Containing the Novel Influenza A (H1N1) Virus

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(See the article by Torres et al, on pages XXX–XXX.)

By the end of November 2009, it was apparent that the first significant wave of the influenza epidemic in the United States that was caused by the novel influenza A (H1N1) virus was on the downward side of the epidemic curve. In all likelihood, a formal assessment of pandemic preparedness will be forthcoming. The extraordinary effort to produce, test, and distribute both seasonal trivalent and novel H1N1 monovalent influenza vaccines certainly will be noted. Although the government-sponsored efforts to replace egg-grown virus antigens with those produced in tissue culture (which might have accelerated the process) did not come to fruition, the amount of vaccine produced and delivered has been impressive. Most assessments did not anticipate having any pandemic vaccine before the first wave.

The first line of defense, in the absence of vaccine, is the use of specific antiviral drugs. Several scenarios for use of antiviral drugs have been proposed, and when the pathogenic avian H5N1 virus was seen as the most likely etiology of the next pandemic, containment strategies were considered [1]. It was suggested that stockpiles of antiviral drugs be maintained in the Far East, where most of the H5N1 activity has occurred. If a facile human-to-human spread of the H5N1 virus should be detected, persons in the geographic area of the human spread should receive specific prophylaxis to create a barrier against a continued spread. Containment strategies were not developed in the United States when the novel H1N1 influenza virus began to spread. Although a national stockpile of antiviral drugs had been established, only ~35% has been distributed to the states. The use of the stockpiled antiviral drugs in the clinical setting has been limited. Few clinicians are aware that these drugs can be prescribed from stockpiles free of charge to patients from low-income groups.

The article by Torres et al [2] in this issue of the journal describes a modified containment strategy utilizing antiviral drugs during the first wave of the novel H1N1 influenza pandemic in Chile during the southern hemisphere winter of 2009. Virtually all patients presenting to the emergency department of the Clínica Las Condes were treated with neuraminidase inhibitors (oseltamivir or zanamivir), and almost all received treatment within the first 48 h after onset of symptoms. There were no deaths, and only 199 patients were hospitalized among >10,000 patients treated. Of 11 patients admitted to intensive care, 8 patients were referred from other hospitals. Even though Clínica Las Condes serves an upper income (and apparently compliant) population in Santiago, Chile, the benign outcomes are remarkable. The strategy of early treatment for all who present to urgent care facilities deserves consideration as a means of reducing serious complications of influenza.

Other evidence to support this approach is presented by Halloran et al [3] in their analysis of clinical trials with neuraminidase inhibitors, which demonstrated a reduction in the infectiousness of the treated index patient. Aoki and Boivin [4] assessed the influenza A viral load in the upper tract secretions of patients treated during the first 24 h after onset of symptoms, compared with those treated later who were twice as likely to have a positive polymerase chain reaction result after 48 h of treatment with oseltamivir. McGeer et al [5] found reduced mortality among hospitalized adult patients who were treated with antiviral drugs, and Piedra et al [6] found that early treatment reduced serious morbidity among pediatric patients with underlying conditions (including asthma).

Advisory bodies in the United States have been reluctant to recommend treatment for all patients presenting with influenza-like illness. Several reasons have been stated. One, of course, is the fear that resistance will develop with increased use. However, most of the resistance to neuraminidase inhibitors has occurred among hospitalized patients (especially immunocompromised patients), who have been

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recommended by all advisory bodies to receive treatment, and not among ambulatory patients, who usually have no underlying conditions [7]. The rapid development of oseltamivir resistance in prevalent seasonal H1N1 viruses did not appear in Japan, where oseltamivir use is highest, but in areas of Europe where oseltamivir use was minimal, and this H274Y mutation rapidly spread throughout the world. A similar mutation could occur with the novel H1N1 influenza virus; it would be unfortunate if it occurred with millions of doses of antiviral drugs stored in stockpiles after many had died of infections due to sensitive strains of the novel H1N1 influenza virus.

Advisory bodies have reserved antiviral treatment for those who are likely to develop serious disease. The outcome is often difficult to predict within the first 48 h of illness when therapy is most effective; many of the deaths due to the novel H1N1 influenza virus have occurred among persons without chronic underlying conditions. A more effective use of antiviral drugs would be to treat all persons who present with an influenza-like illness during times when influenza viruses are prevalent, as was done in Chile. Effective short-term therapy in a largely healthy population is not likely to hasten the emergence of drug-resistant viruses. In addition to reducing complications for treated individuals, early treatment could also limit the spread of infection to those who have contact with treated patients. The effective use of antiviral treatment can fill the gap in influenza control produced by those who refuse to be vaccinated.

Another concern of advisory bodies has been the supply of antiviral drugs. The manufacturers have been able to respond to demand as needed, including during the "surge" when many countries were stockpiling antiviral drugs. The principle reason for supply problems has been the low demand for antiviral drugs during seasonal epidemics. This might be reasonable if seasonal epidemics were controlled, but yearly epidemics take a toll, with an average of 50,000 all-cause excess deaths [8] and >300,000 excess hospitalizations during the last decade of the 20th century [9]. If use of antiviral drugs increases, supply will follow. More importantly, development of new drugs will be expedited to prepare for the emergence of resistance to the currently used drugs.

The program in Chile did not include prophylaxis of household contacts. Although it was recommended initially, implementation of this type of prophylaxis was difficult, and therefore it was quickly discontinued. Prophylaxis of contacts for each introduction of infection into the household during the epidemic season is cumbersome and expensive. Prophylaxis for contacts with serious underlying conditions might be implemented if the drug supply is sufficient.

The message of the Chilean investigators for the northern hemisphere is to vaccinate school children. In the early stage of the epidemic in Santiago, two-thirds of the patients presenting with influenza-like illness 6–18 years of age. The shift in age distribution that they recorded during the epidemic was similar to that observed previously in the United States [10, 11]. Most of the pediatric deaths due to the novel H1N1 influenza virus reported in the United States occurred in school-aged children. School-based vaccine clinics could facilitate the rapid distribution of vaccine to a high proportion of children, not only reducing mortality but also reducing the spread of the virus in the community to allow more time to vaccinate all other segments of the population [12].

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