.

Containment levels for pandemic flu need to be established ahead of time. This will have a direct impact on clinical as well as basic science research labs with respect to allocating space to meet with increased diagnostic, virus isolation and virus growth/characterization needs. Will the viruses be considered BSL3 or BSL2? It seems to me this decision could be made immediately, and should be to categorized a pandemic influenza as a BSL2 pathogen. BSL3 classification seems pointless if the virus is currently circulating and spreading freely in the human population. This classification will be immensely important in ensuring appropriate laboratory and hospital space is available during an influenza pandemic.

bullet 2 - Pandemic influenza vaccine

My most immediate and pressing concern is in the generation of a pandemic influenza vaccine. There are two main points I would like to comment on 1) maintaining adequate vaccine to circulating, nonpandemic influenza strains and 2) pandemic flu vaccine preparation.

1) Maintaining adequate vaccine to nonpandemic influenza strains. It is not apparent to me that sufficient emphasis is placed on maintaining vaccine production of nonpandemic influenza strains. Sacrificing the production of standard vaccine for pandemic vaccines may have very negative effects with respect to dealing with influenza cases. As the 2003-2004 influenza season clearly showed, lack of effective vaccination to currently circulating influenza strains can lead to widespread outbreaks. An increase in nonpandemic flu cases, brought about by lack of vaccination, will further compound the influenza surveillance problem and place an even greater burden on the healthcare system. Vaccine production increases for nonpandemic strains should be a priority, as well as devoting additional resources/equipment to develop a vaccine against the pandemic strain. It is also quite possible that people/institutions will emphasize pandemic influenza vaccination at the expense of nonpandemic vaccination. Public and private education should be a priority in order to maintain population immunity to all circulating influenza strains.

2) The vaccine against pandemic flu should be considered separately from the currently licensed influenza vaccine, particularly with respect to regulations concerning vaccine generation and production. The emergence of pandemic influenza would be an event of massive public health importance and therefore requires the government to take unprecedented steps to ensure rapid production and availability of pandemic flu vaccines without compromising safety. This can be accomplished. Specifically, the appropriate authorities must allow for the following:

a) allow the use of plasmid based reverse genetics to generate appropriate vaccine strains (the pandemic flu vaccine).

b) allow the pandemic flu vaccine to be grown on Vero or other appropriate mammalian cell line.

c) present the vaccine in addition to, not as a component of or in place of the vaccine for nonpandemic influenza

If this plan is implemented for pandemic vaccines, the vaccine developers could move forward immediately with H5Nl based vaccines, generated with the above protocol. Those vaccines could enter into phase IIII trials to assess concerns about side effects resulting from this new way of generating flu vaccines. The results of this H5Nl vaccine study could then be proof that this alternate vaccine generation strategy can lead to an effective safe flu vaccine. The infrastructure needed to produce pandemic vaccines would then be independent of that needed for nonpandemic flu vaccines therefore the production of nonpandemic flu vaccine would be unaffected by the emergence of a pandemic influenza strain.

bullet 3 - Distribution of all influenza vaccines - pandemic and nonpandemic - must be handled by a central authority if an influenza pandemic is imminent. This is the only logical way to ensure an ordered distribution to prioritized populations across the country.

bullet 7 - all local jurisdictions should have a spokesperson responsible for disseminating information to the press. This person should meet at least once but perhaps twice a day with representatives of all the major media outlets in order to distribute relevant information as well as correct the false or misleading anecdotes that inevitably circulate during times of public health concerns.

While outside ofHHS jurisdiction, I would hope that similar plans are being made to deal with the immense nonmedical issues associated with an influenza pandemic. I sincerely hope the Dept. of

20048-0212 - Pandemic Influenza Preparedness Plan

FDA Comment Number: EC4

Submitter: Dr. Clara Witt

Date & Time: 09/28/200401:09:19

Organization: Dr. Clara Witt

Category: Health Professional

Issue Areas/Comments

GENERAL

GENERAL

Sirs: Please see attachment.
Thank you.

Sirs.

Thank you for the opportunity to comment on the draft Pandemic Influenza Preparedness and Response Plan, DHHS, August 2004. I congratulate the authors on their excellent and comprehensive approach to providing information necessary for public health authority and private sector preparedness planning for aninfluenza pandemic. I especially appreciate the decision to use the format of a general core document with targeted annexes. This helps the reader achieve an overall appreciation of the issue while also permitting the reader to focus on those issues of particular relevance to the reader's interest. I also very much appreciate the complementary bedding of the US plan into the basic framework of the WHO pandemic plan. This coordinated preparedness approach will enhance the plan's effectiveness in the US, but more importantly provide guidance to other countries interested in developing their own plans. It serves as a demonstration of the complementariness needed between national and international efforts. I believe that this draft plan, once finalized and implemented will greatly further the US ability to effectively respond to a pandemic should one occur.

In reading through the draft document, however, I have noted a few items that the authors may wish to review and consider for amendment.
1.

Executive Summary. Page 8, D, first bullet: '... mortality *at* from influenza .. .'.
Page 8, E, first bullet: does 'virologic' mean 'laboratory'? Unclear what is intended.
Page 8, E, third and forth sub-bullet under first bullet: uncommon use of English leading to confusion on what is intended.
Page 9,2), second sentence: double verb.

Annex 1. page 11, C.1. second paragraph, second bullet, : 'f.t.-i.s, should be ... .'

Annex 1 Page 17, E 1. last paragraph: 'Timely ... involved.': very confused English.
E 2. fifth bullet,: 'establish 9. hotline'?

Annex 3, page 4, Section V: This is a very different and unfortunately I believe more realistic interpretation of the potential impact of influenza and pandemics than what is presented in Annex 12, II page 2. Please see comments on Annex 12.

Annex 4, page 16, VI first paragraph: While there is nothing truly incorrect about what is stated in the paragraph, the first few lines suggest that WHO should have an animal disease surveillance program. However as WHO is a human public health organization, it has no mandate or authority to conduct animal disease surveillance. That activity rightly comes under the mandate of the FAO. WHO can encourage zoonotic disease surveillance, as a human or public health measure if a human health threat is identified. With the H5N1 virus, because of the human threat suggested by known cases of H5N1 infection, WHO was able to facilitate countries' efforts to implement avian and swine influenza surveillance in support of human disease prevention and control. Without an explicit statement of human health risk, however, WHO activities in animal health are rightly subject to criticism by other international organizations. Unfortunately, in the 2004 H5N1 outbreak in Asia, some other international organizations, more specialized in animal health, were slower than WHO to respond to the rapidly growing crisis.

Annex 6 page 9 , B. second paragraph, second line: 'the groups what? are at highest risk'

Annex 10, page 6, B, first paragraph: See comments in Annex 4. It may be helpful to change the wording to avoid impling that WHO is mandated to conduct animal disease surveillance. It is not. The first sentence could be modified to focus more on the animals as the source of the human influenza threat. For example: ' While no organized WHO program currently exists to conduct influenza surveillance in probable sources, avian species and swine, the value of this type of surveillance in assessing the human health risk is understood and such activities are likely to be expanded.'

Annex 12, page 2, IIA: While much needs to be learned about H5N 1, I believe strongly that we should not automatically equate the pandemic potential of a virus with its virulence. Given what we have experienced to date with the H5N1 outbreak in susceptible species, humans and poultry, I believe the assumptions made in this section are very optimistic. We obviously do not have good numbers from Asia to determine a true human attack rate for this virus. But the estimated case fatality rate in known cases lies somewhere between 60 and 70 %, not the 1% projected in the draft as based on the experience with the other two pandemics in 1957 and 1968. We experienced in poultry, the other non-reservoir susceptible species, that both the exposed flock attack rate and case fatality rate are very high, close to 100%. I cannot discuss the virulence of the 1957 and 1968 viruses, but from what I've seen of the H5N 1, this virus kills and kills quickly. The duration of symptomology in infected poultry was about 4to 6 hours only. Signs noted in poultry were compatible with a massive cytokine disregulation. If the speed and pathogenic mechanism is similar in humans, I am not certain that the US health care system will be able to keep a fatality rate near a 1% level. even with an adequate (quality and quantity) surge capacity in the US. I question the assumption that with ancillary home care measures we will be able to provide quality health care to all those in need. While significant improvement have been made in medical care over the last 90 years, routine nursing care will not prevent many fatalities, health care providers and volunteers will again be afraid and reluctant to aid the ill, and as our capacity to safely handle the ill becomes overtaxed, care centers will be avoided by the general public. I believe that what we know of the 1918 pandemic will be a closer model for a H5N 1 pandemic that we would like. Given my pesimissim, I do applaud every effort being done to develop an effective H5N 1 vaccine. Adequate vaccine supplies will do much to counter the threat of H5N1.

CONOPS, page 6, OSG bullet: The professional category 'veterinarians' is not listed. While a small PHS Commissioned Corps Category, veterinarians are as required to participate in CCRF as other professionals and can contribute to medical emergencies in more roles than just food safety inspectors. For example, as stated in the main draft influenza pandemic plan, influenza originates as a veterinary disease, and zoonotic disease surveillance and zoonotic disease prevention and control activities, that is the practice of veterinary public health, are currently underway and expanding. The contribution of veterinarians to mitigating medical emergencies should be no more relegated to 'other' than some of the other professions listed in the paragraph.

Again, the minor nature of these comments demonstrate the quality of the work undertaken.

Sincerely,

Clara J. Witt, VMD, MPH
9505 Woodstock Ct
Silver Spring, MD 20910
clara.witt@na.amedd.army.mil

20048-0212 - Pandemic Influenza Preparedness Plan

FDA Comment Number: EC2

Submitter: Dr. howardweinblatt

Date & Time: 09/07/200408:09:13

Organization: Dr. howard weinblatt

Health Professional

Category:

Issue Areas/Comments

GENERAL

GENERAL

I fInd very little in the plan that suggests the use of the large private ambulatory health care system including offices and professionals that will likely not be utilized through hospitals or the health dept. I know in our juristiction there is not even an inventory of resources. I would think this a high priority for local health departments and national strategy planning.

Current professionals and offices could voluntewer to become part of the emergency network with special training and perhaps on site supplies as well as a communication plan.

20048-0212 - Pandemic Influenza Preparedness Plan

FDA Comment Number: EC23

Submitter: Ms. Tricia Hosch-Hebdon

Date & Time: 11/09/200401:11:26

Organization: Idaho Department of Health and Welfare

State Government

Category:

Issue Areas/Comments

GENERAL

GENERAL

October 26, 2004

Idaho Department of Health and Welfare, Immunization Program Comments on the Draft National Influenza Pandemic Plan.

1. Priority Vaccination Groups: Members of the Immunization Program, Office of Epidemiology and Food Safety, Health Preparedness Program and several of the Idaho's Public Health Districts have indicated the need for the National Influenza Pandemic Plan to describe the process for assigning priorities groups, what priorities groups would look like if they differed from currently established priority groups and how such information would be disseminated to the state and local level. Priority groups are frequently mentioned through out the draft document but no where does it state how such priority groups will be established and how the states are suppose to implement and enforce vaccinations in these groups during a vaccine shortage. In addition, states need to know the level of flexibility that state and local governments would have in adjusting priority groups based on regional differences. In light of the current influenza vaccine shortage and the desperate need for federal guidance and input during this crisis, it is felt that during an influenza pandemic that key national guidance would be even more important and must be thoroughly addressed by the National Influenza Pandemic Plan. Further more, the necessity of standardization of guidelines across state jurisdictions will be critical for consistency and to limit regional disparities, especially in areas where cross-jurisdictional boundaries are plentiful.

2. Anti-virals: A detailed explanation of how anti-virals will be acquired and rationed during a pandemic influenza event is critical. Currently there is a great deal of confusion about how anti-virals would be acquired or distributed to state and local areas. Without a good understanding of which national programs and entities are coordinating these efforts it will make it harder for the states to be able to clearly and objectively direct resources and communications. In addition, in light of the 2004-2005 influenza vaccine shortage and the CDC's release ofInfluenza Antiviral Medications: 2004-05 Interim Chemoprophylaxis and Treatment Guidelines, it will be necessary to see how such guidelines effect disease transmission and treatment.

3. Vaccination Plans: A recommendation for more clear and concise guidelines for vaccine distribution, vaccine funding, vaccine redistribution and to the extent vaccine will remain private or public or a mixture of both is desperately needed. The current draft plan does not adequately address any

of these topics and has only a vague commentary on how such vaccine management and distribution practices should happen.

Landry, Sarah

From: JVbarry@aol.com
Sent: Tuesday, October 12, 20041 :29 PM
To: NVPO
Subject: comment on draft preparedness document

I am the author of the book The Great Influenza: The Epic Story of the Deadliest Plague in History and have a couple of comments.

Over-alii find the document a fine one, but I would like to make a couple of criticisms. First, the estimate of the death toll from the 1918 pandemic of "more than 20 million deaths worldwide" is technically accurate but so low as to be misleading. As you probably know, a consensus has formed among experts now that the death toll was at least 40 million, and possibly much higher. (Nobel laureate Frank macfarlane Burnet believed deaths were at least 50 million, and may ahve reached 100 million.)

Second, the estimate you cite from CDC of the death toll from a new pandemic (89,000 to 207,000) has been widely criticized, not only by me but by a consensus of the June, 2004, Insititute of Medicine meeting on pandemic influenza. This number seems to come from simply averaging the three pandemics of the 20th century. In reality, 2 of those 3 actual pandemics had death tolls outside this predicted range: 1968 was somewhat under, and 1918 way over, demonstrating how poor this number is. The chief variable and the chief determinant is the virulence of the virus, which is very difficult to predict, but any virulent virus will cause far more deaths than the worst case in this prediction.

I believe you should adjust these numbers to give people a more accurate sense of the threat.

John M. Barry
Distinguished Visiting Scholar
Center for Bioenvironmental Research of Tulane University

20048-0212 - Pandemic Influenza Preparedness Plan

FDA Comment Number: EC3

Submitter: Mr. John Hoyle

Date & Time: 09/23/2004 06:09:56

Organization: DHS/FEMA

Category: Health Professional

Issue Areas/Comments

GENERAL

GENERAL

HHS is counting on using DMAT teams to assist in a pandemic. DMAT members need to have training to "de-mystify" influenza and what protective equipment to wear, modes of transmission info etc. They need a concrete, foolproof, 24/7 plan to be vaccinated and/or prophylaxed and must have confidence that the HHS leadership will support them. Ifnot, I fear that their members will not answer the call and we cant make them.

John Kelley
401 Florence St.
Palo Alto, CA 94301
Tel: 650-327-9811
Fax: 650-327-3737
jkelley@computerlaw.com

October 28,2004

Via Email and Federal Express

National Vaccine Program Office
Office of the Assistant Secretary for Health
Department of Health and Human Services
Hubert H. Humphrey Building
200 Independence Ave, SW -- Room 725H
Washington, DC 20201-0004

Dear Sir or Madam:

Introduction.

I am submitting the following preliminary comments regarding the "PANDEMIC INFLUENZA PREPAREDNESS AND RESPONSE PLAN," Department of Health and Human Services ("DHHS"), Draft, August 2004 (the "Draft Pandemic Preparedness Plan") (http://www.hhs.gov/ nvpo/pandemics/execsumm8.12.doc. http://www.hhs.gov/nvpo/ pandemicplan/index.html). If there is a later opportunity to modify these comments or submit additional comments, or if these comments must be submitted in a different format, please let me know.

A. The Present State of a Possible Pandemic.

From published reports (M., "Enhanced: Public Health Risk from the Avian H5Nl Influenza Epidemic," *Science* 14 May 2004; 304: 968-969; "Experts Probe Flu Death, Call for Poultry Vaccination," *Science* 1 October 2004; 306: 31), avian influenza now appears to be somewhere between pandemic phases 0.2 and 0.3 (as that terminology is used in the Draft Pandemic Preparedness Plan, Executive Summary, p. 5). Accordingly, preparedness for a possible avian influenza pandemic should be a national - and international - priority.

B. General Comments Regarding Annex 5: "Vaccine Development and Production."

The *New York Times* recently reported that Chiron was also one of only two U.S. companies working on developing a vaccine for avian influenza A(H5Nl). (See "Experts Confront Hurdles in Containing Bird Flu," September 30, 2004.) Whether the recent

developments regarding Chiron's production of other influenza vaccines will adversely affect its work on an avian influenza vaccine remains to be seen.

Furthermore, that article also reported that "[0]ther drug makers have given several reasons for not making vaccines," including (a) "that intellectual property rights on new techniques used to make the vaccine remain unsettled" and (b) the worry that "they could be exposed to considerable liability if they put out a new vaccine without lengthy safety tests first." I am very concerned that these legal issues - in addition to numerous scientific and financial issues - are impeding the rapid development and manufacture of vaccines for avian influenza in large volumes. (If avian influenza becomes truly virulent, one suspects that demand for such a vaccine in the United States, and throughout the world, could make the current controversies over failures to produce sufficient quantities of other influenza vaccines appear almost inconsequential.)

I have not seen where such legal issues are specifically addressed in the Draft Pandemic Preparedness Plan. For example, while Appendix 5 does recommend an action to, "[p]rovide incentives for new vaccine manufacturers to enter the U.S. market to increase production capacity and, through diversification, enhance the probability that vaccine will be produced rapidly and made available early," p. 9, this is not the same as removing legal disincentives for new vaccine manufacturers to enter that market. While Appendix 5 also refers to $150 million in RFPs between FY'04 and FY 'OS, p. 8, it does not demonstrate that those RFPs will be sufficient to overcome the legal concerns identified in the *New York Times* article.

C. Specific Preliminary Questions Regarding Annex 5: "Vaccine Development and Production."

While considerable work appears to have gone into the Draft Pandemic Preparedness Plan, I believe there are additional questions that it should address, particularly with regard to Annex 5. Although the limited number of influenza vaccine manufacturers licensed for the U.S. market is noted in the Executive Summary, at p. 9, my questions focus on the overall issues of whether the plan could and should do more to ensure that there will be a sufficient number of developers and manufacturers capable of producing a vaccine, in a timely manner, to avert a true pandemic.

My specific questions are:

1. Has adequate information been obtained?

Has the DHHS obtained sufficient information from potential developers and manufacturers of avian influenza vaccines (including private companies, universities, other research institutions, and other non-profit organizations, both within and outside the United States) to know (a) whether there are additional such organizations that would

consider developing or manufacturing such a vaccine for the U.S. market, and (b) ifso, what concerns are keeping them from doing so?

What information has the DHHS obtained in this regard?

What surveys have been conducted?

What are the concerns of such potential additional developers and manufacturers?

Does the Draft Pandemic Preparedness Plan address all of those concerns? If not, how will such additional concerns be addressed in new actions to improve vaccine development and production?

If all such information has not been obtained, should it be obtained? If so, how will it be obtained, by when, and how will it be made available for further public comment?

2. What metrics will be used?

The Draft Pandemic Preparedness Plan discusses several actions "to improve vaccine development and production" (Appendix 5, pp. 6f.), but what metrics will be used to assess the effectiveness of such actions?

How will responsible persons - and the public - know whether these actions are successful or not?

What metrics will be used to assess whether timely progress is being made to increase the number of potential developers and manufacturers of avian influenza vaccines?

How many doses of an avian influenza vaccine should be stockpiled to protect the entire U.S. market?

What are reasonable numbers of (a) developers and (b) manufacturers to ensure the timely delivery - even in the face of periodic manufacturing difficulties - of a sufficient number of doses of an avian influenza vaccine to protect the entire U.S. market?

How will success be established?

How will possible failure be noted? How will possible failure be noted sufficiently quickly to allow time for pursuing other courses of action before a pandemic arises?

//
//
//

3. What specific timetables will be followed?

Again, with regard to the actions "to improve vaccine development and production" (Appendix 5, pp. 6f.), what specific timetables will be followed?

How will responsible persons - and the public - know whether the contemplated actions are being carried out in a timely manner?

How long will it take to improve development and production sufficiently to have available at least 30 million doses of an avian influenza vaccine? (Best, worst, and likely cases?)

How long will it take to improve development and production sufficiently to have available at least 300 million doses of an avian influenza vaccine? (Best, worst, and likely cases?)

How long will it take to improve development and production sufficiently to have available at least I billion doses of an avian influenza vaccine? (Best, worst, and likely cases?)

4. Who will be held accountable?

Again, with regard to the actions "to improve vaccine development and production" (Appendix 5, pp. 6f.), who will be held accountable for ensuring that these, or other actions, are successful?

Which individuals are directly and personally responsible for these matters? How will their performance be monitored and reviewed?

Who supervises such persons? How will the actions of those supervisors be monitored and reviewed? Who will monitor and review their supervisory work?

5. How will Congress and the public be kept informed?

By what means will the responsible persons and their supervisors make known the status of all actions "to improve vaccine development and production" (Appendix 5, pp. 6f.) to Congress and the public?

Are periodic reports contemplated? If so, how frequently will they be made, and what information will they provide? How will such reports be distributed?

//
//
//

6. Is funding adequate?

Is the funding described in the Draft Pandemic Preparedness Plan truly adequate to support all necessary actions "to improve vaccine development and production"? (Appendix 5, pp. 6f.)

How would the timetable for developing and manufacturing at least 30 million doses of an avian influenza vaccine be affected if funding were increased by 300% in the current fiscal year? By 1OOO%?

How would the timetable for developing and manufacturing at least 300 million doses of an avian influenza vaccine be affected if funding were increased by 300% in the current fiscal year? By 1OOO%?

How would the timetable for developing and manufacturing at least 1 billion doses of an avian influenza vaccine be affected if funding were increased by 300% in the current fiscal year? By 1OOO%?

Would a prize or guaranteed contract for a certain number of doses have a material effect on increasing the speed of developing and manufacturing an avian influenza vaccine? If so, how large must a prize be to have a significant material effect? If so, how many doses must be included as part of such a guaranteed contract?

7. Are actual or perceived legislative or regulatory obstacles preventing other developers and manufacturers from entering the market?

Have actual or perceived legislative or regulatory obstacles been addressed with possible new developers or manufacturers?

If so, what obstacles have been identified? How could any such obstacles be overcome?

If not, why have such issues not been addressed?

How long is it likely to take to obtain regulatory approval for the release of experimental versions of avian influenza vaccines? What could be done to shorten the time for obtaining such regulatory approval? In a true pandemic emergency, what authority exists for expediting regulatory approval in the United States?

8. Have the legal concerns identified in the *New York Times* article been addressed?

Is it true "that intellectual property rights on new techniques used to make the vaccine remain unsettled"? If so, what are those specific issues, and how could they best be

addressed? What specific patents or other intellectual property rights are at issue, and who controls the rights to those patents or other rights?

Is it true that potential developers or manufacturers of an avian influenza vaccine worry that "they could be exposed to considerable liability ifthey put out a new vaccine without lengthy safety tests first"? If so, what could be done, specifically, to overcome such concerns?

How could existing legislation concerning indemnification for vaccine production and distribution be modified (a) to address such concerns, if any, and (b) to ensure that experimental avian influenza vaccines are covered?

9. How are efforts being coordinated internationally?

How are efforts to increase the number of potential developers and manufacturers of avian influenza vaccines being coordinated internationally?

What could be done to enhance international cooperation in this regard?

10. How can others help?

How can individuals and groups outside the DHHS support the DHHS and help improve the Draft Pandemic Preparedness Plan? How can we help prepare for a possible pandemic?

Conclusion.

The Draft Pandemic Preparedness Plan is an extremely important step towards addressing what may become a problem of global proportions. At the present time, no one knows whether, or how quickly, avian influenza may transform itself into an extremely virulent disease. Current mortality rates for the disease are extremely worrisome. How mortality rates would be affected in the event of an actual pandemic - when health care resources could be stretched to the breaking point - is not known. What we do know is that avian influenza could, even in a very short time, become extremely dangerous.

It is my sincere hope that these comments may be of use in strengthening the Draft Pandemic Preparedness Plan. We should all work to prepare as well as we can for a possible pandemic. Thank you for taking the time to consider these questions. If I can provide you with any additional information, or if there are other means by which I can stimulate further dialogue concerning these issues, please let me know. Any responses from you would be most appreciated.

Sincerely yours,

John Kelley

20048-0212 - Pandemic Influenza Preparedness Plan

FDA Comment Number: ECll

Submitter: Dr. Jonathan McCullers Date & Time: 10/26/200404:10:10

Organization: St. Jude Children's Research Hospital

Academia

Category:

Issue Areas/Comments

GENERAL

GENERAL

I would like to express my appreciation to Secretary Thompson and the HHS for their foresight in preparing this pandemic preparedness plan. This is a much needed step towards protecting the world from an incipient pandemic. In particular, a renewed focus on basic science research is vital if we are to meet this challenge.

I would like to make a brief comment on Annex 10: Pandemic Influenza Research. The goals for this section are laudable and I do not disagree with any of the research priorities laid out there. However, I feel the area of pathogenesis in humans has been relatively undervalued in the prioritization. Although influenza is one of the leading causes of death in the world, the primary viral infection is rarely the direct cause of mortality. Instead, infected persons die of cardiac disease (usually patients with pre-existing co-morbidities) or succumb to secondary bacterial pneumonia. Around 25% of all mortality during a typical influenza season is due secondary bacterial infections. This association is even stronger during pandemic influenza, where around 70% of influenza cases are complicated by bacterial co-infections. Thus, it can be predicted that the virulent influenza virus strains that are most likely to cause the next pandemic, or to be utilized as agents ofbioterrorism, would achieve much of their impact through secondary infections. Despite this association being appreciated since 1803 and being the focus of the majority of research following the 1918 pandemic, little is known about the pathogenesis of either cardiac death or secondary bacterial infections following influenza. A clearer understanding of the pathogenesis that underlies these interactions will provide targets for drug or vaccine-based interventions. For instance, it could be hypothesized that the statio class of drugs, a widely available and inexpensive set of compounds that have anti-inflammatory activity, could ameliorate the cardiac complications of influenza reducing the death toll during a pandemic. However, no basic research into this area has been attempted.

Thus, I would respectfully suggest that the following Goal and Priority Actions be added to Annex 10 under the Basic Virology and Molecular Virology section:

Goal: To understand the mechanisms by which influenza viruses predispose to bacterial infections.

Goal: To understand the mechanisms by which influenza viruses contribute to pulmonary, cardiac, and circulatory deaths.

Priority Actions:

- Conduct studies to determine the mechanisms that predispose to bacterial infections during influenza so that vaccine and drug based interventions can be developed.
- Determine the contribution of specific viral virulence factors to secondary bacterial infections to aid in identification of viruses or gene segments with the potential to contribute to epidemic and pandemic mortality.
- Conduct studies to determine the mechanisms by which influenza exacerbates pre-existing pulmonary or cardiac disease.

Thank you,

Jonathan A. McCullers
81. Jude Children?s Research Hospital
jon.mccullers@stjude.org
(901) 495-5164

PANDEMIC INFLUENZA PREPAREDNESS AND RESPONSE PLAN

Review and Response to Annexes
Jonathan L. Temte, *MD/PhD*

Annex 2:
This annex provides an overview of extensive needs presented for the healthcare system to tackle in preparation for an influenza pandemic. It documents estimated health care system burden imposed by a pandemic and the responses needed for health care facilities, planning for distribution of antiviral medications and vaccine, infection control practices, outbreak control, and non-traditional facilities for provision of health care.

Recommendations are as follow:

(1) small rural hospitals are often staffed by the same physicians that provide emergency services and provide routine outpatient care in ambulatory settings. Hence, special consideration must be made in rural settings to ensure that healthcare needs in these potentially competing spheres can be met [page 5].

(2) The triage process will often start with a telephone call to an ambulatory primary care clinic and be fielded by a triage nurse, medical assistant, or receptionist. Planning needs to be made to provide sound advise and phone triage to minimize patients arriving to clinical settings to those that need to be seen [page 6].

(3) Plans to provide segregated seating, waiting and possible entry at ambulatory centers need to be considered. The bulk of pandemic patients will be seen, evaluated and (possible) treated in outpatient, primary care centers, where usually medical care provision will still need to occur [page 7].

(4) The is significant concern regarding the role of medical trainees (e.g., resident physicians) that provide a bulk of inpatient care in academic settings. The legal ramifications of required work duties in highly dangerous settings must be established during a pre-pandemic period [page 9]

(5) Functional lists for equipment and supplies for out-patient settings and mechanisms to maintain some active supply is needed [page 10].

(6) Many ambulatory settings are eliminating pharmaceutical samples, thus eliminating a potentially important "stockpile" of broad spectrum antibiotics, which may be useful for secondary infections. Outpatient facilities may wish to modify their policies [pagel0].

(7) Patient education material should be written at a 4th or 5th grade level and be available III appropriate languages for usual patient populations [page 18]

Annex 4:
This annex discusses the issues surrounding surveillance in the inter-pandemic and pandemic periods. It provides excellent background on the existing surveillance mechanisms, challenges, and needed enhancements. The role of veterinary surveillance is also discussed.

Recommendations are as follow:

(1) Despite being readily available via the internet and comprehensive, the "Weekly Influenza Surveillance Report" is vastly underutilized by practicing clinicians because it not provided in a clinically-relevant format. Efforts to create state level, brief clinician influenza updates could serve as an excellent vehicle to connect practicing clinicians with their public health agencies [page 5].

(2) To facilitate better buy-in of professional organizations, CDC should form cooperative agreements with professional societies to better populate the U.S. Influenza Sentinel Provider Surveillance Network, especially in under-represented states. Options could include accessing practice-based research networks to facilitate recruitment and dissemination of feedback to clinicians [page 7].

(3) A need exists to create credible clinician liaisons on a state-by-state basis to work with the state's influenza coordinator to better present clinically-relevant information to clinicians during inter-pandemic periods [page 13].

Annex 6:

This annex discusses issues around influenza vaccine supply, population susceptibility and risk, and the current system of vaccine distribution. It reviews the likely vaccine status and strategies during a pandemic, identifying goals and priorities. Vaccine safety issues are discussed as well as the role of pneumoncoccal vaccine use in inter-pandemic periods.

Recommendations are as follow:

(1) A great deal of work is needed to develop plans for efficient and equitable vaccine distribution during periods of limited supply (either during a pandemic or during inter-pandemic periods when there is a failure in manufacturing/distribution). Efforts should be made to bring together stakeholders to discuss lessons learned (e.g., after the 2004 vaccine shortage) and to formulae action plans that can be taken back to their constituencies [page 6].

(2) The likelihood of significant regional differences in priority populations for vaccine should be acknowledged and endorsed (e.g., snowplough and fuel oil truck drivers in the Midwest), along with the role and responsibility of setting these priority populations by state pandemic planners [page 8].

Annex 7:

This annex provides a reasonable overview of antiviral chemistry, clinical use, efficacy, adverse effects, known resistance patterns, and issues around production and supply. Section II describes the goals of antiviral therapy and is well-balanced. Section IV-in providing strategies for antiviral use-leaves much open ground for states and local jurisdictions to attempt to fill without sufficient guidance.

Recommendations are as follow:

(1) Provide an exhaustive list of examples for priority populations for antiviral therapy and prophylaxis. [page 9]

(2) Provide guidance on [and perhaps legislative sanction/protection for] individuals who should be designating the "high priority" groups. [page 9]

(3) Set standards for appropriate distribution of antiviral medications on a national scale. Provide regulatory oversight for distribution. [page 9]

(4) Suggest that states and other jurisdiction enumerate estimated levels of priority age groups, high risk medical groups, and other "high priority" groups from which to better gage the relative emphasis on prophylaxis and treatment. [page 10]

(5) For point-of-care distribution strategies, the role of community-based clinics and clinicians must be considered. A plan that uses only hospitals and emergency department seriously skews point-of-care services to urban centers. [page 11]

(6) Professional organizations should be designated [and funded] to develop and make available appropriate fact sheets (in conjunction with CDC). [page 12]

(7) Rank priority population in case antivirals become in short supply.

Annex 8:

This annex provides background and guidance on strategies to limit transmission. Appropriate information is provided on the routes of transmission. Such efforts are significantly hindered by the nature of influenza infection in humans and the plethora of clinical manifestations noted across ages, virus strains, and immune system status.

Recommendations are as follow:

(1) There will be a need to rapidly assess a broad spectrum of illness presentation across age groups [and potentially other demographic parameters] and to rapidly disseminate this information to healthcare providers. [page 2]

(2) "High risk" clinical/medical procedures should be clearly identified and could be informed by studies of SARS (e.g., use of nebulizers, tracheal intubation). [page 5]

(3) Closure of daycare centers should be explicitly identified as one other method of community-based transmission prevention. [page 5]

(4) A tool for health care settings should be developed and disseminated to provide guidance on appropriate supplies, such as surgical masks, to have on hand, based on historic levels of acute respiratory infections, number of patients per year, and number of health care providers. [page 6]
(5) There needs to be in place a widespread system that can be rapidly activated to collect material for virological studies. One such system would be to engage primary care practice-based research networks. [page 8]
(6) Professional organizations should be designated [and funded] to develop (in conjunction with CDC) and make available appropriate handout materials to distribute to patients on home isolation. This would need to provide basic information and strategies for home isolation, written at a 5th grade reading level. [page 9]
(7) Information material should be created and made available to air travelers with destinations in novel strain endemic areas along with material designed for passengers returning from such areas. [page 10]

Annex 9:
This annex provides an overview of the goals of communication and education. Guidance is informed by recent events related to the SARS emergence. The role of a well-planned communication response forms the bulk of the narrative.

(1) Efforts to create and continuously update both "just-in-case" and "just-in-time" educational materials for healthcare workers is a priority [page 3].
(2) There exists an unmet need for clinician liaisons from representative healthcare professional societies [and perhaps from each state] to inform the creation of messages to healthcare providers and to serve as potential "clinician colleague experts" at times of need for clinical competence and credibility, working closely with public health colleagues [page 4].
(3) Efforts should be made to partner with professional societies to (a) get clinically-oriented education to regular CME meetings and (b) establish a cadre of discipline-specific "experts" to help get messages across to the wider membership [page 9].

Annex 10:
This annex provides an overview of research goals and priority actions as they apply to basic virology, animal surveillance, human surveillance and epidemiology, diagnostic tools, antiviral agents, vaccine development, research support and training, and communication strategies. The narrative provides a good description of current research mechanisms.
Recommendations are as follow:
(1) There is insufficient attention provided in most of the research endeavors to include the primary care arena wherein most people with influenza present. Also, there is heavy emphasis on hospitalized patients as opposed to non-hospitalized patients. Consequently, primary care researchers have been excluded from funding because of their lack of expertise and/or training and/or hospital-based venues. Efforts to enhance translational aspects of influenza research must include the clinicians that actually deal with most medical of influenza in the United States. [general comment]
(2) Efforts to develop new technologies for pandemic influenza prevention and control must also be coupled with some economic and cost-effectiveness analyses to assess the effect of technology creep into routine practice. [page 4]
(3) The role of feedback of surveillance information to practicing clinicians should be examined in terms of enhancing clinician awareness and reactivity to annual influenza outbreaks and/or pandemic influenza. [pages 8 ~nd 16]
(4) Efforts to develop new vaccine production methods.
(5) Model effects of annual universal immunization recommendation.

20048-0212 - Pandemic Influenza Preparedness Plan

FDA Comment Number: EC6

Submitter: Ms. Kathleen LeDell Date & Time: 10/08/200404:10:08

Organization: Minnesota Department of Health

Category: Health Professional

Issue Areas/Comments

GENERAL

GENERAL

My comment relates to Annex 8, section B, recommended inlfuenza precautions in health care settings, page 4: The guidance states that health care personnel should wear a surgical mask when entering the room of a patient with known or suspected influenza.

I strongly disagree with the recommendation of a surgical mask for health care workers caring for influenza patients. Surgical masks are not adequate PPE for airborne infections. Even though influenza is primarily spread via droplet, even this "document acknowledges that there may also be airborne spread. I think most experts would agree that influenza is more infectious than SARS and it does not seem reasonable to recommend a lower level of protection for pandemic influenza, which is likely to be at least as deadly as SARS. I think that an N95 respirator or PAPR should be recommended, at least in the initial stages of a pandemic and while supplies last. Thank you for allowing me to comment.

COMMENTS ON 2004S-02l2 - Pandemic Influenza Preparedness Plan
Submitted October 25, 2004 by:

Marc Lipsitch, D.Phil.
Associate Professor
Departments of Epidemiology and
Immunology and Infectious Diseases
Harvard School of Public Health
677 Huntington Avenue
Boston, MA 02115
(617) 432 4559
mlipsitc@hsph.harvard.edu

Christina Mills
M.D.lD.Sc. Candidate
Harvard Medical School and
Department of Epidemiology
Harvard School of Public Health
677 Huntington Avenue
Boston, MA 02115
(617) 432 1476
cmills@hsph.harvard.edu

We wish to submit the following comments on the Pandemic Influenza Response and Preparedness Plan.

1. OVERALL COMMENTS. The document overall is comprehensive, is well thought-out, and generally reflects up-to-date science. In particular, we support the Plan's emphasis on providing a safe and effective vaccine for an emerging strain as fast as possible. The plan makes note of research whose findings can be expected to help speed this process, and we believe that this research deserves very high priority, in light of the high probability of another pandemic in the coming decades and the near certainty that the pandemic will have significant impact in the US.

For vaccine production technologies as well as other control, communication and epidemiologic activities, it will be critical to engage in "practice" and test runs during interpandemic years to ensure that they are as effective as possible during the disruptions that will likely result during a pandemic.

Our major concern is that, given the nonspecificity of influenza symptoms and the ability to transmit before symptom onset, most "traditional" public health measures, including those that were successful in containing SARS, will have limited utility [1,2]. While the Plan acknowledges this risk, *we believe the Plan could be improved by further consideration of measures that can be taken if indeed control by isolation, Quarantine, and related measures are impractical prior to vaccine availability.* Many of our suggestions below (2-4) address the data needs and possible interventions available during this period.

2. PREPAREDNESS FOR RAPID EPIDEMIOLOGIC DATA GATHERING AT THE OUTSET OF THE PANDEMIC BY DEVELOPMENT AND TESTING OF STUDY PROTOCOLS. With the emergence of a new pandemic strain, several basic epidemiologic quantities (in addition to the reproductive number, see below) will be

unknown, and knowledge of these quantities will be important to the scientifically based design of control measures. Baseline estimates will be needed as early as possible, and continuous monitoring will be required as many of these quantities will change over time. Specifically, these quantities include:

(a) The case-fatality proportion in various risk groups
(b) The clinical risk factors for hospitalization, mortality and other severe outcomes
(c) The time course of viral shedding relative to time of infection
(d) The time course of symptoms relative to time of infection and to viral shedding
(e) The effectiveness of the vaccine (once available) in various demographic groups, both in preventing infection (shedding) and in preventing illness and severe illness.
(f) The proportion of infections that are susceptible to antiviral agents by laboratory criteria (this is a number that is particularly prone to change).
(g) The proportion of hospitalized cases in which evidence of bacterial superinfection is present as an exacerbating factor
(h) The effectiveness of nonspecific therapies, such as steroids, in treatment of severe cases.

As in the case of the surveillance indicators described above, it will be difficult to gather these data in the context of a pandemic. *Protocols, questionnaires and (where required) information systems should be developed in advance and tested/rehearsed in interpandemic years wherever possible to facilitate the estimation of these quantities, which characterize a novel strain and inform the design of control measures.*

3. EXPANDED SURVEILLANCE DURING A PANDEMIC. *Monitoring the effectiveness of control measures* is an important objective of surveillance that is largely overlooked in Annex 4 and the plan as a whole. Throughout the pandemic, and especially in the period prior to widespread vaccine availability, decisionmakers and the public will need to know the extent of ongoing transmission and the effectiveness of containment measures. An overall measure of the effectiveness of containment is the instantaneous estimate of the reproductive number of the infection. The reproductive number at a given time, represented as $R(t)$, is the average number of secondary cases infected by each primary case infected at time t. This number must be held steadily below one for the spread of the virus to decline; while this objective mayor may not be possible for pandemic influenza without a vaccine, the level of $R(t)$ is perhaps the best single measure of the effectiveness of control measures at a given time.

Fortunately, methods for calculating this quantity in real time have been described in a recent publication [3,4]. Existing surveillance systems should incorporate this method, or a variant of it, to provide decisionmakers with data to monitor containment activities.

In addition to this overall measure of effectiveness, there are a number of process measures that may be relevant to monitoring the impact of particular interventions. These depend on the type of intervention, but include such indicators as:

(a) The mean (and distribution) of time from identification ofa case to isolation of that case (if isolation is used)
(b) The mean (and distribution) of time from identification of a case to antiviral prophylaxis and/or quarantine of contacts (if targeted prophylaxis and/or quarantine is used)
(c) The number and proportion of travelers testing positive for influenza (if border controls are used)
(d) The effectiveness of antiviral medications for prevention of defined endpoints.
(e) The number of individuals quarantined, the number and fraction of these who go on to develop disease (if quarantine is used).

The gathering of such data, as shown by the SARS experience, is difficult; indeed, Singapore was the only country for which these data were available in nearly real time in a comprehensive way. *Thus we recommend the advance development of specific plans for rapidlv eatherine, analvzine, and communicatinl! indicators of epidemic prOl!ress and of the effectiveness of control measures. Protocols should be developed despite the fact that these plans are not easilv "practiced" in nonpandemic years (unlike those in 2 above).*

4. SPECIFIC PLANS FOR TRIGGERING INTERVENTIONS TO REDUCE CONTACT BY "INCREASED SOCIAL DISTANCE." In the event of a pandemic that causes widespread disease before vaccines are available in adequate quantities, there may be a need to implement "social distance" interventions, including school closings, encouragement of telecommuting, cancellation of large gatherings, etc. This general class of interventions is mentioned very briefly in Annexes 8 and 12. The value of such interventions in previous pandemics is said to be limited (Annex 8), but few specifics are given. We suspect that these measures (as well as those recommended elsewhere in the Plan and in these comments) may be important, even if they have limited effectiveness, in "buying time" before vaccines become available. *It is important, durinl! the interoandemic period, to develop principles for when "social distance" interventions should be implemented. Specific means of assessinl! the usefulness of these and other interventions should be developed (see point 2 above) so that thev can be maintained with public support if appropriate, or discontinued if ineffective and disruptive. Plans should also be made to determine who will bear the costs of reduced work attendance, unavailabilitv of childcare, and other likelv consequences of such interventions.*

5. PLANS FOR INTERNATIONAL COOPERATION IN TREATMENT AND USE OF LIMITED ANTIVIRAL MEDICATIONS TO CONTAIN EARLY HUMAN-TO-HUMAN SPREAD. Ifhuman-to-human transmission ofa new strain with pandemic potential is detected, it may be possible to contain this transmission by intensive interventions in the first population in which this transmission occurs, before spread becomes widespread (phase 0, level 3) [5]. This intervention may occur overseas, and may involve use of antiviral medicines that are being stockpiled in the United States for an eventual pandemic. *Plans for appropriate use of stockpiled antiviral medications as a preventive measure should be developed.*

6. ADVANCE PLANNING FOR COMMUNICATION AND LOGISTICS TO PREVENT AND TREAT SEQUELAE OF INFLUENZA INFECTION. The impact of an influenza pandemic is likely to be felt not only as an increase in both mild and severe respiratory infections, but also as an increase in complications and deaths from ischemic heart disease, diabetes, stroke, and other conditions [6], as well as in secondary bacterial pneumonias, including many in which the bacteria may go undetected [7]. These considerations emphasize the need to plan measures to alleviate these consequences.

(a) In a pandemic setting, especially before an appropriate influenza vaccine is available, pneumococcal polysaccharide vaccine may be indicated not only for existing risk groups, but for healthy children (>=2 years) and adults. While the plan justifiably emphasizes pre-pandemic vaccination of existing risk groups, broader vaccine coverage may require vaccine supplies that exceed those currently available. Moreover, given that children under 2 are considered a high-risk group for severe complications of influenza, and that the pneumococcal conjugate vaccine (but not the polysaccharide vaccine) is effective in this age group, it will be important to improve immunization coverage with the 7-valent pneumococcal conjugate vaccine, currently at 68%, the lowest of any childhood vaccine (http://www2a.cdc. gov/nip/coverage/nis/nis_iap.asp?fmt=v &rpt=tab02_antigen_iap&qtr =Q1/2003-Q4/2003). *Thus stockpilinJ! of pneumococcal polysaccharide vaccine should be considered. In addition to the Plan's recommendation for improved coveraJ!e of the polysaccharide vaccine in adults. efforts to improve coveraJ!e of the coniuJ!ate vaccine in infants should be enhanced.*

(b) Much of the morbidity caused by pandemic influenza will involve comorbidities, including asthma, diabetes, and cardiovascular disease. Plans should be in place to educate the public and the medical community about these elevated risks and to deal with increases in demand for treatment of these and other related outcomes, as well as with "traditional" influenza pathology. Educating the public about modifiable risk factors for influenza disease, most importantly smoking, may also be valuable in the setting of elevated concern that will surround a pandemic. *Plans should be developed to prevent and treat the likelv complications ofinfluenza. and to encouraJ!e avoidance of risk behaviors such as smokinJ! in the context of a pandemic. In addition. J!iven the*

nonspecificity ofinfluenza symptoms. plans should be developed for cohortinl! of patients with known or suspected influenza.

7. RESEARCH ON THE USE OF VACCINES IN TRANSMISSION RISK GROUPS (E.G. SCHOOLCHILDREN). The Plan makes a strong recommendation that first priority for vaccination, when vaccines are available, should be given to individuals at high risk for severe disease and their close contacts. There is considerable evidence - though not, as noted in the Plan, in the setting of a pandemic - that the vaccination of schoolchildren may be as effective as, or more effective than, vaccination of elderly and other high-risk populations in reducing total mortality. This effect occurs because of schoolchildren's important role in transmitting and amplifying infection. Further research on this strategy is urgently needed. An ethical approach during interpandemic years might be to design community-randomized studies in which high-risk individuals are vaccinated in all communities, but schoolchildren are also vaccinated in a randomized subset of communities, and attack rates in all age groups compared. *It is important in the interTJandemic period to refine our understandinJ! of the usefulness of vaccines in various all e J!roups and to consider seriously the possibility of vaccination to block transmission. rather than only to protect the most vulnerable.*

8. RAPID DIAGNOSTICS. The importance of specific influenza diagnosis will be increased during a pandemic, for many reasons: epidemiologic tracking, isolation of influenza-infected individuals, etc. The plan makes little or no mention of the role of diagnostic kits. *Further consideration should be J!iven to ensurinJ! adequate supplies. so that (for example) hospitals can accurately monitor which patients are infected and prevent nosocomial spread.*

9. LEGAL ISSUES FOR VACCINE PRODUCTION. The Plan does not make reference to the issue of providing legal protection for vaccine manufacturers. *Given the prominence of this issue in the response to Swine Influenza. it should be included in the plan.*

REFERENCES

1 Ferguson NM, Fraser C, Donnelly CA, Ghani AC, Anderson RM (2004) Public health. Public health risk from the avian H5Nl influenza epidemic. Science 304: 968-969.

2 Fraser C, Riley S, Anderson RM, Ferguson NM (2004) Factors that make an infectious disease outbreak controllable. Proc Natl Acad Sci USA 101: 6146-6151.

3 Walling a J, Teunis P (2004) Different epidemic curves for severe acute respiratory syndrome reveal similar impacts of control measures. Am J Epidemiol 160: 509-516.

4 Lipsitch M, Bergstrom CT (2004) Invited commentary: real-time tracking of control measures for emerging infections. Am J Epidemioll60: 517-519; discussion 520.

5 Enserink M (2004) Influenza: girding for disaster. Looking the pandemic in the eye. Science 306: 392-394.

6 Reichert TA, Simonsen L, Sharma A, Pardo SA, Fedson DS, et al. (2004) Influenza and the winter increase in mortality in the United States, 1959-1999. Am J Epidemioll60: 492-502.

7 Madhi SA, Klugman KP (2004) A role for Streptococcus pneumoniae in virus-associated pneumonia. Nat Med 10: 811-813.

Landry, Sarah

From: mcdonaldrn [mcdonaldrn@msn.com]

Sent: Monday, August 30, 2004 8:36 AM

To: NVPO

Subject: physical measures to reduce transmission of pandemic influenza

Thank you for making the Draft Pandemic Influenza Preparedness and Response Plan available for public comment. I am an Infection Control consultant with over 20 years experience in the field, and I am frequently asked by members of the public what they can do to protect themselves from whatever disease is the current source of concern. I would like to be able to provide evidence-based answers on the subject on pandemic influenza.

My review of the Draft Pandemic Influenza Preparedness and Response Plan did not find attention to PHYSICAL measures the public can take to minimize their risk of pandemic influenza. I believe that physical measures will be of great importance, especially in the time before vaccine is available. Our experience with SARS showed that the public is highly interested in doing what they can to protect themselves, as evidenced by the photographs of people on the streets wearing masks. My searches of the internet for answers to these questions has not been sucessful.

Specifically, please add to the Plan evidence-based answers for the following questions:

- How far away is a safe distance from a person with influenza when you have no personal protective equipment?
- Do we know what type of a mask is effective in preventing transmission, or is a mask entirely worthless, as some have alleged?
- How important is eye protection?
- How big a factor is hand or fomite transmission?
- How far in advance of the onset of symptoms is a person contagious for influenza?

Clearly, we cannot know these answers in advance for the specific pandemic strain, but it would be helpful to have them for any strain of influenza. If we do not have evidence on these questions, perhaps an effort could be made to gather such evidence now in the inter-pandemic phase.

Thank you very kindly for your commendable efforts to prepare our country to respond to this worrisome threat, and thank you for allowing us "in the trenches" to participate.

Marian McDonald, RN, MSN, CIC
Infection Control at YOUR Service!
(707) 829-2315
MCDONALDRN@msn.com

2004S-0212 - Pandemic Influenza Preparedness Plan

FDA Comment Number : EC19

Submitter : Dr. Marion Kainer **Date & Time:** 11/09/2004 01:11:36

Organization : Tennessee Department of Health

State Government

Category :

Issue Areas/Comments

GENERAL

GENERAL

See Attachment

Annex 8: Strategies to Limit Transmission

Overall comment.

This section would benefit from including details presented in the WHO document attached (pages 20-29, especially the tables 26-29). The WHO document specifies clearly what measures are effective, and which ones are not. Stating what should NOT be done is as important as stating what should be done, so that valuable resources are not diverted to activities that are unhelpful.

Specific comments:

II. Background

The amount of virus shed ??? IS HIGHER???/ LOWER??? and the length of time of viral shedding may be prolonged during initial infection with a new influenza subtype. Need to specify what happens to the AMOUNT of virus—does it get higher or lower (I assume higher)

B. Transmission and Infection Control Strategies in Healthcare Settings

Routes of influenza transmission

Direct and indirect contact transmission

Direct transmission involves direct body-to-body surface contact. Indirect transmission occurs via contact with contaminated intermediate objects such as contaminated hands or inanimate objects such as needles or countertops. To introduce the term "Needles" here is confusing—these often cause percutanous exposures—and would be classified as something different than indirect contact

Droplet transmission

Droplet transmission occurs when contagious droplets produced by the infected host are propelled a short distance through coughing or sneezing and can come into contact with another person's conjunctiva, mouth or nasal mucosa. Since these droplets generally are large (greater than10 micrograms and do not stay suspended in the air, this mode of transmission is not affected by special air handling or control of room pressures.

Droplet nuclei (airborne) transmission

This entails the production of infectious droplet nuclei, generally 5 micrograms or less in diameter. In contrast with larger droplets, these droplets can remain suspended in the air and be disseminated by air currents in a room or through a facility to be inhaled by a susceptible host. Preventing the spread of droplet nuclei requires the use of special air handling and ventilation procedures. The size is measured in micrometers not micrograms (grams is a WEIGHT measure)

Landry, Sarah

From: Mark Korbitz [mwkorbitz@yahoo.com]
Sent: Monday, September 20,200411 :25 AM
To: NVPO
Subject: Comments on the plan

Thank you for this opportunity to comment on the pandemic influenza plan.

I don't have specific criticisms to make but one general suggestion and a question about influenza research.

I. Infectious disease surveillance systems need to be improved worldwide. Although it is true that we have some of the better systems in existence here in the U.S., outbreak recognition and reporting remain haphazard at best in this country today. We need to concentrate efforts and training on prioritizing detection and reporting. One way to do this would be to incorporate epidemiologic methods as a requirement in all clinical practice programs from LPN programs through MD and DO programs. All clinical training programs should include a public health/investigation rotation. Systems for reporting should be streamlined, modernized and made more widely available to clinics and practioners (including veterinary care providers) such as the Colorado Electronic Disease Reporting System. One requirement for licensure or relicensure in each state should be proof of disease reporting competency.

II. Has any significant research been done to investigate the possibility of reducing the rate of antigenic drift and shift in influenza viruses through the introduction of an "error-proofing mechanism"? Intentional manipulation of the genome ofRNA viruses would likely be controversial (as it should be), but antigenic stabilization might someday hold some promise as an overall strategy if a large proportion of the viruses in existence had such an "error-proofing mechanism". Are there viral ecologists exploring such a strategy?

Thank you,

Mark W. Korbitz
Science instructor and epidemiologist
623 Jachim St.
La Junta, CO 81050

(719) 384-0308 home
Email: mwkorbitz@yahoo.com

Landry, Sarah

From: Mary Manley [mmanley@cincLrr.com]

Sent: Sunday, August 29,200412:04 PM

To: NVPO

Subject: preparedness and response plan

As a registered nurse working in an acute care hospital setting, I am very concerned about our nation's preparedness in the coming predicted flu pandemic.

After a thorough reading of the response plan, I am concerned at how little is addressed about the specific needs of our nation's health care workers in the first days of an outbreak. Much is discussed about the necessity of adequate health care for our public. How can this be accomplished without a specific plan to protect health care workers immediately? In light of the information presented, it can be assumed that there is a real likelihood of a viral mutation that will not respond to the currently available vaccination. And even if there is adequate funding for the seed vaccinations, a real time response for our health care workers will come too late. The plan admits there is a real shortage of the antiviral medications, and what is available is being stockpiled by the SNS. How efficiently that drug would be distributed remains to be seen.

Common infection control methods currently in place will not protect our workers, although it might prevent patient to patient contact in the event the health care worker is not infected. It is my understanding that the paper masks we now use are not effective in blocking any virus. Just by being in the same room with an infected person all health care workers put their lives at risk. And common sense states that hospitals will be overrun with sick patients.

I am a dedicated nurse but I am not willing to place my life in real jeopardy because my country is unprepared for this very real threat. Today's paper (The Cincinnati Enquirer) reports that the H5N1 virus has killed three people in Viet Nam, and 26 of 39 people in Thailand and Viet Nam from avian flu. In Thailand, avian flu has been found in 98 locations. It is coming to the US and sooner rather than later by the looks of it. In order for me to feel safe, I need to know that my hospital has enough antiviral medication to be distributed to all employees as a first response. What can I do to help in this effort?

Mary Manley
9253 Gregg Drive
West Chester, OH 45069
513-777-0816
mmanley@cinci.rr.com

20048-0212 - Pandemic Influenza Preparedness Plan

FDA Comment Number: EC22

Submitter: Dr. Merritt Schreiber **Date & Time:** 11/091200401:11:56

Organization: Dr. Merritt Schreiber

Category: Health Professional

Issue Areas/Comments

GENERAL

GENERAL

Revised comments are attached and reflect the following issues:
?a Address the Mental Health consequences of pandemic induced mass fatalities
?a Address the Behavioral health components to the section of the draft report concerning community response strategies(isolation! quarantine,etc, mass vaccination)
?a Augment the plan! Is strategy for communication to a broader, dynamic model of combined public education about risk and response efforts and risk messages
?a Need to specifically address the unique issues that will face children, parents and children! Is !?systems of care including schools and child care settings.
?a Develop strategies to build community resilience to all hazards events in the pre-event period or inter-pandemic period.

Comments on Draft Pandemic Influenza Preparedness and Response Plan:

In addition to the comprehensive public health preparedness and response strategies outlined in the *Plan,* there is a need to also comprehensively address the myriad of behavioral, social and mental health consequences that stem from the potential mass casualties projected to be in the hundreds of thousands.

~~Address the Mental Health consequences of pandemic induced mass fatalities
~~Address the Behavioral health components to the section of the draft report concerning community response strategies (isolation/quarantine,etc, mass vaccination}
~~Augment the plan's strategy for communication to a broader,dynamic model of combined public education about risk and response efforts and risk messages
~~Need to specifically address the unique issues that will face children, parents and children's "systems of care including schools and child care settings.
~~Develop strategies to build community resilience to all hazards events in the pre-event period or inter-pandemic period.

There is also a compelling need to address the unique impact of pandemic (and the associated preparedness and response strategies) on children, families, and children's "disaster systems of care". Historically, there has been a national focus of concern on the impact of events on the nations' most vulnerable: it's children. This focus is appropriate given long term evidence from natural disasters and terrorism events that suggest that children are at the highest risk for developing chronic clinical disorders and impairment with tremendous costs to children, their families and our nation. Recent evidence emerging from the Anthrax attacks and SARS in Canada (including the impact of quarantine) also suggest significant behavioral and mental health issues that will require significant bolstering of planning efforts for children and families among others. Another population that may require articulation of specialized strategies are first responders and their families, including public health and hospital staff. A pandemic event will likely create a range of traumatic effects ranging from transitory, discrete fears and symptoms in many to long term distress and disorder in others, based on their dose of traumatic exposure. A system to provide rapid mental health triage and linkage to targeted interventions may be useful in this regard.

Given the plan's mortality estimates of up to several hundred thousand, there will be an exponentially greater number of adults and children facing the burden of traumatic grief that results. Although not all, but certainly significant numbers of adults and children will be at extended risk for depression, associated impairment and co-morbidity's There will be a need to bolster the public mental health response to address a surge of mass mental health casualties of parents and children. Addressing the primary mental health repercussions of pandemic will be important not only for the enduring mental health of the population, but also emerging evidence indicates that even mild depressive symptoms can prolonged inflammatory response after Influenza vaccination and thus may influence the basic strategies of response. There is also evidence that untreated PTSD, which may result, can lead

to increased health care costs and utilization. In children, there is evidence that a number of behavioral factors are tied to maternal pediatric resource use in acute pediatric illnesses. The needs of single parent families, especially those composed of health care workers may be particularly important to target.

To address augmentation of the Pandemic Response Plan with reference to these issues, it is suggested that the recommendations from the National Advisory Committee for Children in Terrorism (DHHS, 2003) be fully incorporated into the Pandemic Response plan. The issues of how the plan'S strategies will relate to the functioning of schools,child care settings and other community activities of children and families will require significant cooperative activities over the course of preparedness and response.

In terms of the behavioral components, to the extent that containment strategies including movement restrictions, vaccine or antiviral distribution strategies, etc. are based on public (or provider) compliance, the behavioral factors that underlie compliance and adherence need to be specifically addressed. Although post-event risk communication/messaging will be key, there is also an opportunity to mitigate many of the response issues with a comprehensive pre-event public education and risk communication strategy (in addition to Annex 9/Section IV) following the range of recommendations of the Secretary's Advisory Committee on Emergency Public Information and Communications, EPIC, (DHSS, 2003). There will be a need to have a dynamic, interactive communication process with numerous public constituencies (broadly defined) beyond draft plans focus on tone/content of messages to include a process to continuously update the critical information needed for the public and to determine what the public does know and comprehensive informational strategies to then "close the gap" (Fischoff, 2003).

As a means to mitigate both the mental health and behavioral consequences of pandemic threats, there is also an opportunity to incorporate and build on evolving strategies of community resilience. By building on capacities of communities to respond to "all-hazards" events and in-process CDC and HRSA BT preparedness initiatives, the public can become a key collaborator and partner with public health efforts in the inter-pandemic period.

Thank you for the opportunity to comment on this critical health effort.

Merritt D. Schreiber, Ph.D.
Program Manager,
Terrorism and Disaster Branch
National Center for Child Traumatic Stress
NPI/David Geffen School of Medicine at UCLA

20048-0212 - Pandemic Influenza Preparedness Plan

FDA Comment Number: ECI0

Submitter: Ms. Cynthia Findley

Date & Time: 10/26/200404:10:07

Organization: Pennsylvania Department of Health

State Government

Category:

Issue Areas/Comments

GENERAL

GENERAL

See Attachment

Pennsylvania Pandemic Influenza Response and Preparedness Plan Comments
10-6-04

Issue: Organization of information comparing outbreak characteristics, preparedness and response activities information.

PIRP Location: Pg:3, 8,9,10,11

Comments: The information provided for comparison on Pandemic Influenza and SARS is quite useful however comparison of this information in this format can be confusing and time consuming.

Recommendations and Rationale:

?? To develop a Biological Agent Algorithm.
Such an algorithm would group biological agents of similar outbreak characteristics requiring a common response activity. Identification of a causative biological agent at the onset of an outbreak may not be as important as rapidly determining the response necessary to protect the health of the victims, health care workers and faci1itie. Final determination of an agent would further define response activities. Algorithms of this type could also be developed for chemical and radiological events.

Issue:
Multiple Suggestions for Annex 1

Comments:

?? State Executive Committee needs "real" in-the- field representation from the private sector.

?? Pg. 16 - Section E - Communications section is too brief.

?? General Comment: Note the lack of reference to mental/behavioral health issues. These need to be addressed more fully in the overall plan.

Recommendations and Rationale:

?? Recommend the addition of 2 Infectious Disease medical practitioners (not within the government) on the Executive Committee - 1 from an academic organization and the other from a community physician group.

?? Much advance work is needed including the formation of state and local teams ready to spring into action possibly even prior to CDC guidance.

Discuss any anticipated barriers:

?? Traditional organization of state and other governmental agencies and personnel doesn't include (by history and inclination) full and initial participation by private sector. This approach should be considered in advance, perhaps by identifying likely private sector consultants to join the Executive Committee upon its mobilization.

Issue:
Suggestions for Annex 2

Comments:

?? Plan didn't adequately address issue relating to the legal rights of staff and hospital to restrict patient and family movement, quarantine in the hospital and in after-care at home, etc.

?? Hospital Preparedness Teams - Pg. 5, Item III. A
This team should also include representatives from employee training & development and media relations.

?? Pre-Event Training for Staff - Pg. 8, 3rd paragraph
It will be important to stress pre-event information, family planning, and training for staff as well. This will hopefully prevent some of the anticipated labor impacts of staff not reporting for work during an emergency.

?? Credentialing of medical volunteers - Pg. 9, 2nd paragraph, bullet 6
The issue of credentialing for volunteer (retired) medical staff must be addressed per JCAHO requirements.

?? Surge CapacitylNon- Traditional Sites - Pg. 23, 2nd paragraph
The guideline needs to require that hospitals work with local Health Departments in this area. The document implies that health care facilities should handle this on their own.

?? There should be a mechanism to screen healthcare workers for diseases in the setting of a phase 3 pandemic (might also be useful in phase 2).

?? Of use for hospitals, would be a reference table of guidelines linked to each phase of the pandemic (similar to one in the core document). Relevant issues for hospitals would be: when to devise separate triage areas for patients with respiratory symptoms, when to advise visitors with respiratory symptoms to stay away from hospital, when to implement mass vaccination clinics or chemoprophylaxis, etc.

General Comment: Note the lack of reference to mentallbehavioral health issues. These need to be addressed more fully in the overall plan.

Recommendations and Rationale:

- ?? Recommend that these issues be addressed specifically through education and suggestions made in the plan.
- ?? Employee information and public communication strategies will be key.
- ?? Add some language recommending the development of family emergency plans (such as the Red Cross model) for flu pandemic situations.
- ?? Add some language to address the need for hospitals to have in place an emergency credentialing process to ensure the veracity of volunteer medical and clinical staff credentials.
- ?? Strengthen recommendation to work co-operatively with p1.blichealth in this area.

Discuss any anticipated barriers:

- ?? Need for strong interaction, planning and mutual dependency of local officials and health care providers. Also, appreciation of the immense worry and public fear unless pre-planned and continuous public communication is provided.

Issue:
Suggestions for Overall Plan

Comments:

- ?? The most important strategy for saving lives in a pandemic situation is prevention of infection. Toward that end, a specific restriction on travel for hospital personne Iis essential.

- ?? Some additional points that need to be expanded in the plan are:
- ?? Home care strategy for use after capacity in hospitals is reached.
- ?? Care policy for dense population centers (schools, dormitories, prisons, etc.)
- ?? Specific recommendations on care degradations during periods of overflow, i.e., what care is not given during a pandemic?Ventilators will be the most critical shortage in a pandemic. Specific recommendations on use and strategies for surge capacity should be given.

Issue:
Referen::e to *"need to ration vaccine will require substantial public education and adequate security measures"* - without additional guidance this statement is inadequate.

PIRP Location (page number, paragraph, etc.)

Annex 1 : Page 12, second full paragraph

Comments:

?? Rationing, of any type, is simply unheard of in today's healthcare environment. Weare unconvinced that any effort to educate the public will make "rationing" terminology palatable to the general public.

Recommendations and Rationale:

?? Understanding that a limited number and/or amount of vaccine would be available for treatment and/or prophylaxis in the early stages of an influenza pandemic, an alternative would be to pre-position available vaccine where it will benefit the most and provide maximum usefulness - i.e., within hospitals.

?? Include with this deployment specific guidance for use - either for treatment of the sick or for vaccination of healthcare workers. It will be more effective for physicians and infection control/infectious disease specialists to implement established guidelines for use than to try to provide mass education to the public on who will / will not receive vaccine(s).

Pennsylvania Pandemic Influenza Response and Preparedness Plan Comments
10-6-04

Issue: Organization of information comparing outbreak characteristics, preparedness and response activities information.

PIRP Location: Pg: 3,8,9,10,11

Comments: The information provided for comparison on Pandemic Influenza and SARS is quite useful however comparison of this information in this format can be confusing and time consuming.

Recommendations and Rationale:

- To develop a Biological Agent Algorithm.
  Such an algorithm would group biological agents of similar outbreak characteristics requiring a common response activity. Identification of a causative biological agent at the onset of an outbreak may not be as important as rapidly determining the response necessary to protect the health of the victims, health care workers and facilitie. Final determination of an agent would further define response activities. Algorithms of this type could also be developed for chemical and radiological events.

Issue:
Multiple Suggestions for Annex 1

Comments:

- State Executive Committee needs "real" in-the- field representation from the private sector.
- Pg. 16 - Section E - Communications section is too brief.

- General Comment: Note the lack of reference to mentallbehavioral health issues. These need to be addressed more fully in the overall plan.

Recommendations and Rationale:

- Recommend the addition of 2 Infectious Disease medical practitioners (not within the government) on the Executive Committee - 1 from an academic organization and the other from a community physician group.

- Much advance work is needed including the formation of state and local teams ready to spring into action possibly even prior to CDC guidance.

Discuss any anticipated barriers:

- Traditional organization of state and other governmental agencies and personnel doesn't include (by history and inclination) full and initial participation by private sector. This approach should be considered in advance, perhaps by identifying likely private sector consultants to join the Executive Committee upon its mobilization.

Issue:

Suggestions for Annex 2

Comments:

- Plan didn't adequately address issue relating to the legal rights of staff and hospital to restrict patient and family movement, quarantine in the hospital and in after-care at home, etc.

- Hospital Preparedness Teams - Pg. 5, Item III. A
  This team should also include representatives from employee training & development and media relations.

- Pre-Event Training for Staff - Pg. 8, 3rd paragraph
  It will be important to stress pre-event information, family planning, and training for staff as well. This will hopefully prevent some of the anticipated labor impacts of staff not reporting for work during an emergency.

- Credentialing of medical volunteers - Pg. 9, 2nd paragraph, bullet 6
  The issue of credentialing for volunteer (retired) medical staff must be addressed per JCAHO requirements.

- Surge CapacitylNon- Traditional Sites - Pg. 23, 2nd paragraph
  The guideline needs to require that hospitals work with local Health Departments in this area. The document implies that health care facilities should handle this on their own.

- There should be a mechanism to screen healthcare workers for diseases in the setting of a phase 3 pandemic (might also be useful in phase 2).

- Of use for hospitals, would be a reference table of guidelines linked to each phase ofthe pandemic (similar to one in the core document). Relevant issues for hospitals would be: when to devise separate triage areas for patients with respiratory symptoms, when to advise visitors with respiratory symptoms to stay away from hospital, when to implement mass vaccination clinics or chemoprophylaxis, etc.

General Comment: Note the lack of reference to mentallbehavioral health issues. These need to be addressed more fully in the overall plan.

Recommendations and Rationale:

- Recommend that these issues be addressed specifically through education and suggestions made in the plan.
- Employee information and public communication strategies will be key.
- Add some language recommending the development of family emergency plans (such as the Red Cross model) for flu pandemic situations.
- Add some language to address the need for hospitals to have in place an emergency credentialing process to ensure the veracity of volunteer medical and clinical staff credentials.
- Strengthen recommendation to work co-operatively with public health in this area.

Discuss any anticipated barriers:

- Need for strong interaction, planning and mutual dependency of local officials and health care providers. Also, appreciation of the immense worry and public fear unless pre-planned and continuous public communication is provided.

Issue:
Suggestions for Overall Plan

Comments:

- The most important strategy for saving lives in a pandemic situation is prevention of infection. Toward that end, a specific restriction on travel for hospital personnel is essential.

- Some additional points that need to be expanded in the plan are:
- Home care strategy for use after capacity in hospitals is reached.
- Care policy for dense population centers (schools, dormitories, prisons, etc.)
- Specific recommendations on care degradations during periods of overflow, i.e., what care is not given during a pandemic?Ventilators will be the most critical shortage in a pandemic. Specific recommendations on use and strategies for surge capacity should be given.

Issue:

Reference to *"need to ration vaccine will require substantial public education and adequate security measures"* - without additional guidance this statement is inadequate.

PIRP Location (page number, paragraph, etc.)

Annex 1 : Page 12, second full paragraph

Comments:

- Rationing, of any type, is simply unheard of in today's healthcare environment. Weare unconvinced that any effort to educate the public will make "rationing" terminology palatable to the general public.

Recommendations and Rationale:

- Understanding that a limited number and/or amount of vaccine would be available for treatment and/or prophylaxis in the early stages of an influenza pandemic, an alternative would be to pre-position available vaccine where it will benefit the most and provide maximum usefulness - i.e., within hospitals.

- Include with this deplOYment specific guidance for use - either for treatment of the sick or for vaccination of health care workers. It will be more effective for physicians and infection control/infectious disease specialists to implement established guidelines for use than to try to provide mass education to the public on who will / will not receive vaccine(s).

Pennsylvania Pandemic Influenza Response and Preparedness Plan Comments
10-6-04

Issue: Organization of information comparing outbreak characteristics, preparedness and response activities information.

PIRP Location: Pg: 3,8,9,10,11

Comments: The information provided for comparison on Pandemic Influenza and SARS is quite useful however comparison of this information in this format can be confusing and time consuming.

Recommendations and Rationale:

?? To develop a Biological Agent Algorithm.
Such an algorithm would group biological agents of similar outbreak characteristics requiring a common response activity. Identification of a causative biological agent at the onset of an outbreak may not be as important as rapidly determining the response necessary to protect the health of the victims, health care workers and facilitie. Final determination of an agent would further define response activities. Algorithms of this type could also be developed for chemical and radiological events.

Issue:
Multiple Suggestions for Annex 1

Comments:

?? State Executive Committee needs "real" in-the- field representation from the private sector.

?? Pg. 16 - Section E - Communications section is too brief.

?? General Comment: Note the lack of reference to mentallbehavioral health issues. These need to be addressed more fully in the overall plan.

Recommendations and Rationale:

?? Recommend the addition of2 Infectious Disease medical practitioners (not within the government) on the Executive Committee - 1 from an academic organization and the other from a community physician group.

?? Much advance work is needed including the formation of state and local teams ready to spring into action possibly even prior to CDC guidance.

Discuss any anticipated barriers:

?? Traditional organization of state and other governmental agencies and personnel doesn't include (by history and inclination) full and initial participation by private sector. This approach should be considered in advance, perhaps by identifying likely private sector consultants to join the Executive Committee upon its mobilization.

Issue:
Suggestions for Annex 2

Comments:

?? Plan didn't adequately address issue relating to the legal rights of staff and hospital to restrict patient and family movement, quarantine in the hospital and in after-care at home, etc.

?? Hospital Preparedness Teams - Pg. 5, Item III. A
This team should also include representatives from employee training & development and media relations.

?? Pre-Event Training for Staff - Pg. 8, 3rd paragraph
It will be important to stress pre-event information, family planning, and training for staff as well. This will hopefully prevent some of the anticipated labor impacts of staff not reporting for work during an emergency.

?? Credentialing of medical volunteers - Pg. 9, 2nd paragraph, bullet 6
The issue of credentialing for volunteer (retired) medical staff must be addressed per JCAHO requirements.

?? Surge Capacity/Non- Traditional Sites - Pg. 23, 2nd paragraph
The guideline needs to require that hospitals work with local Health Departments in this area. The document implies that health care facilities should handle this on their own.

?? There should be a mechanism to screen healthcare workers for diseases in the setting of a phase 3 pandemic (might also be useful in phase 2).

?? Of use for hospitals, would be a reference table of guidelines linked to each phase of the pandemic (similar to one in the core document). Relevant issues for hospitals would be: when to devise separate triage areas for patients with respiratory symptoms, when to advise visitors with respiratory symptoms to stay away from hospital, when to implement mass vaccination clinics or chemoprophylaxis, etc.

General Comment: Note the lack of reference to mentallbehavioral health issues. These need to be addressed more fully in the overall plan.

Recommendations and Rationale:

- ?? Recommend that these issues be addressed specifically through education and suggestions made in the plan.
- ?? Employee information and public communication strategies will be key.
- ?? Add some language recommending the development of family emergency plans (such as the Red Cross model) for flu pandemic situations.
- ?? Add some language to address the need for hospitals to have in place an emergency credentialing process to ensure the veracity of volunteer medical and clinical staff credentials.
- ?? Strengthen recommendation to work co-operatively with ptblic health in this area.

Discuss any anticipated barriers:

- ?? Need for strong interaction, planning and mutual dependency of local officials and health care providers. Also, appreciation of the immense worry and public fear unless pre-planned and continuous public communication is provided.

Issue:
Suggestions for Overall Plan

Comments:

- ?? The most important strategy for saving lives in a pandemic situation is prevention of infection. Toward that end, a specific restriction on travel for hospital personne Iis essential.

- ?? Some additional points that need to be expanded in the plan are:
- ?? Home care strategy for use after capacity in hospitals is reached.
- ?? Care policy for dense population centers (schools, dormitories, prisons, etc.)
- ?? Specific recommendations on care degradations during periods of overflow, i.e., what care is not given during a pandemic?Ventilators will be the most critical shortage in a pandemic. Specific recommendations on use and strategies for surge capacity should be given.

Issue:
Referen:e to *"need to ration vaccine will require substantial publir: education and adequate security measures"* - without additional guidance this statement is inadequate.

PIRP Location (page number, paragraph, etc.)

Annex 1 : Page 12, second full paragraph

Comments:

?? Rationing, of any type, is simply unheard of in today's healthcare environment. Weare unconvinced that any effort to educate the public will make "rationing" terminology palatable to the general public.

Recommendations **and** Rationale:

?? Understanding that a limited number and/or amount of vaccine would be available for treatment and/or prophylaxis in the early stages of an influenza pandemic, an alternative would be to pre-position available vaccine where it will benefit the most and provide maximum usefulness - i.e., within hospitals.

?? Include with this deployment specific guidance for use - either for treatment of the sick or for vaccination of healthcare workers. It will be more effective for physicians and infection control/infectious disease specialists to implement established guidelines for use than to try to provide mass education to the public on who will / will not receive vaccine(s).

Pennsylvania Pandemic Influenza Response and Preparedness Plan Comments
10-6-04

Issue: Organization of information comparing outbreak characteristics, preparedness and response activities information.

PIRP Location: Pg: 3,8,9,10,11

Comments: The information provided for comparison on Pandemic Influenza and SARS is quite useful however comparison of this information in this format can be confusing and time consuming.

Recommendations and Rationale:

?? To develop a Biological Agent Algorithm.
Such an algorithm would group biological agents of similar outbreak characteristics requiring a common response activity. Identification of a causative biological agent at the onset of an outbreak may not be as important as rapidly determining the response necessary to protect the health of the victims, health care workers and facilitie. Final determination of an agent would further define response activities. Algorithms of this type could also be developed for chemical and radiological events.

Issue:
Multiple Suggestions for Annex 1

Comments:

?? State Executive Committee needs "real" in-the- field representation from the private sector.

?? Pg. 16 - Section E - Communications section is too brief.

?? General Comment: Note the lack of reference to mentallbehavioral health issues. These need to be addressed more fully in the overall plan.

Recommendations and Rationale:

?? Recommend the addition of 2 Infectious Disease medical practitioners (not within the government) on the Executive Committee - 1 from an academic organization and the other from a community physician group.

?? Much advance work is needed including the formation of state and local teams ready to spring into action possibly even prior to CDC guidance.

Discuss any anticipated barriers:

?? Traditional organization of state and other governmental agencies and personnel doesn't include (by history and inclination) full and initial participation by private sector. This approach should be considered in advance, perhaps by identifying likely private sector consultants to join the Executive Committee upon its mobilization.

Issue:

Suggestions for Annex 2

Comments:

?? Plan didn't adequately address issue relating to the legal rights of staff and hospital to restrict patient and family movement, quarantine in the hospital and in after-care at home, etc.

?? Hospital Preparedness Teams - Pg. 5, Item III. A
This team should also include representatives from employee training & development and media relations.

?? Pre-Event Training for Staff - Pg. 8, 3rd paragraph
It will be important to stress pre-event information, family planning, and training for staff as well. This will hopefully prevent some of the anticipated labor impacts of staff not reporting for work during an emergency.

?? Credentialing of medical volunteers - Pg. 9, 2nd paragraph, bullet 6
The issue of credentialing for volunteer (retired) medical staff must be addressed per JCAHO requirements.

?? Surge Capacity/Non- Traditional Sites - Pg. 23, 2nd paragraph
The guideline needs to require that hospitals work with local Health Departments in this area. The document implies that health care facilities should handle this on their own.

?? There should be a mechanism to screen healthcare workers for diseases in the setting of a phase 3 pandemic (might also be useful in phase 2).

?? Of use for hospitals, would be a reference table of guidelines linked to each phase of the pandemic (similar to one in the core document). Relevant issues for hospitals would be: when to devise separate triage areas for patients with respiratory symptoms, when to advise visitors with respiratory symptoms to stay away from hospital, when to implement mass vaccination clinics or chemoprophylaxis, etc.

General Comment: Note the lack of reference to mentallbehavioral health issues. These need to be addressed more fully in the overall plan.

Recommendations and Rationale:

- ?? Recommend that these issues be addressed specifically through education and suggestions made in the plan.
- ?? Employee information and public communication strategies will be key.
- ?? Add some language recommending the development of family emergency plans (such as the Red Cross model) for flu pandemic situations.
- ?? Add some language to address the need for hospitals to have in place an emergency credentialing process to ensure the veracity of volunteer medical and clinical staff credentials.
- ?? Strengthen recommendation to work co-operatively with pthlic health in this area.

Discuss any anticipated barriers:

- ?? Need for strong interaction, planning and mutual dependency of local officials and health care providers. Also, appreciation of the immense worry and public fear unless pre-planned and continuous public communication is provided.

Issue:

Suggestions for Overall Plan

Comments:

- ?? The most important strategy for saving lives in a pandemic situation is prevention of infection. Toward that end, a specific restriction on travel for hospital personne ▌is essential.

- ?? Some additional points that need to be expanded in the plan are:
- ?? Home care strategy for use after capacity in hospitals is reached.
- ?? Care policy for dense population centers (schools, dormitories, prisons, etc.)
- ?? Specific recommendations on care degradations during periods of overflow, i.e., what care is not given during a pandemic?Ventilators will be the most critical shortage in a pandemic. Specific recommendations on use and strategies for surge capacity should be given.

Issue:

Referen::e to *"need to ration vaccine will require substantial public education and adequate security measures"* - without additional guidance this statement is inadequate.

PIRP Location (page number, paragraph, etc.)

Annex 1 : Page 12, second full paragraph

Comments:

?? Rationing, of any type, is simply unheard of in today's healthcare environment. We are unconvinced that any effort to educate the public will make "rationing" terminology palatable to the general public.

Recommendations and Rationale:

?? Understanding that a limited number and/or amount of vaccine would be available for treatment and/or prophylaxis in the early stages of an influenza pandemic, an alternative would be to pre-position available vaccine where it will benefit the most and provide maximum usefulness - i.e., within hospitals.

?? Include with this deployment specific guidance for use - either for treatment of the sick or for vaccination of healthcare workers. It will be more effective for physicians and infection control! infectious disease specialists to implement established guidelines for use than to try to provide mass education to the public on who will! will not receive vaccine(s).

Pennsylvania Pandemic Influenza Response and Preparedness Plan Comments
10-6-04

Issue: Organization of information comparing outbreak characteristics, preparedness and response activities information.

PIRP Location: Pg: 3,8,9,10,11

Comments: The information provided for comparison on Pandemic Influenza and SARS is quite useful however comparison of this information in this format can be confusing and time consuming.

Recommendations and Rationale:

- To develop a Biological Agent Algorithm.
  Such an algorithm would group biological agents of similar outbreak characteristics requiring a common response activity. Identification of a causative biological agent at the onset of an outbreak may not be as important as rapidly determining the response necessary to protect the health of the victims, health care workers and facilitie. Final determination of an agent would further define response activities. Algorithms of this type could also be developed for chemical and radiological events.

Issue:
Multiple Suggestions for Annex 1

Comments:

- State Executive Committee needs "real" in-the-field representation from the private sector.
- Pg. 16 - Section E - Communications section is too brief.

- General Comment: Note the lack of reference to mentallbehavioral health issues. These need to be addressed more fully in the overall plan.

Recommendations and Rationale:

- Recommend the addition of2 Infectious Disease medical practitioners (not within the government) on the Executive Committee - 1 from an academic organization and the other from a community physician group.

- Much advance work is needed including the formation of state and local teams ready to spring into action possibly even prior to CDC guidance.

Discuss any anticipated barriers:

- Traditional organization of state and other governmental agencies and personnel doesn't include (by history and inclination) full and initial participation by private sector. This approach should be considered in advance, perhaps by identifying likely private sector consultants to join the Executive Committee upon its mobilization.

Issue:

Suggestions for Annex 2

Comments:

- Plan didn't adequately address issue relating to the legal rights of staff and hospital to restrict patient and family movement, quarantine in the hospital and in after-care at home, etc.

- Hospital Preparedness Teams - Pg. 5, Item III. A
  This team should also include representatives from employee training & development and media relations.

- Pre-Event Training for Staff - Pg. 8, 3rd paragraph
  It will be important to stress pre-event information, family planning, and training for staff as well. This will hopefully prevent some of the anticipated labor impacts of staff not reporting for work during an emergency.

- Credentialing of medical volunteers - Pg. 9, 2nd paragraph, bullet 6
  The issue of credentialing for volunteer (retired) medical staff must be addressed per JCAHO requirements.

- Surge Capacity/Non- Traditional Sites - Pg. 23, 2nd paragraph
  The guideline needs to require that hospitals work with local Health Departments in this area. The document implies that health care facilities should handle this on their own.

- There should be a mechanism to screen healthcare workers for diseases in the setting of a phase 3 pandemic (might also be useful in phase 2).

- Of use for hospitals, would be a reference table of guidelines linked to each phase of the pandemic (similar to one in the core document). Relevant issues for hospitals would be: when to devise separate triage areas for patients with respiratory symptoms, when to advise visitors with respiratory symptoms to stay away from hospital, when to implement mass vaccination clinics or chemoprophylaxis, etc.

General Comment: Note the lack of reference to mentallbehavioral health issues. These need to be addressed more fully in the overall plan.

Recommendations and Rationale:

- Recommend that these issues be addressed specifically through education and suggestions made in the plan.
- Employee information and public communication strategies will be key.
- Add some language recommending the development of family emergency plans (such as the Red Cross model) for flu pandemic situations.
- Add some language to address the need for hospitals to have in place an emergency credentialing process to ensure the veracity of volunteer medical and clinical staff credentials.
- Strengthen recommendation to work co-operatively with public health in this area.

Discuss any anticipated barriers:

- Need for strong interaction, planning and mutual dependency oflocal officials and health care providers. Also, appreciation of the immense worry and public fear unless pre-planned and continuous public communication is provided.

Issue:
Suggestions for Overall Plan

Comments:

- The most important strategy for saving lives in a pandemic situation is prevention of infection. Toward that end, a specific restriction on travel for hospital personnel is essential.

- Some additional points that need to be expanded in the plan are:
- Home care strategy for use after capacity in hospitals is reached.
- Care policy for dense population centers (schools, dormitories, prisons, etc.)
- Specific recommendations on care degradations during periods of overflow, i.e., what care is not given during a pandemic?Ventilators will be the most critical shortage in a pandemic. Specific recommendations on use and strategies for surge capacity should be given.

Issue:
Reference to *"need to ration vaccine will require substantial public education and adequate security measures"* - without additional guidance this statement is inadequate.

PIRP Location (page number, paragraph, etc.)

Annex 1 : Page 12, second full paragraph

Comments:

- Rationing, of any type, is simply unheard of in today's healthcare environment. Weare unconvinced that any effort to educate the public will make "rationing" terminology palatable to the general public.

Recommendations and Rationale:

- Understanding that a limited number and/or amount of vaccine would be available for treatment and/or prophylaxis in the early stages of an influenza pandemic, an alternative would be to pre-position available vaccine where it will benefit the most and provide maximum usefulness - i.e., within hospitals.

- Include with this deplOYment specific guidance for use - either for treatment of the sick or for vaccination of health care workers. It will be more effective for physicians and infection control/infectious disease specialists to implement established guidelines for use than to try to provide mass education to the public on who will / will not receive vaccine(s).

20048-0212 - Pandemic Influenza Preparedness Plan
FDA Comment Number: EC8

Submitter: Dr. Susan Smith Date & Time: 10/16/200404:10:04

Organization: Rensselaer Polytechnic University

Category: Academia

Issue Areas/Comments
GENERAL

GENERAL

I) This document has a serious flaw that undermines confidence in all of its conclusions. It does not address fundamental underlying conditions that lead to frequent recombination between viruses from different hosts, a major cause of differences in yearly flu strains and periodic pandemic- causing strains: the agricultural practices in Southeast Asia, where humans, birds, and pigs live in unhygienic proximity. HHS should take the lead with WHO, the World Bank, the health arm of the European Union, regional Asian health organizations, and other international governmental and non-governmental organizations in addressing this problem, which already has great economic and social impacts, even without the inevitable pandemic. This is a long term, very expensive undertaking, but the investment in influenza prevention will be paid back in less work lost, less catastrophic health care costs, and greatly increased ability to prevent widespread outbreak of species-crossing flu strains (as was possible in Holland).

2) The proposals regarding increasing vaccine production capacity are good, but too conservative. The recently announced vaccine shortage made it clear that relying on two companies to meet even current vaccine needs is unwise. At least 10 companies, foundations, and/or other research organizations should be recruited through contracts for development of other vaccine manufacturing methods, development of new types of vaccines, etc. Contracts should include provisions for the government to order increased production in case of emergency. We pay lip service to the development of a 'bioshield' capable of protecting the population against engineered threats, but in reality we cannot even adequately deal with threats that periodically arise through natural gene transfer.

3) More production and stockpiling of existing antiviral drugs is a clear necessity, and development of new drugs is also imperative. Again, this draft is too conservative. Many more companies and other research organizations should be recruited to participate in this effort through government contracts and grants. Government contracts and grants for this work should also contain provisions for ordering of increased production in case of emergency.

4) Vaccination for flu of all school-age children in public schools in the U.S. should be required and conducted routinely at the schools themselves. This policy would have the immediate advantages that large amounts of vaccine would have to be produced every year, increasing the existing production capacity; distribution could be shifted in case of pandemic. In addition, several studies have shown that schools are essentially incubation vessels for flu and other viruses; reducing the incidence of flu in schools would cut down on yearly flu incidence in the general population, which would have immediate beneficial economic impacts.

5) As was also made clear by the recently announced vaccine shortage, in the case of a pandemic or other health emergency, government health organizations should control the supply and delivery of flu vaccines and antiviral treatments. Federal support to schools, hospitals and other health organizations can be subject to requisition of facilities and staff to dispense vaccine and/or antiviral treatments in case of national emergency; failure to do so will result in ridiculous local decisions (as we have seen in this flu vaccine shortage) that will have disastrous health, economic, and social effects in the case of a pandemic. Social unrest (read widespread riots and looting) will inevitably occur during a pandemic as soon as people

realize that the distribution is being conducted inequitably, which will happen (as we have seen in the latest vaccine shortage) if left to private organizations. The priority of distribution as laid out in the draft document seems reasonable. It should be made enforceable.

2004S-0212 - Pandemic Influenza Preparedness Plan

FDA Comment Number : EC13

Date & Time: 10/26/2004 04:10:17

Submitter : Dr. Robert Stroube

Organization : Virginia Department of Health

State Government

Category :

Issue Areas/Comments

GENERAL

GENERAL

See Attachment.
If problems with attachment, please contact Dr. Diane Woolard at 804.864.8124 or diane.woolard@vdh.virginia.gov

Comments on the Draft Pandemic Influenza Plan from the Virginia Department of Health:

October 25, 2004

Thank you for providing such an informative draft pandemic influenza plan for the nation. The plan contains a great deal of important information that will help public health officials and medical care providers understand what to expect in the event of a pandemic, guide state and local planning efforts, and move us closer to being better prepared to respond appropriately if such a large scale public health crisis occurs. The Virginia Department of Health has some comments to offer about clarifications that would enhance the plan and additional subject matter that would be beneficial. Our suggestions are presented below by subject matter category.

Prioritization. It is very important to have national leadership in ranking the priority groups and defining sub-priorities within each group to ensure some consistency across the country regarding who may receive vaccine and antivirals in a time of extremely limited supply. The vaccination goals listed in the annex help identify broad priority groups, but not everyone in those groups will have access to vaccine. Thus, more specific definitions of priorities are needed. Similarly, antiviral priorities are listed in the healthcare system annex but need further definition. For example, the definition of front-line health care workers should be standardized. This priority ranking needs to occur in the inter-pandemic years and not wait until Phase I of the pandemic. Of course, it may need to be modified in Phase I depending on the epidemiology of the epidemic.

Along with specific priority group definition, we need the rationale for each priority group to be developed in advance so communication messages can be clear and consistent and delivered in a timely manner if a pandemic were to occur. Public education will be so critical to the success of any disease control campaign. Messages are needed about what people who are not in the priority groups can do during a time of crisis. It is important for these messages to be crafted in interpandemic years to ensure a standardized message comes out nationally during a time of need. The public information annex also mentions conducting assessments of provider and public information needs; tools to standardize the methods used for these assessments are needed. Perhaps an entire portfolio of communication materials surrounding pandemic influenza preparedness and response may be created.

Laboratory. It is imperative that the national pandemic influenza preparedness and response plan address laboratory capacity. Laboratory results are critical for influenza surveillance and for public health decisions during an influenza epidemic or pandemic concerning isolation, quarantine, prioritization of vaccination when vaccine supplies are limited, and appropriate use of antiviral agents. Therefore, an annex devoted to laboratory preparedness should be added to the national plan.

The laboratory capacity annex of the pandemic influenza preparedness and response plan should address all relevant laboratory issues, including the following: (1) sufficient laboratory capability for interpandemic surveillance, including influenza culture to assure adequate tracking of virus strains; (2) development and deployment of

rapid influenza virus detection and subtyping methods within the state public health laboratories, to enable rapid detection of Influenza A and its H subtype; (3) laboratory surge capacity for a nationwide pandemic; (4) provision for surge capacity in the supply of laboratory reagents for influenza detection and subtyping. Laboratory reagents have become a limiting factor even in years of moderately increased demand for laboratory testing (e.g., in the 2003-2004 season, several laboratories had to limit their laboratory testing for influenza because sufficient laboratory reagents could not be obtained). Planning for laboratory reagent supply is essential because laboratory reagent supplies could rapidly become one of the first and most critical elements to limit appropriate public health response to pandemic influenza.

Data Systems. The need for data systems is mentioned throughout the plan. It would be helpful if the plan could contain more information about suggested data elements and if the Centers for Disease Control and Prevention could develop some databases in advance so consistent data collection would be assured. Examples of databases mentioned include tracking who received the vaccine, who needs a second dose of vaccine, adverse reactions, antiviral use, drug resistance, vaccine supply, medical and material supplies and their allocation, beds available vs. patients waiting, monitoring the quality of care in non-traditional settings, priority group status and demographics of vaccine recipients, vaccination status of people making medical visits or being hospitalized, compliance with antiviral therapy recommendations, compliance with containment measures, etc. Clearly, a lot of data needs have been identified. The development of tools to meet these needs would aid public health capacity to respond and document critical information .

Surveillance. Surveillance challenges are presented in the annex, providing a good list of reasons why it is very difficult to count all cases of influenza. In the surveillance annex, very reasonable approaches to influenza surveillance are outlined by pandemic phase. However, if a pandemic occurs, the expectation will be that we can count all cases, hospitalizations, and deaths and provide those data daily. States need national guidance and recommendations about flu surveillance that is above and beyond what is normally done, rather than statements that states should develop strategies for monitoring deaths and hospitalizations. Public health leaders need to determine how we are going to handle the expectation of the public for daily counts, which are so difficult to determine for influenza. The communication and education annex mentions the need to collect data daily, including morbidity and mortality figures, geographic location of cases, number of persons affected, number hospitalized. The healthcare annex mentions ongoing monitoring of hospitalizations and deaths and monitoring nosocomial influenza infection. Surveillance for adverse events is also mentioned in the plan, although it is unlikely that resources would be available to conduct interviews at specific intervals after vaccination. These concepts are not addressed in the surveillance annex and clearer surveillance goals are needed. Additionally, states need national recommendations regarding the applicability for influenza of the use of emergency department or discharge data currently being used for syndromic surveillance for bioterrorism detection. Statements about the expected number of hospitalizations should be updated to reflect the data presented in the September 15, 2004 edition of the *Journal of the American Medical Association.*

Epidemiologic Studies. The plan mentions epidemiologic studies that would be recommended during a pandemic. These include monitoring for antiviral resistance and vaccine effectiveness and evaluating the effectiveness of interventions and impact on communities and the health care system. Guidelines for study methodologies and data collection tools for these types of studies would be helpful.

Antiviral distribution. The draft plan presents the use of antivirals as a critical component to the control of disease. The need for definitions of priority groups to receive these products has already been mentioned above. Additional information is needed about antivirals, some of which are mentioned but may deserve greater emphasis. Neuraminidase inhibitors are so difficult to make and not likely to be available in sufficient quantities. Yet they are a cornerstone of the planned method of control. More detailed estimates of the demand for antivirals if used for treatment and if used for both treatment and prophylaxis are needed. Those estimates could then be linked with estimates of available supply and permit more specific planning for what populations should receive them given the anticipated supply and demand. It needs to be very clear that the use of antivirals for prophylaxis should be limited to certain populations because it will drain the supply so quickly.

Some points that were made in the plan that need further emphasis are 1) that antiviral prophylaxis should not be used with live-virus vaccination; 2) how people should be asked to document that they are in a priority group; 3) how vaccines and antivirals will be distributed, including a plan for public and private sector distribution. We believe distribution plans need to be standardized. Information sheets should be developed and disseminated in advance, covering topics such as contraindications, drug interactions, and adverse events.

Fatality Management. The plan does not address any plans for management of mass casualties. This is an important component that deserves more attention and planning.

Disease control strategies/infection control. 1) More specific recommendations should be provided regarding methods of environmental decontamination, including cleaning procedures for common items (horizontal surfaces, floors, toys) as well as acceptable disinfectants to use. 2) The definition of a contact to include those working within 6 feet of a suspected case may be problematic to implement, especially if those contacts are asked to stay home for 7 days. 3) The communication and education annex mentions "intense contact tracing". This may be impractical to do during a large-scale event. Guidelines are needed on how much contact tracing is recommended. Further enhancement of isolation and quarantine plans is also indicated. 4) Consideration should be given to including terminology and guidelines to communicate a healthcare worker's ability to remain at or return to work (as in the Canadian Pandemic Influenza Plan), such as Fit for Work, Unfit for Work, and Fit for Work with Restrictions. 5) The healthcare system annex was a particularly strong component of the draft plan. A point made therein, however, raises concern regarding disease control. That is the recommendation to consider expediting patient discharge into a skilled nursing facility, which would increase the risk of institutional outbreaks among high risk populations. 6) Hospital

partners in Virginia have voiced a desire for more clarity about expectations and legal authority if isolation of infected individuals is needed.

Roles and Coordination. In the core plan, in section 3 on pandemic influenza response, more information about the roles and degree of coordination between the Departments of Health and Human Services (HHS) and Homeland Security is needed as well as the method of coordinating federal roles with those of state and local responders. A further indication of coordination would be demonstrated if the web sites for National Center for Infectious Diseases and the National Vaccine Program Office and cdc.gov/flu could be consolidated into an overall HHS flu site with a common link from each.

I have great appreciation for the magnitude of the effort that went into creating the draft national plan for pandemic influenza. The information provided is invaluable. I appreciate the opportunity to comment on the plan and look forward to continued work at all levels of government to assure public health preparedness for pandemic influenza. Thank you for the profound guidance you have provided thus far.

Sincerely,

Robert B. Stroube, M.D., M.P.H.
State Health Commissioner
Virginia Department of Health

Robert.stroube@vdh.virginia.gov