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LEARNING OBJECTIVES After studying the literature presented in this issue, participants will be able to:

- Explain the complications of influenza that contribute to mortality
- Relate the impact that priming with a prepandemic vaccine can have on enhancing antibody response to avian influenza with a single dose vaccination

TARGET AUDIENCE This educational activity is designed for pediatricians, primary care physicians, pediatric and family nurse practitioners, neonatologists, infectious disease specialists, allergists, pulmonologists, immunologists, and other healthcare professionals involved in the care and management of pediatric respiratory patients.

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Bacterial Pneumonia Is Major Contributor to Mortality in Pandemic Influenza

Limited information exists specific to the causes of death in the United States resulting from the 20th-century influenza pandemics—the "Spanish flu" (1918–1919), "Asian flu" (1957–1958), and "Hong Kong flu" (1968–1969). In the present study, Morens et al examined lung tissue sections obtained during autopsy from 58 influenza victims from the "Spanish flu" pandemic, and reviewed epidemiologic, pathologic, and microbiologic data from more than 100 published autopsy series that described more than 8,000 autopsy investigations. These series included 8,398

autopsy investigations from 15 countries: 96 postmortem lung tissue culture autopsy series (5,266 cases), 42 blood culture series (1,887 cases), and 35 pleural fluid culture series (1,245 cases). The authors also reviewed relevant pathologic information on the Asian flu and Hong Kong flu pandemics, which were descendants of the 1918 virus. The "Spanish flu" pandemic was the last pandemic before antibiotics became available for use in humans.

In nearly all cases, the examination of recut lung tissue revealed considerable histologic

evidence of severe acute bacterial pneumonia caused by common upper respiratory-tract bacteria—either as the principal pathology or in association with underlying pathologic features now believed to be related to influenza virus infection. A high incidence of secondary pneumonia associated with standard bacterial pneumopathogens was seen among the influ-

The majority of pulmonary deaths from pandemic influenza viruses are a byproduct of poorly understood interactions between the virus and secondary infections due to upper-respiratory bacteria.

enza-associated pneumonia pathologies. Other unforeseen facets of these fatalities included the frequency of pneumonia caused by mixed pneumopathogens (especially pneumococci and streptococci) and other mixed upper respiratory-tract bacteria; the aggressiveness of bacterial invasion of the lung, massive infiltration of polymorphonuclear neutrophils, necrosis, vasculitis, and hemorrhage; and the predominance of bronchopneumonia and lobular pneumonia.

Among 68 "higher-quality" postmortem lung culture series (3,074 autopsies), in which the possibility of unreported negative cultures could be excluded, 92.7% of lung tissue samples were positive for ≥1 bacterium. Out of a total 96 autopsy series (5,266 cases), 82 reported pneumopathogens in ≥50% of lungs assessed, either alone or in mixed culture results

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Disclosures:

Dr Piedra is professor of pediatrics and molecular virology and microbiology at Baylor College of Medicine, Houston, Texas.

He has indicated that he receives grant/research support from Juvaris BioTherapeutics, Inc., MedImmune, Inc., Sanofi Pasteur, and Novartis Pharmaceuticals; is a speaker for MedImmune, Inc.; and is an ad hoc consultant for MedImmune, Inc., Sanofi Pasteur, Novartis Pharmaceuticals, Hoffmann-La Roche Inc., and Merck & Co., Inc.

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Predominant Role of Bacterial (Continued)

that included other bacteria. *Streptococcus pneumoniae*, *Streptococcus hemolyticus*, and *Haemophilus influenzae* were the sole pathogens isolated in 23.5%, 17%, and 9.9% of the 5,266 cases, respectively.

The authors suggest that the majority of pulmonary deaths from pandemic influenza viruses are a byproduct of not well understood interactions between the influenza virus and upper-respiratory bacteria, resulting in an overwhelming bacterial pneumonia. They further suggest that any influenza virus that can spread to and damage bronchial and/or bronchiolar epi-

thelial cells may hasten the appearance of severe and potentially fatal bacterial pneumonia. Thus, if death in pandemic influenza is predominantly a problem of viral-bacteria copathogenesis, pandemic planning must incorporate not only a virus strategy but also the prevention, diagnosis, prophylaxis, and treatment of bacterial pneumonia.

Morens DM, Taubenberger JK, Fauci AS. Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness. *J Infect Dis*. 2008;198(7):962-970.

COMMENTARY

JAY M. LIEBERMAN, MD, Professor of Clinical Pediatrics, University of California, Irvine.

The 1918-1919 Spanish flu pandemic was responsible for an estimated 675,000 deaths in the United States and more than 40 million deaths globally. In contrast to our current annual "seasonal flu" outbreaks in which >90% of deaths occur in the elderly, >99% of deaths from the Spanish flu occurred among those younger than 65 years. This fascinating report in The Journal of Infectious Diseases suggests that bacterial superinfection, caused by Streptococcus pneumoniae, Group A streptococcus, or Staphylococcus aureus, was the predominant cause of death during the Spanish flu outbreak. A report in the October 2008 issue of Pediatrics highlighted the importance of Staphylococcus A infections, particularly methicillin-resistant Staphylococcus A, as a cause of death among children with influenza in the present day.¹ The take-home message is that planning for the inevitable next influenza pandemic (whether or not it is avian influenza) should include not only the need for a vaccine against the pandemic strain but also consideration for expanded use of pneumococcal vaccines and continued development of an effective Staphylococcus A vaccine.

1. Finelli L, Fiore A, Dhara R, et al. Influenza-associated pediatric mortality in the United States: increase of *Staphylococcus aureus* coinfection. *Pediatrics*. 2008;122(4):805-811.

Single Dose of Avian Influenza Vaccine Generates Immune Response in Individuals Primed With Antigenic Variant

The threat of avian influenza viruses of the H5N1 subtype has precipitated planning for the control of a potential pandemic. To that end, considerable effort is being made toward the development of effective vaccines for H5N1. This effort has been impeded by the observation that 2 doses of inactivated vaccine are necessary to yield serum antibody responses. Prevacination could possibly occur in advance of a pandemic; but because the H5 viruses in birds have evolved at least 3 genetically distinct

clades, it is important to investigate whether an antibody booster effect can occur when revaccination is with a single dose of a variant of the initial vaccination clade. It is also important to determine the breadth of the antibody responses to other H5N1 clades.

Goji and colleagues enrolled 37 of the 117 subjects who were previously vaccinated (in 1998) with 2 doses of baculovirus-expressed recombinant H5 (rH5) hemagglutinin of the A/Hong Kong/156/1997 (clade 0) vaccine. In

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Immune Responses (Continued)

the present study, the subjects received a single intramuscular dose of 90 µg of egg-derived, subvirion A/Vietnam/1203/2004 (clade 1) vaccine in 2006. Serum samples for assessment of hemagglutination-inhibition (HI) and microneutralization (MN) responses were obtained before vaccination and on Days 28 and 56 post-vaccination. Antibody responses were compared with those measured after one or two 90-µg doses of the subvirion A/Vietnam/1203/2004 (clade 1) vaccine in H5-naïve subjects from a previous study. The breadth of the antibody response was compared to H5N1 viruses in clade 0 (A/Hong Kong/156/1997), clade 1 (A/Vietnam/1203/2004), and clade 2 (A/Indonesia/05/2005).

On Day 28 after a single 90-µg dose, the geometric mean titer (GMT) of neutralizing antibody in primed subjects was 94 (95% confidence interval [CI], 60-147; $P < 0.001$), with 76% having a "protective" antibody response). Conversely, on Day 28 after the second dose (Day 56 of outcome measurement), H5-naïve subjects who received two 90-µg doses had a GMT of

23 (95% CI, 18-29), with 41% responding with protective levels of neutralizing antibodies. Subjects who were primed with a clade 0 virus and boosted with a clade 1 virus had significantly higher antibody response to the clade 2 virus compared with H5-naïve subjects who received 2 doses of the clade 1 virus. Importantly, vaccination of primed subjects was not associated with increased local or systemic reactivity compared with H5-naïve subjects receiving 1 or 2 dose of the subvirion vaccine.

The authors suggest that if priming can result in enhanced antibody response to a single vaccine dose, then pre-pandemic vaccination programs could be considered, especially in people who are first responders, healthcare workers and the military.

Goji NA, Nolan C, Hill H, et al. Immune responses of healthy subjects to a single dose of intramuscular inactivated influenza A/Vietnam/1203/2004(H5N1) vaccine after priming with an antigenic variant. *J Infect Dis.* 2008;198(5):635-641.

Clinical Insights® in Pediatric Respiratory Care Post-Test

- In the study by Morens et al, what did high-quality postmortem lung cultures indicate?
 - The presence of ≥ 1 bacterium in 92.7% of samples
 - Minimal histologic evidence of severe acute bacterial pneumonia
 - Severe, virus-induced tissue damage in most samples
 - A high incidence of nonpneumopathogenic bacteria
- According to Goji et al, which of the following statements is accurate regarding priming for avian influenza with an antigenically variant strain?
 - Pre-vaccination offers no priming advantage when an avian influenza pandemic is of an antigenic variant
 - Pre-vaccination with an antigenic variant offers some priming effect, but the geometric mean titer is higher for H5-naïve individuals who receive dual vaccination of the pandemic strain
 - Priming can result in immune responses to a single dose of an antigenically variant H5N1 influenza virus strain significant enough to be useful in pandemic control
 - The study findings are inconsistent with previous reports that a third dose of H5 vaccine can result in significant increases in antibody level for both the H5N1 and H5N3 vaccines

ANSWERS

Question 1 answer: a. In the study by Morens et al, high-quality postmortem lung cultures indicated the presence of ≥ 1 bacterium in 92.7% of samples.
Question 2 answer: c. According to Goji et al, priming can result in immune responses to a single dose of an antigenically variant H5N1 influenza virus, which may be useful in pandemic control.

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