Unveiling the Burden of Influenza-Associated Pneumococcal Pneumonia

Carlos G. Grijalva and Marie R. Griffin

Department of Preventive Medicine, Vanderbilt University, Nashville, Tennessee

(See the article by Weinberger et al, on pages 458-65.)

In the United States alone, seasonal (interpandemic) influenza is responsible for an average of 226 000 hospitalizations and >23 000 deaths per year [1, 2]. Although all age groups are susceptible to influenza virus infections, children experience the highest disease incidence, whereas older adults suffer the most serious disease-related complications and mortality. Many of these events are secondary bacterial pneumonias, most of which are thought to be caused by *Streptococcus pneumoniae* (the pneumococcus). Although several observations have suggested that influenza plays an important role in the pneumococcal pneumonia incidence, its contribution has been difficult to appreciate. In this issue of the *Journal*, Weinberger and colleagues present an elegant assessment that helps to clarify the contribution of influenza virus infections to pneumococcal pneumonia hospitalizations during the 2009 influenza pandemic [3].

Several lines of evidence indirectly support an interaction between influenza virus and the pneumococcus: First, pneumococcal nasopharyngeal acquisition patterns mirror the seasonal patterns of influenza outbreaks [4]. Second, increases in pneumococcal pneumonias during previous influenza pandemics have been documented [5, 6]. Third, concurrent influenza infections and pneumococcal pneumonias have been described [7, 8], and prevention of these pneumonias has been demonstrated in an efficacy trial of a 9-valent pneumococcal conjugate vaccine in South African children. In that randomized study, vaccination with pneumococcal conjugate vaccine reduced the incidence of influenza-associated pneumonia (ie, pneumococcal pneumonia with concurrent influenza infection) by 45% compared with controls [9]. This decline, however, was seen only in human immunodeficiency virus–infected children, and significant reductions were also observed for concurrent infections with parainfluenza viruses and human metapneumovirus [9, 10]. Last, mouse and squirrel monkey models suggest that the experimental infection with pneumococcus in animals previously infected with influenza results in severe disease and death [11–14]. Whether factors common to both pathogens (eg, neuraminidase) [12, 13, 15] or other immunological host factors (eg, interferon γ) [16] mediate this interaction is unclear. More recently, studies in mouse and ferret models suggested that influenza infection also facilitates the transmission of the pneumococcus [17, 18].

Direct quantification of the burden of influenza is challenging. Influenza diagnosis requires laboratory confirmation, but testing is not routinely conducted. Furthermore, available rapid diagnostic tests have important limitations, and molecular diagnostic techniques are not widely available for routine use. Thus, the burden of influenza is usually estimated through labor-intensive active prospective surveillance or, alternatively, by using statistical modeling. Although different strategies for influenza modeling exist, the underlying principle is usually the same: During periods of influenza activity, the observed or predicted disease incidence is compared with a baseline estimated from periods when influenza was not circulating, and the difference between these values represents the excess of disease attributable to influenza. These strategies have been widely used to estimate both excess morbidity and mortality associated with influenza [1, 2]. Nevertheless, most of these comparisons have been restricted to seasonal (interpandemic) periods, where influenza circulated predominantly during winter months. An important difficulty these ecologic estimations often face is that other winter-related factors, including the concurrent activity of other noninfluenza respiratory pathogens (eg, respiratory syncytial virus or human metapneumovirus) during influenza seasons could also be associated with significant disease and death. When complete information on these factors

Received and accepted 14 October 2011; electronically published 7 December 2011.

Correspondence: Carlos G. Grijalva, MD, MPH, Department of Preventive Medicine, Vanderbilt University School of Medicine, 1500 21st Ave, Suite 2600, The Village at Vanderbilt, Nashville, TN 37232-2637 (carlos.grijalva@vanderbilt.edu).

The Journal of Infectious Diseases 2012;205:355–7

DOI: 10.1093/infdis/jir753

and the activity of these viruses is available, it is possible to isolate their contributions statistically, but otherwise disentangling the direct contribution of influenza is complicated.

During the 2009 influenza pandemic, influenza circulated before the winter months, during a period when many other respiratory viruses were not circulating, and other typical winter-related environmental factors (eg, low temperature or changes in daylight hours) [19] and social factors (eg, winter holidays) [20] were not present; thus, their potential influence on the evaluation of the influenza–pneumococcus interaction was minimized. Weinberger and colleagues performed a comprehensive ecologic assessment, using hospital discharge databases and adapting modeling strategies for estimation of influenza burden to calculate the excess of pneumococcal pneumonia hospitalizations during the pandemic year of 2009. Their study demonstrated that the incidence of pneumococcal pneumonia hospitalizations increased above an estimated baseline with increasing influenza activity during the pandemic year. Importantly, they also conducted a number of secondary analyses that lent further support to their main findings. In an age-stratified analysis, significant increases in pneumococcal pneumonia were observed preferentially among age groups that were heavily affected by the 2009 influenza pandemic (ie, the greatest relative increases were observed among participants aged 5–19 years, but no significant increases were observed among seniors). The analysis included additional evaluations of the timing of influenza activity across different states. In those states with earlier influenza waves, earlier increases in pneumococcal pneumonia hospitalizations were observed. Furthermore, *Escherichia coli* septicemia hospitalization was evaluated as a control condition. There was no systematic increase in that condition during the pandemic period, highlighting the specificity of the interaction and showing that the increases in pneumococcal pneumonia were not part of a general increase in hospitalizations.

Overall, these data strongly support the previously suspected synergism between influenza virus and the pneumococcus. However, important questions remain. Is this synergism universal for all influenza viruses and all pneumococcal serotypes? Were particular types of influenza or pneumococcal serotypes responsible for the observed phenomenon? Some animal model studies suggest that the lethal synergism between influenza and pneumococcus may not be a generalized phenomenon but that the synergism may be pneumococcal serotype specific. Similar observations have been derived from recent animal transmission models [18]. This information should be considered when interpreting the data presented by Weinberger et al. In the United States, routine vaccination with a 7-valent pneumococcal conjugate vaccine started in 2000 and substantial reductions in invasive pneumococcal disease and pneumococcal pneumonia have been documented [21, 22]. More important, the circulation of vaccine serotypes have rapidly decreased after vaccine introduction and this decrease has been responsible for the indirect protection observed after implementation of the pneumococcal conjugate vaccination program [21, 23]. Therefore, the increases in pneumococcal pneumonia observed during the 2009 pandemic year likely represent disease caused by nonvaccine serotypes. Whether the clinical severity of pneumonia caused by nonvaccine serotypes differs from that of pneumonia caused by vaccine serotypes remains unclear.

Previous studies have also documented that influenza can interact with other nonpneumococcal bacteria. Reports from previous pandemics identified other *Streptococcus* species, *Staphylococcus aureus,* and *Haemophilus influenzae* associated with influenza-related pneumonia [24, 25]. Determining the etiology of pneumonia, however, is very difficult. No true gold standard diagnostic test exists, available tests are not sensitive or not specific enough, and prior antibiotic use further complicates attempts to assign etiology [26, 27]. In their study, Weinberger and colleagues used coded discharge diagnoses to identify pneumococcal pneumonia. These discharge diagnosis codes likely had high specificity [28], and similar findings were observed when a secondary analysis used coded pneumococcal septicemia as the outcome. These findings are largely consistent with those of a similar study that focused on prospectively identified invasive pneumococcal diseases as the main outcome [29]. Nevertheless, the low sensitivity of available diagnostic tests likely resulted in an underestimation of the true burden of pneumococcal pneumonia [30].

From a public health perspective, influenza and the pneumococcus are arguably the most important respiratory pathogens. To some extent, they appear to operate synergistically in causing disease and death. But probably the most important characteristic these pathogens share is that effective vaccines against both pathogens are available, and, thus, much of the burden of disease associated with these pathogens is vaccine preventable. Routine vaccination of infants with pneumococcal conjugate vaccines has attained very high coverage and has substantially modified the epidemiology of pneumococcal diseases in both vaccinated and unvaccinated individuals. However, the use of seasonal influenza vaccines remains suboptimal despite the wide availability of influenza vaccines and recommendations for annual use in most of the US population [31]. Because influenza infections facilitate the occurrence of many pneumococcal pneumonias, efforts to increase influenza vaccine uptake could effectively prevent related morbidity and delay mortality.

Notes

Financial support. This work was supported by the Thrasher Research Fund (Award

No. 02832-9) and the Centers for Disease Control and Prevention (11-IPA1110211).

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Thompson WW, Weintraub E, Dhankhar P, et al. Estimates of US influenza-associated deaths made using four different methods. Influenza Other Respi Viruses **2009**; 3:37–49.
2. Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the United States. JAMA **2004**; 292:1333–40.
3. Weinberger D, Simonsen L, Jordan R, et al. Impact of the 2009 Influenza Pandemic on Pneumococcal Pneumonia Hospitalizations in the United States. J Infect Dis **2011**; 205:458–65.
4. Gray BM, Converse GM 3rd, Dillon HC Jr. Epidemiologic studies of *Streptococcus pneumoniae* in infants: acquisition, carriage, and infection during the first 24 months of life. J Infect Dis **1980**; 142:923–33.
5. Brundage JF. Interactions between influenza and bacterial respiratory pathogens: implications for pandemic preparedness. Lancet Infect Dis **2006**; 6:303–12.
6. Centers for Disease Control and Prevention (CDC). Deaths related to 2009 pandemic influenza A (H1N1) among American Indian/Alaska Natives–12 states, 2009. MMWR Morb Mortal Wkly Rep **2009**; 58: 1341–4.
7. Michelow IC, Olsen K, Lozano J, et al. Epidemiology and clinical characteristics of community-acquired pneumonia in hospitalized children. Pediatrics **2004**; 113:701–7.
8. Juvén T, Mertsola J, Waris M, et al. Etiology of community-acquired pneumonia in 254 hospitalized children. Pediatr Infect Dis J **2000**; 19:293–8.
9. Madhi SA, Klugman KP; Vaccine Trialist Group. A role for *Streptococcus pneumoniae* in virus-associated pneumonia. Nat Med **2004**; 10:811–3.
10. Madhi SA, Ludewick H, Kuwanda L, et al. Pneumococcal coinfection with human metapneumovirus. J Infect Dis **2006**; 193: 1236–43.
11. Berendt RF, Long GG, Walker JS. Influenza alone and in sequence with pneumonia due to *Streptococcus pneumoniae* in the squirrel monkey. J Infect Dis **1975**; 132:689–93.
12. Peltola VT, McCullers JA. Respiratory viruses predisposing to bacterial infections: role of neuraminidase. Pediatr Infect Dis J **2004**; 23:S87–97.
13. McCullers JA. Insights into the interaction between influenza virus and pneumococcus. Clin Microbiol Rev **2006**; 19:571–82.
14. Gerone PJ, Ward TG, Chappell WA. Combined infections in mice with influenza virus and *Diplococcus pneumoniae*. Am J Hyg **1957**; 66:331–41.
15. McCullers JA, Rehg JE. Lethal synergism between influenza virus and *Streptococcus pneumoniae*: characterization of a mouse model and the role of platelet-activating factor receptor. J Infect Dis **2002**; 186:341–50.
16. Sun K, Metzger DW. Inhibition of pulmonary antibacterial defense by interferon-gamma during recovery from influenza infection. Nat Med **2008**; 14:558–64.
17. Diavatopoulos DA, Short KR, Price JT, et al. Influenza A virus facilitates *Streptococcus pneumoniae* transmission and disease. FASEB J **2010**; 24:1789–98.
18. McCullers JA, McAuley JL, Browall S, Iverson AR, Boyd KL, Henriques Normark B. Influenza enhances susceptibility to natural acquisition of and disease due to *Streptococcus pneumoniae* in ferrets. J Infect Dis **2010**; 202:1287–95.
19. Talbot TR, Poehling KA, Hartert TV, et al. Seasonality of invasive pneumococcal disease: temporal relation to documented influenza and respiratory syncytial viral circulation. Am J Med **2005**; 118:285–91.
20. Walter ND, Taylor TH Jr, Dowell SF, Mathis S, Moore MR; Active Bacterial Core Surveillance System Team. Holiday spikes in pneumococcal disease among older adults. N Engl J Med **2009**; 361:2584–5.
21. Pilishvili T, Lexau C, Farley MM, et al; Active Bacterial Core Surveillance/Emerging Infections Program Network. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. J Infect Dis **2010**; 201:32–41.
22. Grijalva CG, Nuorti JP, Arbogast PG, Martin SW, Edwards KM, Griffin MR. Decline in pneumonia admissions after routine childhood immunisation with pneumococcal conjugate vaccine in the USA: a time-series analysis. Lancet **2007**; 369:1179–86.
23. Huang SS, Hinrichsen VL, Stevenson AE, et al. Continued impact of pneumococcal conjugate vaccine on carriage in young children. Pediatrics **2009**; 124:e1–11.
24. Brundage JF, Shanks GD. Deaths from bacterial pneumonia during 1918–19 influenza pandemic. Emerg Infect Dis **2008**; 14:1193–9.
25. Chien YW, Klugman KP, Morens DM. Bacterial pathogens and death during the 1918 influenza pandemic. N Engl J Med **2009**; 361:2582–3.
26. Klugman KP, Madhi SA, Albrich WC. Novel approaches to the identification of *Streptococcus pneumoniae* as the cause of community-acquired pneumonia. Clin Infect Dis **2008**; 47:S202–6.
27. Bartlett JG. Diagnostic tests for agents of community-acquired pneumonia. Clin Infect Dis **2011**; 52:S296–304.
28. Guevara RE, Butler JC, Marston BJ, Plouffe JF, File TM Jr, Breiman RF. Accuracy of ICD-9-CM codes in detecting community-acquired pneumococcal pneumonia for incidence and vaccine efficacy studies. Am J Epidemiol **1999**; 149:282–9.
29. Walter ND, Taylor TH, Shay DK, et al; Active Bacterial Core Surveillance Team. Influenza circulation and the burden of invasive pneumococcal pneumonia during a non-pandemic period in the United States. Clin Infect Dis **2010**; 50:175–83.
30. Obaro SK, Madhi SA. Bacterial pneumonia vaccines and childhood pneumonia: are we winning, refining, or redefining? Lancet Infect Dis **2006**; 6:150–61.
31. Setse RW, Euler GL, Gonzalez-Feliciano AG, et al; Centers for Disease Control and Prevention. Influenza vaccination coverage—United States, 2000–2010. MMWR Surveill Summ **2011**; 60:38–41.