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Lessons from the Past in Preparedness for Pandemic Influenza

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There is ample material from which to draw lessons relevant to needed preparations for pandemic influenza. The 1918 epidemic is well and vividly documented and, surveillance data along with estimates of influenza mortality are reasonably complete over the past 50 years. Meanwhile, over the past three years in the U.S., there has been growing interest and concern about the challenges of dealing with mass casualties, including influenza and those that might result from bioterrorism. Several table-top exercises have been conducted and these have proved to be most illuminating. But, to date, the response, specifically preparations for dealing with a serious pandemic of influenza remain more in the realm of academic reflection than meaningful action. True, a great deal of time has been devoted to the development of a national response plan. The need for rapid production of large quantities of a new strain influenza vaccine is universally acknowledged. Efforts to make a live attenuated vaccine have been actively pursued for more than 20 years. And, regularly, the disastrous 1918 influenza pandemic is invoked to justify special programs of surveillance and planning.

However, I personally don't have the sense that we are now much better equipped to deal with a new pandemic of influenza than we were in the spring of 1957 when the H2N2 strain of influenza A emerged. That time I remember well when, as Chief of CDC's Surveillance Program, we faced a burgeoning epidemic whose virulence and propensity for spread were as yet unknown. We had to design a program of surveillance and field epidemiology to better define the epidemic. At the same time, preparations were needed for distribution and use of a new strain influenza vaccine --if it arrived in time. I'll return to the 1957 era later. It is notable, however, that after 33

years, the influenza vaccine hasn't much changed other than that it is now grown in bacteria-free eggs. Antiviral drugs have become available that offer some protection if given earlier enough. Meanwhile, managed care programs have sharply reduced the number of hospital beds to the point that there is little capacity to deal with the regularly recurring flu epidemics.

However much has been written about the 1918 epidemic, I believe that it is, in fact, actually perceived by most as an interesting but questionably relevant tale of death and disease during an earlier, pre-antibiotic era of medicine. My sense is that few actually believe that an epidemic of this severity could possibly occur today. Let me touch on just a few of the facts. First, it is important to recognize that, for the U.S., it dwarfed all other outbreaks of the 20th century. At least 20 million and perhaps as many as 40 million died worldwide. In the United States, there were more than 500,000 registered deaths. From various studies, it is thought that, overall, perhaps 40% of the population became ill, of whom about 2% died. Medical services were overwhelmed but, other than for supportive care, there wasn't a great deal that curative medicine could offer. Pictures from the time provide at least a pale illumination of that catastrophic period. SLIDES-SLIDES-SLIDES

The effect of the disease was anything but uniform. Surveys revealed morbidity rates ranging from 15% to more than 50% in different parts of the country. Some remote and rural areas escaped the disease entirely but in some areas, it was remarkably lethal. Western Samoa, then a New Zealand protectorate, registered 8500 deaths in a population of 38,000 -- This represented 22% of the entire population.

What was surprising and unique about the 1918 epidemic and for which we have no explanation was the fact that more than half of all deaths were in persons between 15 and 45 years of age -- an age bracket in which death is a relatively uncommon phenomenon. Pregnant women and those with cardiac problems were at highest risk but

most who died were otherwise in good health. A substantial number in this age group died of a fulminant, rapidly progressive pneumonia marked by severe cyanosis with death occurring within a matter of 2 to 3 days -- in brief, what seemed to be, almost certainly, a primary influenza pneumonia that would have benefited little from antibiotics, had they been available.

Today, a better outcome might be foreseen with better ventilatory support in intensive care units; with the administration of amantadine or rimantadine; and with the administration of antibiotics for the treatment of secondary pulmonary infections. But under epidemic circumstances and we must bear in mind that, in each city, the bulk of cases in a new pandemic would occur over a period of only 3 to 6 weeks, how many patients could be accommodated in suitable hospital settings, let alone appropriate intensive care units? What quantity of antiviral drugs is available for emergency use? Where do we obtain the added quantities of the standard antibiotics when, today, antibiotics, like so many products, are produced on a just-in-time basis -- when, during a period when clinical facilities are not stressed, we are regularly experiencing antibiotic shortages on a regular, rotating basis

Prevention

The rapid production and administration of large volumes of vaccine effective against the emergent new strain has been a basic building block of the strategy for dealing with pandemic influenza and, understandably so, given the limitations of curative medicine and the capacity of clinical services. The first real test of this strategy came during the 1957 epidemic. The first notice of a major outbreak occurred in mid April; specimens were received in the U.S. on 13 May; and field testing of new lots of the vaccine began in July. Not a bad record. It was foreseen that 60 million doses would be required. With good fortune in adapting the virus to grow at reasonably high titer on egg membrane and provided that sufficient fertilized eggs could be obtained, it was expected

that a production target of 1 February could be met. Even this was a problematical date given that the seasonal peak of epidemic influenza usually occurs between the end of December and the end of February. Still, it was believed that substantial numbers would be able to be protected.

However, 1957 was not a typical year, and such, one must note, was the case when the 1918 epidemic strain first appeared. Scattered outbreaks occurred in military units and on some college campuses but soon died out. The first significant outbreaks began occurring in mid to late September, fully two months before they were anticipated. More than half of all counties reported epidemics by mid-October and by the end of October the peak incidence had past, long before any significant quantity of vaccine became available. Given these experiences with a new strain, could we expect another new strain to behave differently today?

Extensive studies have been conducted in the search for a satisfactory live attenuated vaccine and for various approaches in production which would permit new antigenic variants to be produced rapidly and in quantity in tissue cell culture. However, we are still today producing influenza vaccine on the chorioallantoic membrane of hens' eggs; procuring adequate supplies of fertile eggs in a timely manner remains a serious problem; and difficulties in adapting new strains to CAM continues to bedevil the process. We are, as you know, short of vaccine this year and many are arguing the need for rationing. And, we are informed, as we have been for at least the past 20 years, that a new tissue cell culture vaccine, able to be rapidly produce, is just over the horizon.

Were we able to solve the vaccine production problem for our own country, this would not be the end to the practical quandary of dealing with the pandemic. Few countries have influenza vaccine production capability and the international implications of the U.S. having all or much of the vaccine supply are profound. These considerations

were vividly brought home to me in 1976 following the swine influenza outbreak at Fort Dix, New Jersey. The United States, as you will recall, embarked on a crash program to rapidly produce an appropriate vaccine. At that time, I was working in Geneva with the World Health Organization. Since I had had experience with the 1957 Asian influenza pandemic, Charles Cockburn, then Director of the Virus Diseases Unit, asked that I join him in convening a special meeting of epidemiologists and vaccine producers to consider what advice should be given to other countries. At that meeting, it was made quite clear that the capacity for influenza vaccine production in Europe itself, let alone any where else in the world, was so marginally relevant as to be insignificant. The Committee's recommendation was that the Fort Dix situation be carefully monitored -- wise and sensible advice as events subsequently showed but, in fact, the only option open to us --basically, wait and hope. But as those at the meeting commented in corridor conversations -- they would not wish to face the ethical and political dilemma the United States would face were there a pandemic and the U.S. was the only nation with substantial quantities of vaccine.

Challenges today in dealing with surges in demand for medical services

Over the past year, our Center staff has held a series of meetings with national and local hospital authorities to explore current capabilities of the medical system to deal with sudden surges in demand such as might follow release of a biological weapon. Such a release would result in an epidemic that would stress the system not unlike the way it would be stressed by a pandemic of severe influenza.

A primary need is for a surge capacity for beds and for staff to care for patients. As we have discovered, however, the elasticity of the nation's bed supply has been significantly reduced as drives for financial efficiency and the increasing use of out-patient procedures have sharply reduced the numbers of beds in all hospitals. Even the directors of large hospitals have said that for them to accept as many as 50 acutely ill

patients on an emergency basis would tax their resources. Meanwhile, managed care-driven market pressures and federal government reimbursement reductions have driven large numbers of hospitals into operating deficits. Under these circumstances, none are in a position to devote resources needed for extensive planning and, as necessary, physical changes to accommodate additional patients. Many of the municipal hospitals, once a primary source of care for the less prosperous and uninsured have been privatized. Meanwhile, the hospitals are experiencing severe labor shortages, especially for nursing and technical personnel.

Reserves of antibiotics, as noted earlier, are marginal to nil; the public health infrastructure needed to deal with epidemic disease is grossly understaffed, underpaid and under trained; mechanisms for the development and implementation of community-wide plans are largely unexplored.

The reality

What might a new strain of influenza mean in terms of numbers of cases and deaths. Estimates of past pandemics suggest that perhaps 40% of the population has been affected in a first wave. Today, with rising proportions of the population in urban areas, the greater and more rapid mixing of populations through travel, a figure of not less than 60% would seem more reasonable. Thus, in a city of 3.0 million, one might expect two million cases of influenza. It is doubtful that either antibiotics or antiviral agents would be of much help given the number of cases and the dearth of reserve supplies. The number of deaths would vary greatly depending on the strain. In Hong Kong, a recent new strain, H5N1, resulted in death among 6 of 18 persons infected. It did not spread readily, however. If it did, we would be dealing with a catastrophe that would dwarf the 14th century plague epidemics in Europe and those of smallpox in the Americas during the 16th and 17th centuries. More reasonably, one might select, as a high figure, the 2% who died in 1918 and, as a low estimate, the figure of about 0.2%,

the proportion who died during the 1957 pandemic. Thus, in a city of 3 million persons, one might anticipate between 3600 and 36,000 deaths over a period of 3 to 4 weeks

Medical care would consist largely of supportive therapy given the numbers of those ill. Public health measures, likewise, would consist of little more than reassurance given the likelihood that vaccine supplies would not be available. Producing sufficient antiviral drugs to permit any substantial number in the population to receive such drugs daily for perhaps 60 to 90 days would be prohibitively expensive, even if technically feasible. Even it the drugs were available, the logistics of a population-wide drug distribution program would be staggering. And what then, if the drugs forestalled the epidemic? Would it not leave a population fully susceptible to develop influenza as soon as drug administration ceased? Many would argue for the closing of such as schools, churches and other places of public gathering but experience suggests that such actions produce little of benefit. The wearing of masks was once a favored intervention but this, too, has been discredited. In brief, without vaccine, there would be little that could be done of practical benefit except to treat secondary infections to the extent that antibiotics were available and to reassure the community that the epidemic would someday pass. The bottom line is that we are probably less well equipped to deal with a pandemic than in 1957 and perhaps only marginally better prepared than we were in 1918.

What lesson is to be learned

It seems to me that the lessons to be derived from past experience are four in number:

1) The threat of pandemic influenza caused by an especially virulent strain is a continuing threat that has to be taken seriously.
2) Adequate supplies of an effective vaccine, available in a timely manner, are absolutely critical for dealing with pandemic influenza. Unless this problem is solved, all other measures will be of little import. It would seem obvious that

solving this problem should command top priority for research and development.

3) Special plans, programs and funding are needed within the health care system to permit development of an adequate hospital and community-wide response to the occurrence of mass casualties whatever the cause.
4) Additional research in influenza is sorely needed in order to better understand its pathogenesis and epidemiology with the expectation that better preventative measures might eventuate.

Note: Dr. Kanta Subbarao, CDC, an influenza virologist quoted estimates of likely burdens on the curative care system caused by a new pandemic

300,000-730,000 hospitalizations

18 to 42 million outpatient visits

Note that these are CDC estimates and would need to be scrutinized with special care.