

ID CONSULT

Focus on Immediate Flu Concerns, Not Fears

We should be concerned but not panicked about avian influenza. As clinicians, we need to reassure families about the small but perhaps increasing potential for pandemic flu and answer their questions, but at the same time focus our immediate efforts on prevention and management of the nonpandemic annual influenza season that is just around the corner.

There appears to be confusion out there—even among some physicians—about the details concerning what avian influenza is and what would need to happen for it to become a pandemic. In fact, avian influenza isn't new—periodic outbreaks have occurred and been reasonably controlled in animals worldwide, including in the United States, for decades.

At least one strain of avian influenza, an H5N1 strain, is now endemic in much of Asia and has recently spread to Europe, killing poultry and other birds in several countries. The H5N1 strain was first recognized in 1997, when it infected 18 people and killed 6 in Hong Kong. Since 2003, it has been diagnosed in more than 100 humans in several countries in Southeast Asia with greater than a 50% mortality.

But this avian H5N1 strain in humans has not become pandemic. A true pandemic requires sustained human-to-human transmission. To date, nearly all of the infected individuals have been in direct contact with infected poultry. For a pandemic to occur, a human influenza strain and an avian influenza strain need to si-

multaneously infect an intermediate host (usually a pig but perhaps even a cat). Then the strains would need to exchange genes via reassortment, and a reassortment mutant would then need to reemerge and reinfect humans.

This hasn't happened yet, and if we're lucky it never will. Indeed, H5N1 has been circulating among birds in the Far East since 1997 without this reassortment occurring.

But humans packed densely into small geographic areas together with avian species and intermediate mammalian hosts—the current situation in parts of Asia—do increase the chance that reassortment might happen.

This theoretical possibility is why many officials are concerned. The U.S. Department of Health and Human Services has now developed a \$7.1 billion national strategy to address pandemic influenza (www.pandemicflu.gov). The plan includes four major components:

1. Intensifying surveillance and collaborating on containment.
2. Stockpiling antivirals and vaccines.
3. Creating a network of federal, state, and local preparedness agencies.
4. Increasing public education and communication.

Although not perfect or complete, this plan is evolving rapidly.

For this reason, I have recently changed my view about personal stockpiling of antivirals. A few months ago, when there were apparently ample supplies, I believed that families and first responders should

keep a neuraminidase inhibitor on hand, anticipating influenza season. I no longer support this practice because demand has risen, and there simply isn't enough antiviral medication to go around.

Now I think it makes more sense to keep these drugs in central locations to be distributed to outbreak sites for pandemic influenza—instead of scattered among individuals around the country.

Of course, if you have a patient with confirmed influenza for less than 48 hours, it still makes sense to treat with oseltamivir or zanamivir if these drugs are available. When the local type is an influenza A, you could also use rimantadine or amantadine, depending on their availability and on the patient's age, if no other contraindications to these two drugs are present.

But for now I strongly believe that our top priority should be immunizing our patients against the nonpandemic annual influenza that we know is coming soon. And I mean *all* children, not just those aged 6-23 months or those with high-risk medical conditions. Indeed, I support the emerging viewpoint that immunizing school-aged children is also critical to preventing transmission within a community.

Among the many lines of emerging evidence for this approach is a recent report from Japan saying that although both oral oseltamivir and inhaled zanamivir reduce the duration of influenza symptoms in children, they do not significantly shorten the period of viral shedding (*Pediatr. Infect. Dis. J.* 2005;24:931-2). Another recent study determined that children aged 3-4 years are the first to become infected with influenza each season, and therefore serve as vectors for the rest of the community (*Am. J. Epidemiol.* 2005;162:686-93).

These findings are of concern because children typically go back to school or day care once their symptoms diminish. I agree with Ram Yogev, M.D., who recently called for the policy-making organizations to consider issuing an evidence-based recommendation for routine vaccination of all healthy children (*Pediatrics* 2005;116:1214-5). Of course, there are logistics to overcome with such a large undertaking, but I feel the benefits can be huge, too.

The Centers for Disease Control and Prevention advises, "In addition to the groups for which annual influenza vaccination is recommended, physicians should administer influenza vaccine to any person who wishes to reduce the likelihood of becoming ill with influenza or transmitting influenza to others should they become infected (the vaccine can be administered to children [older than] 6 months), depending on vaccine availability" (*MMWR* 2005;54[RR08]:1-40).

In my mind, that's what we should be doing. Not only will this protect our patients and their contacts, but it will also reduce the chance that garden-variety influenza will be mistaken for H5N1. In fact, the human H5N1 cases seen in Asia have involved more gastrointestinal symptoms in children than does the typical annual flu; the human H5N1 cases have also had leukopenia, thrombocytopenia, and elevated liver enzyme levels, which are not normally seen with the regular flu. Be especially alert for those symptoms, particularly in a child who has traveled overseas where H5N1 has been found. ■

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BY CHRISTOPHER J. HARRISON, M.D.

Empiric Antiviral Therapy Worthwhile During Flu Outbreaks

BY KATE JOHNSON
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Empiric therapy with antiviral medication during an influenza epidemic is superior to both rapid diagnostic test-based therapy and no therapy in symptomatic pediatric patients, according to an analysis based on hypothetical scenarios.

"We found no role for rapid diagnostic testing during local outbreaks, because clinical diagnosis is highly predictive, whereas rapid testing leads to frequent false-negative results," said Michael B. Rothberg, M.D., and colleagues at Baystate Medical Center in Springfield, Mass. (*Arch. Pediatr. Adolesc. Med.* 2005;159:1055-62).

The analysis included hypothetical patients, 2, 7, and 15 years old, presenting to a primary care physician with fever and cough or coryza within 48 hours of symptom onset in a local influenza outbreak.

The costs and benefits of empiric antiviral therapy, test-guided antiviral therapy, or no antiviral therapy were examined using evidence from all trials of the medications in children. Two treatment choices were included in the analysis: amanta-

dine hydrochloride and oseltamivir phosphate (the only drugs currently licensed for the treatment of influenza in children younger than 7 years), and two rapid diagnostic tests were considered: QuickVue (Quidel Corp., San Diego) and ZstatFlu (ZymeTx Inc., Oklahoma City).

The analysis considered vaccinated and unvaccinated patients separately. Consideration was given to outbreaks that were predominantly influenza A (90%) or a mixture of influenza A (55%) and B.

Compared with no treatment, empiric therapy with antiviral medication improved quality-adjusted life expectancy in all scenarios by both shortening the duration of illness and preventing otitis media.

The choice of which medication and whether it saved money depended on the age of the child and which type of influenza was predominant. "When influenza A predominates, both drugs appear equally effective, but amantadine may be better tolerated and is less expensive," said the authors. "Because amantadine is not active against influenza B, however, oseltamivir will be more effective when influenza B is prevalent."

In a scenario where influenza A predominated, empiric amantadine improved quality-adjusted life expectancy for all age groups. It was the least expensive strategy in children under 15 years old, saving \$121 per child, compared with no treatment, because of the savings it gave parents who could return to work faster. However, this treatment resulted in no savings if the child was old enough to stay home alone.

During seasons in which influenza B was common, empiric oseltamivir improved quality-adjusted life expectancy in all age groups and was the least expensive option for 2-year-olds. But the cost increased with weight. And vaccinated children had lower costs and better outcomes in all cases.

Rapid testing was useful only in influenza B (or mixed) outbreaks when a patient's likelihood of infection was low. In such cases, a negative test could avoid the higher cost and side effects of oseltamivir.

Otherwise, "because the rate of adverse effects from oseltamivir and the false-negative rate for QuickVue are identical, a child is more likely to be helped than harmed by empirical oseltamivir whenever the probability of influenza is greater

than 50%," the researchers said.

They noted some obstacles to the implementation of their model in clinical practice. First, some practitioners may be uncomfortable with prescribing empiric therapy, although "such caution avoids unnecessary adverse effects, but leads to undertreatment." Second, parents paying out-of-pocket may be unwilling to purchase the more expensive oseltamivir—especially if a child's illness will not result in loss of parental income. And, despite years of evidence supporting antiviral use, many physicians are unfamiliar with them and many pharmacies may not stock them.

Some potential benefits were not considered in the model, including antivirals' potential to decrease hospitalizations in high-risk children, such as asthma patients.

There also is some suggestion that antiviral therapy can decrease transmission of influenza. The researchers point out that in order to prescribe antivirals in a cost-effective manner, clinicians must be aware of which type of influenza is prevalent. This information is available at state health departments and from the Centers for Disease Control and Prevention (www.cdc.gov). ■