Dual-Resistant Seasonal Flu Viruses on the Rise

Two studies highlight concerns about how easily influenza A(H1N1) viruses can become resistant.

BY JENNIE SMITH

FROM JOURNAL OF INFECTIOUS DISEASES

Two publicly funded studies from the United States and England show that the proportion of seasonal influenza A viruses resistant to two types of antiviral drugs has risen in recent years, and that drug-resistant pandemic influenza A was transmitted person-to-person during one 2009 outbreak.

Both studies, published online Dec. 7 in the journal, highlight concerns about how easily influenza A(H1N1) viruses can develop mutations for resistance, about the paucity of treatment options available for resistant infections, and the risks of using potentially ineffective agents.

For the first study, Tiffany G. Sheu and Dr. Larisa Gubareva of the Centers for Disease Control and Prevention in Atlanta, and their colleagues, tested seasonal H1N1 viruses collected between 2008 and 2010 for resistance to two types of antivirals: oseltamivir and adamantane drugs. The researchers noted that resistance-conferring mutations in an influenza A virus can occur as a result of drug selection, spontaneous mutation, or genetic reassortment with another drug-resistant influenza A virus (J. Infect. Dis. 2011;203[1]:13-7).

Of the nearly 1,500 virus samples submitted by surveillance programs around the world, 28 viruses from five countries in North America, Africa, and Asia, exhibited both adamantane and oseltamivir resistance, the investigators reported. The proportion of resistant viruses increased from 0.06% (1 of 1,753) of those for 2007-2008, to 1.5% in samples for 2008-2009 (21 of 1,426), and to 28% in a smaller number of samples from the 2009-2010 season (7 of 25), when fewer seasonal A strains were circulating. The dual-resistant viruses represented four different genotypes.

"Although dual-resistant viruses are still rare," the researchers wrote, "the increase in prevalence among seasonal influenza A(H1N1) viruses was notable during the last three seasons." Also, the detection of dual-resistant seasonal A(H1N1) viruses from five countries "warrants concern," they wrote, "because of the limited treatment options currently available for dual-resistant influenza A viruses."

In the U.K. study, clinical virologist Catherine Moore and Dr. Elori Davies of the Public Health Wales NHS Trust in Cardiff, and their colleagues, described the first molecularly confirmed person-to-person transmission of oseltamivir-resistant pandemic influenza A(H1N1) 2009 virus. After an outbreak of 11 cases in the hematology wing of a public hospital in October and November 2009, 10 were shown by sequencing to be virologically related, 8 were oseltamivir-resistant, and 4 of the 8 infections occurred by direct transmission of resistant virus.

Though the infected patients had considerable underlying disease, including leukemia, multiple myeloma, and lymphoma, influenza symptoms were generally manageable during the outbreak, and none of the patients died as a result of their resistant infections, Ms. Moore and colleagues reported (J. Infect. Dis. 2011; 203[1]:18-24).

Resistance-conferring mutations in an influenza A virus can occur as a result of drug selection, spontaneous mutation, or genetic reassortment.

Dual treatment with oseltamivir and zanamivir was used when resistant virus was suspected or confirmed. However, Ms. Moore and colleagues noted that "recent data suggest there is possibly no synergy to be gained from this approach."

In an editorial comment accompanying the two studies, Dr. Frederick G. Hayden of the University of Virginia, Charlottesville, and Dr. Menno D. de Jong of the University of Amsterdam, the Netherlands, saw cautions in both. "Together, these findings illustrate that single reassortment events or mutations can lead to the emergence of transmissible variants of pandemic 2009 or seasonal A(H1N1) viruses unresponsive to most, if not all, of our currently available drugs," they wrote (J. Infect. Dis. 2011; 203[1]6-10).

The study by Ms. Sheu and Dr. Gubareva was funded by the Centers for Disease Control and Prevention. The study by Ms. Moore and Dr. Davies was funded by their public institutions; one coauthor acknowledged funding from the Wellcome Trust for a virus-sequencing pipeline project and another received funding from Roche for an influenza virus shedding study in oseltamivir-treated patients.

Dr. Hayden reported that he has received no research grants or personal honoraria from industry since 2006, but that he has served as an unpaid adviser to multiple companies involved in the development of influenza antivirals since 2008, and is member of the Neuraminidase Inhibitor Susceptibility Network, which has received funds from GlaxoSmithKline and Roche. ■

Freezing DTaP Vaccine Linked to Increase in Pertussis

BY SUSAN LONDON

FROM THE ANNUAL MEETING OF THE NORTH AMERICAN PRIMARY CARE RESEARCH GROUP

SEATTLE – Inadvertent freezing of the diphtheria, tetanus, and acellular pertussis (DTaP) vaccine while it is being stored in vaccine refrigerators may be contributing to the rise in pertussis in the community, new data suggest.

Using continuous data loggers, investigators at the Baylor College of Medicine in Houston found that one-quarter of 54 vaccine refrigerators in the city's community health centers had temperatures that dipped into the freezing range, most commonly at night and on weekends.

There was a significant 76% correlation between the percentage of vaccine refrigerators in a health region that had prolonged freezing temperatures and that region's rate of pertussis, the investigators reported at the meeting.

The study establishes only correlation, and there are many possible confounders and explanations, said investigator Dr. Patrick J. McColloster, an associate professor of family medicine at the college.

"But I think though that one thing that has been neglected in looking at the pertussis outbreaks in the United States is inadvertent freezing and the instability of DTaP – back to the cold chain again," he said, referring to the practice of ensuring that the vaccine is continuously kept at the recommended temperature.

In interviews, nursing staff at the centers were skeptical of the freezing because they more often noticed warm temperatures during the workday, he commented. "Whenever they opened and closed the refrigerator doors, they always made sure [the temperature] was within normal range, and if it was a little too hot, they would just crank the refrigerator up a bit more. So basically, they were freezing the vaccines like crazy."

Explaining the rationale for the study, Dr. McColloster noted that the incidence of pertussis fell in the 10 years after introduction of the DTP (diphtheria, tetanus, pertussis) vaccine, but it actually rose in the 9 years after subsequent introduction of the DTaP vaccine.

"All the studies that are out there are saying it's due to seasonal variation, unvaccinated pediatric clusters, and declining adult immunity," Dr. McColloster said. "Gee, it doesn't have anything to do with DTaP, does it?"

The impact of failure of the vaccine cold chain on the occurrence of pertussis has not been studied in the United States. "DTaP uses aluminum as an adjuvant (just like DTP does), but it's a little bit different in that it's more sensitive to freezing," he explained. In fact, the manufacturer recommends discarding any vaccine exposed to freezing temperatures.

In the study, the investigators attached data loggers to 54 vaccine refrigerators in 13 Community Health Centers in the Harris County Hospital District of Houston. The centers provide approximately 580,000 outpatient visits each year to an indigent population.

The loggers sampled the refrigerator temperature every minute for at least 6 days. Data from the first hour were discarded to allow the logger's temperature to equilibrate.

The centers' own procedure for cold chain monitoring consisted of twice-daily readings from approved digital thermometers during weekday work hours, as mandated by the Centers for Disease Control and Prevention.

The investigators obtained data on the incidence of pertussis in the district for the years 2005-2009 from the City of Houston Health Department.

Results showed that 48% of refrigerators maintained temperature in the correct range (2°C to 8°C), Dr. McColloster reported. But 19% experienced cold temperatures (0.1°C to 1.9°C) and 24% experienced freezing ones (0°C or lower). The remaining 9% had temperatures rising into the warm range (greater than 8°C), but this usually was so transient that it was unlikely to alter temperature of the vaccine itself, he said.

Among the refrigerators with freezing temperatures, the average time spent at freezing was 2 hours per day. Freezing usually occurred on nights and over weekends.

Across the six health regions within the district, the percentage of refrigerators in the region having freezing temperatures for more than 2 hours daily ranged from 14% to 80%. And the average annual pertussis rate ranged from 2.9 to 6.3 cases per 100,000 population.

The higher the percentage of refrigerators in a region experiencing freezing temperatures for more than 2 hours daily, the higher the pertussis rate for that region (*P* less than .05), Dr. McColloster reported. ■

VITALS

Major Finding: Some 24% of refrigerators used to store DTaP vaccine experienced freezing temperatures. The higher the percentage of refrigerators with prolonged freezing in a health region, the higher that region's rate of pertussis.

Data Source: An observational study of 54 vaccine refrigerators in 13 community health centers having about 580,000 outpatient visits annually.

Disclosures: Dr. McColloster said he did not have any conflicts of interest related to the study.