Pandemic Influenza and Pneumonia Due to Legionella pneumophila: A Frequently Underestimated Coinfection

To the Editor—Secondary bacterial pneumonia is recognized as one of the most common causes of death in influenza cases. Coinfection has been found in ~30% of all influenza cases in persons with seasonal influenza, and the pathogens most often involved are Streptococcus pneumoniae, Staphylococcus aureus, and Haemophilus influenzae [1, 2]. However, the role of bacterial coinfection in complicating pandemic flu is not well described, because of the scarcity of data.

From July 2009 through February 2010 in Italy, 2500 confirmed cases of pandemic influenza and 4.5 million cases of influenza-like illnesses were reported to the sentinel surveillance system. Of the confirmed cases of pandemic influenza, 1278 (~50%) were hospitalized. Of the patients hospitalized, 271 (21%) presented with pneumonia, which was attributed to bacterial coinfection in 33 cases.

Of the 33 cases with pneumonia due to bacterial coinfection, 6 (18%) were caused by Legionella pneumophila serogroup 1, and both the national legionellosis and the Italian mandatory 2009 A(H1N1) virus surveillance systems [3] were notified. The 2009 A(H1N1) virus reporting system is Web-based and was established in July 2009, whereas the national legionellosis surveillance system was established in 1983. Both systems include information about symptoms and risk factors, such as chronic illness, previous hospitalization, and travel.

The 6 legionellosis cases (5 confirmed and 1 presumptive) were reported from the end of August to the beginning of November. These patients were aged 25–70 years, with a median age of 53 years and a male-to-female ratio of 5:1. All 6 patients were hospitalized with a clinical picture of pneumonia, and 2 required intensive care unit admission. In the first case, reported in August, the patient developed symptoms after returning from a 1-week travel abroad. All case patients were tested for 2009 A(H1N1) virus (by reverse-transcription polymerase chain reaction test) and for Legionella (by urinary antigen test). Five patients had positive results for both assays, whereas 1 had positive results for 2009 A(H1N1) virus and Legionella serology (single titer) and therefore was classified as a presumptive case. Only 2 patients reported an underlying condition (diabetes), and all 6 patients fully recovered.

With prompt identification of the bacterial etiology of pneumonia, appropriate treatment can be started with both antibacterial therapy and antiviral medications. Therefore, the length of hospital stay and the mortality of both pandemic and seasonal influenza can be reduced.

The emergence of the new virus strain 2009 A(H1N1) has been a unique opportunity to investigate the etiology of bacterial coinfection during a pandemic. The cases described in this report do not derive from a systematic ascertainment of all pneumonia cases associated with pandemic influenza, and the number might be underestimated, because the decision to perform etiological diagnosis rests with the individual physician. However, 6 legionellosis cases in a total of 33 bacterial coinfections may indicate that Legionella is involved more often than expected. In addition, our findings highlight that cross-linkage of different surveillance systems can be a useful method to quantify and to describe pneumonia cases related to influenza.

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References

Long-Term Outcomes of HIV-Infected Patients with <95% Rates of Adherence to Nonnucleoside Reverse-Transcriptase Inhibitors

To the Editor—Persons with human immunodeficiency virus (HIV) infection have a greater likelihood of HIV suppression with the use of nonnucleoside reverse-transcriptase inhibitor (NNRTI)–based regimens than with the use of protease inhibitor–based regimens if there is <95% adherence to the antiretroviral regimen [1–3]. Plausible reasons for this consistent finding in short-term clinical studies include inherent antiretroviral potencies of NNRTI drugs, long half-life of plasma drugs, tolerability, and convenient once- or twice-daily dosing schedules [1–6]. To further assess sustained HIV suppression among persons with <95% adherence to NNRTI regimens, we prospectively observed a Thai cohort for 3 years.

The study population comprised 199 patients who were prescribed a regimen of fixed-dose, twice-daily stavudine, lamatrns...
Treatment success was defined as viral load suppression to <50 copies/mL at months 24, 30, and 36. Subsequently, participants were categorized into 3 adherence strata: ≥95%, 75%–94%, and <75% adherence according to both scheduled visits and pill count ratios.

Of the 199 participants, 64 (32%) were men; the median age was 37 years (range, 15–61 years), the baseline median CD4 count was 84 cells/μL (range, 0–200 cells/μL), and 163 participants (82%) had prior opportunistic infections; all consented to study participation. At 6-month follow-up, 195 participants (98%) had viral suppression of <50 copies/mL; 4 patients (2%) had interrupted treatment as a result of a severe rash attributed to the stavudine, lamivudine, and nevirapine regimen and were excluded from subsequent time interval assessments. All 195 patients whose treatment was successful had ≥75% visit compliance, and 192 patients (96%) had ≥75% adherence, as measured according to scheduled and unannounced pill counts (Table 1). None of the 26 patients who had initial 75%–94% adherence to the stavudine, lamivudine, and nevirapine regimen at month 6 subsequently achieved 95% adherence. Six (3%) of 195 patients with initial ≥95% adherence during the first 6 months were subsequently less adherent (<95%) to the drug regimen, according to both scheduled visit count and pill count measurements at months 24, 30, and 36; these 6 patients were censored from further time interval analyses.

The major finding of this 3-year study was that among patients with short-term HIV suppression, those with initial 75%–94% adherence were less likely to achieve durable HIV suppression, compared with patients with initial ≥95% adherence. Notably, the relatively consistent compliance with scheduled medical visits in this population may reflect the unmeasured yet relevant role of the HIV care team in the effective delivery of antiretroviral therapy. During the 3-year study period, the total rate of staff turnover was 10% among physicians, nurses, pharmacists, and ancillary staff, and the association of adherence

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**Table 1. Assessment of Adherence Measures among Patients with Human Immunodeficiency Virus (HIV) Infection Who Achieved Durable Suppression of the HIV Load to <50 copies/mL with Use of Generic, Fixed-Dose Stavudine, Lamivudine, and Nevirapine during a 3-Year Period**

<table>
<thead>
<tr>
<th>Scheduled medical visits and pill counts (n = 199)</th>
<th>Month 6 (n = 195)</th>
<th>Month 12 (n = 195)</th>
<th>Month 18 (n = 195)</th>
<th>Month 24 (n = 193)</th>
<th>Month 30 (n = 191)</th>
<th>Month 36 (n = 189)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit complianceb</td>
<td>95%–100% (n = 172 [86%])</td>
<td>169/172 (98)</td>
<td>169/172 (98)</td>
<td>169/172 (98)</td>
<td>167/172 (97)</td>
<td>165/172 (96)</td>
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<tr>
<td></td>
<td>75%–94% (n = 26 [13%])</td>
<td>26/26 (100)</td>
<td>26/26 (100)</td>
<td>26/26 (100)</td>
<td>20/26 (77)c</td>
<td>18/26 (69)c</td>
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<tr>
<td></td>
<td>&lt;75% (n = 1 [1%])</td>
<td>1/1 (100)</td>
<td>1/1 (100)</td>
<td>1/1 (100)</td>
<td>0/1 (0)</td>
<td>0/1 (0)</td>
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<tr>
<td>Combined pill countsd</td>
<td>95%–100% (n = 155 [77%])</td>
<td>155/155 (100)</td>
<td>155/155 (100)</td>
<td>155/155 (100)</td>
<td>153/155 (99)</td>
<td>151/155 (97)</td>
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<tr>
<td></td>
<td>75%–94% (n = 37 [18%])</td>
<td>37/37 (100)</td>
<td>37/37 (100)</td>
<td>37/37 (100)</td>
<td>29/37 (78)c</td>
<td>27/37 (73)c</td>
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<tr>
<td></td>
<td>&lt;75% (n = 7 [5%])</td>
<td>3/7 (43)c</td>
<td>0/7 (0)</td>
<td>0/7 (0)</td>
<td>0/7 (0)</td>
<td>0/7 (0)</td>
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<tr>
<td>NOTE. Data are proportion (%) of patients. Four patients interrupted treatment as a result of rash after initiation of stavudine, lamivudine, and nevirapine regimen, and 6 patients with initial &gt;95% adherence during the first 6 months were subsequently less adherent (&lt;95%) to the drug regimen according to both scheduled visit count and pill count measurements at months 24, 30, and 36; these 10 patients were censored from further time interval analyses. Categorical variables were compared using the Pearson χ² or Fisher exact test as appropriate.</td>
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<td>a Calculated using the number of patients who achieved viral suppression of less than 50 copies/mL in each adherence stratum divided by the total number of patients in the same adherence stratum.</td>
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<td>b Calculated as no. of patients who achieved viral suppression of less than 50 copies/mL in each adherence stratum divided by the total number of patients who had initial 95% adherence during the first 6 months were subsequently less adherent (&lt;95%) to the drug regimen.</td>
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<td>c Subsequently, participants were censored from further time interval analyses according to both scheduled visit count and pill count measurements at months 24, 30, and 36.</td>
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<td>d Calculated as no. of pills taken divided by prescribed pills determined at routine medical visits and unannounced home visits.</td>
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with treatment success was a prominent theme of continuing education for staff. Combination fixed-dose, NNRTI-based regimens have been widely used in low- and middle-income countries, and switching to second-line regimens is now more frequently reported [7]. We emphasize the potential benefits of promoting high rates of adherence to antiretroviral medication regimens to optimize the long-term success of antiretroviral treatment, as well as minimizing treatment fatigue and the need to switch regimens because of treatment failure.

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Household Data from the Ugandan Hepatitis E Virus Outbreak Indicate the Dominance of Community Infection

To the Editor—Teshale et al [1] assessed the potential for person-to-person transmission of the hepatitis E virus (HEV) during a large outbreak in Uganda. The following 2 findings were suggestive of person-to-person transmission: (1) the long-lasting outbreak despite the absence of a common source, and (2) no virus was isolated from environmental sources. However, I have serious concerns regarding the analysis of the household data.

There has been extensive discussion about serial intervals (the time interval between the onset of symptoms in 2 cases within a household) in infectious disease epidemiology [2–4]. Figure 1A shows the serial intervals within households resulting from 3 distinct epidemiological mechanisms: (1) independent infection (in which both case patients are infected independently within the community), (2) coprimary cases (in which 2 case patients are infected within the community at the same time), and (3) household transmission (in which one case patient is infected in the community and the other is infected by the primary case patient within the household). Ideally, this argument applies to households with only 2 case patients [2]. To prove person-to-person transmission from the household data, one must identify a second peak in the observed bimodal distribution of the serial interval attributable to household transmission (mechanism 3). The second peak should correspond to the sum of the mean incubation period and the mean time from the onset of symptoms in the primary case to secondary transmission [5], 3–9 weeks in the case of HEV.

Figure 2 in the article by Teshale et al [1] implicates the presence of a second peak in the observed serial intervals. How-

Figure 1. Time intervals between symptom onset in 2 cases within households. A, There are 3 underlying epidemiological mechanisms for the observed serial intervals. The bold line shows the situation when both case patients were infected independently within the community. The dashed line represents when both were infected at an identical time in the community. The unbroken line represents secondary transmission within households. The dominance of household transmission is indicated if a second peak (expected at ∼10 weeks in this panel) of the bimodal mixture distribution is apparent. B, The serial intervals observed during the hepatitis E virus outbreak in Uganda in 2007–2008. The media by Teshale et al [1]. Figure 2 shows the number of cases observed over different periods of time, whereas this Figure shows a modified version in which the vertical axis denotes the average number of cases per week. Because it is not technically feasible to identify coprimary cases manually, 1280 household cases in which the second case was observed within 2 weeks of the first were grouped in 1 category. For the interval denoted as >20 weeks, the length of the interval was assumed to be 20 weeks, because the outbreak continued for >40 weeks.