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Short Article

Concurrent influenza virus infection and tuberculosis in patients hospitalized with respiratory illness in Thailand

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Thailand, where influenza viruses circulate year-round, is one of 22 WHO-designated high-burden countries for tuberculosis (TB). Surveillance for hospitalized respiratory illness between 2003 and 2011 revealed 23 (<1% of 7180 tested) with concurrent influenza and TB. Only two persons were previously known to have TB suggesting that acute respiratory illness may bring patients to medical attention and lead to TB diagnosis. Influenza/TB was not associated with higher disease severity or mortality.

Keywords Influenza, pneumonia, respiratory diseases, surveillance, Thailand, tuberculosis.

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Background

Influenza viruses interact with some bacteria causing more severe disease among patients with concurrent infections.[1] Little is known about concurrent infection with influenza viruses and *Mycobacterium tuberculosis* (MTB) active disease. Mortality data from the 1918 influenza pandemic demonstrated significant overlap between the populations most affected by influenza and tuberculosis (TB). Preexisting TB may have predisposed to death from influenza, or alternatively influenza mortality was simply highest among the same demographic groups affected by TB.[2]

There are few data about influenza virus and MTB interactions at the patient level. Two case reports documented concurrent influenza virus infection and TB in immunosuppressed persons; one died.[3,4] Chronic respiratory disease is a known risk factor for severe disease with seasonal influenza, as demonstrated in Thailand,[5] and data from the 2009 influenza A (H1N1) pandemic suggest that TB predisposed H1N1-infected patients to a severe clinical course.[6,7]

In Thailand, influenza viruses are found in ~10% of patients hospitalized with respiratory illness.[8] Thailand is also a high TB-burden country,[9] and 12% of adults hospitalized with clinical respiratory illness who are adequately evaluated have sputum smear-positive TB.[10] Given the substantial independent burdens and lack of data on patients with concurrent disease, we aimed to describe hospitalized patients with both influenza virus infection and TB.

Methods

We retrospectively reviewed active surveillance data on patients of all ages who were hospitalized for acute lower respiratory illness (ALRI) in Sa Kaeo and Nakhon Phanom provinces between August 2003 and December 2011 and enrolled into an etiology study.[11,12] From 2003 to 2007, only patients with a chest radiograph (CXR) taken were approached for enrollment; from 2008 on, every other patient (independent of CXR) was approached. CXRs were digitized and interpreted by radiologists.[11]

Influenza virus testing was by reverse transcriptase–polymerase chain reaction (RT-PCR) on nasopharyngeal swab specimens (and by hemagglutination inhibition assay on paired serum in year one).[12] Testing for MTB was performed at clinician discretion by acid-fast bacilli (AFB) stain of patient sputum and on few occasions by culture until late 2008, when recommendations were made to test all hospitalized patients with respiratory illness aged ≥15 years for TB. At the end of 2008, all AFB-positive

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patients had sputum sent for culture and drug sensitivity testing. HIV testing was performed at the doctor's discretion until January 2005, when we actively approached patients for consent.

A TB case was defined as microbiologically confirmed TB (>1 AFB-positive sputum or sputum culture positive for MTB).[9] An influenza case was defined as a positive RT-PCR or serology test for influenza. An influenza/TB case met criteria for both during the same admission. When available, original paper surveillance forms and district TB registers were reviewed for additional clinical details.

We compared descriptive characteristics of influenza/TB cases to influenza-only cases and TB-only cases using the chi-squared test for dichotomous variables and *t*-test to compare means. All analyses were performed using SPSS (Version 18; SPSS Inc., Chicago, IL, USA). A *P*-value < 0·05 was considered significant.

Results

During August 15, 2003–December 31, 2011, surveillance detected 107 292 persons hospitalized with ALRI and 25 452 (24%) were enrolled into the etiology study. Enrolled patients were significantly more likely to be older (median age 28 versus 14 years, $P \leq 0.001$), less likely to be intubated (3·7% versus 5·8%, $P < 0.001$) and less likely to die (1·9% versus 3·3%, $P < 0.001$). Almost all, 25 410, were tested for influenza viruses but only 7180 (28%) were also tested for TB. Persons tested for TB were significantly older (median age 61 versus 5 years, $P < 0.001$), more likely to be intubated (7·0% versus 2·4%, $P < 0.001$) and more likely to die (3·9% versus 1·1%, $P < 0.001$). TB testing was performed in 1% of children <15 years; testing for persons >15 increased significantly from 39% in 2003 to 2007 to 60% in 2008–2011 ($P < 0.01$) (see Figure S1). Twenty-three persons (<1%) (2 aged <15 years and 21 aged >15 years) met the case definition for influenza and TB (influenza/TB, Table 1).

Excluding the partial year of 2003, there was an average of 2·8 influenza/TB cases per year (2/year 2004–2007 versus 3·5/year 2008–2011). Pulmonary TB was noted as the admission diagnosis for 10 (53%) patients and as the discharge diagnosis for 18 (78%). Review of records revealed that two influenza/TB patients had been diagnosed with TB prior to admission. Nineteen (83%) influenza/TB patients were discharged, three were transferred to other hospitals, one self-discharged, and none died during hospitalization.

The median age of the influenza/TB cases was 44 years. Influenza A virus was identified in 15 (65%), influenza B virus in seven (30%), and both viruses in one (4%). Twenty-two of 23 were sputum smear positive; five of six were sputum culture positive. Fifteen (83%) of 18 CXRs reviewed had pneumonia; six (33%) of 18 had a cavity or abscess.

Of the 7180 patients tested for both pathogens, 23 were influenza/TB cases, 604 influenza-only cases, and 646 TB-only cases. Presenting signs and symptoms were similar between the influenza/TB cases and the influenza-only and TB-only cases, with most patients reporting cough, fever, and sputum production (Table S1). Hemoptysis was uncommon. Influenza/TB cases were more likely than influenza-only cases (13% versus 2·6%, $P = 0.03$) but as likely as TB-only cases (13% versus 10%, $P = 0.72$) to be HIV positive. Influenza/TB cases were more likely than influenza-only cases (83% versus 43%, $P \leq 0.01$) and less likely than TB-only cases (83% versus 96%, $P = 0.03$) to have CXR-confirmed pneumonia. The median length of hospital stay was similar (4 days for influenza, five for influenza/TB, and six for TB). Complications during hospitalization were uncommon and 0 influenza/TB, 17 (2·8%) influenza-only and 30 (4·6%) TB-only cases died.

Fifteen patients had documented influenza virus infection and a discharge diagnosis of pulmonary TB, but did not meet criteria for a laboratory-confirmed TB case. Their median age was 64 years (range, 21–78 years) and median length of hospital stay was 8 days (range, 3–21 days). Nine (56%) had AFB sputum smears sent for testing (all negative), none had TB sputum cultures performed, and none were HIV positive; one died.

Discussion

We describe a series of patients with concurrent influenza virus infection and pulmonary TB. Concurrent disease appears to be relatively uncommon (<1%) among hospitalized patients with clinical respiratory illness in rural Thailand, a group in whom TB and influenza infections are each relatively common. Our data suggest that only two of the influenza/TB patients had their TB disease diagnosed before admission, whereas up to 21 patients were first diagnosed with TB around the time of their hospital admission. It is possible that acute influenza infection led patients with undiagnosed TB disease to seek medical treatment or made the symptoms severe enough to require hospital admission and prompt testing.

Patients with both influenza and TB were more likely to be HIV positive than patients with influenza alone and less likely to have radiologically confirmed pneumonia than patients with TB alone. Although the number of influenza/TB cases was small, thus limiting our ability to detect significant differences, our analyses did not reveal evidence that concurrence increased risk of severe outcomes or mortality when compared to patients hospitalized with influenza infection only or TB only. However, severe and fatal cases were less likely to be in our analysis.

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Table 1. Characteristics of 23 hospitalized patients with influenza virus infection and microbiologically confirmed TB

No.	Admit date (month/year)	Age (years)	Sex	Admission diagnosis	Discharge diagnosis	HIV status	Smoker	CXR findings	TB status	Influenza virus	Length of stay (days)	Disposition
1	11/03	49	M	Pneumonia	Pulmonary TB	Unknown	Unknown	Pneumonia, alveolar	AFB+ Cx n/d	B/Hong Kong	2	Discharge
2	8/04	37	F	Pneumonia	Pulmonary TB	Unknown	Unknown	Pneumonia, alveolar	AFB+ Cx n/d	A/Wyoming B/Sichuan & Brisbane	24	Discharge
3	9/04	42	M	PTB, suspected	Pulmonary TB	Negative	Unknown	Pneumonia, alveolar, cavity	AFB+ Cx n/d	B/Brisbane	4	Discharge
4	2/05	12	F	Bronchitis	Pulmonary TB	Unknown	Unknown	Not pneumonia	AFB+ Cx n/d	B	3	Discharge
5	6/05	85	M	PTB, previously diagnosed	Pulmonary TB	Unknown	Unknown	Pneumonia, alveolar	AFB+ Cx n/d	A (not subtyped)	6	Discharge
6	8/05	85	M	PTB, not specified	Pulmonary TB	Negative	No	Pneumonia, interstitial	AFB+ Cx n/d	A (not subtyped)	14	Discharge
7	8/05	68	F	Asthma	Pulmonary TB	Negative	No	Pneumonia, alveolar	AFB+ Cx n/d	A (not subtyped)	7	Discharge
8	4/07	70	M	Fever of unknown origin	Pulmonary TB	Unknown	No	Pneumonia, alveolar	AFB+ Cx n/d	A (not subtyped)	5	Self discharge
9	12/07	44	F	HIV-related infectious disease	HIV-related infectious disease	Positive	No	No CXR	AFB+ Cx n/d	A (not subtyped)	12	Discharge
10	4/08	36	M	PTB, not specified	Pulmonary TB	Negative	Yes	Pneumonia, alveolar, cavity	AFB+ Cx n/d	A (not subtyped)	3	Discharge
11	5/08	61	F	PTB, not specified	Pulmonary TB	Negative	No	No CXR	AFB+ Cx n/d	B	2	Discharge
12	6/08	43	M	Bronchitis	Pulmonary TB	Negative	Yes	Pneumonia, alveolar, cavity	AFB+ Cx n/d	A (not subtyped)	3	Transfer to different hospital
13	8/08	38	M	PTB, previously diagnosed	Pulmonary TB	Negative	No	Pneumonia, alveolar, cavity	AFB+ Cx n/d	B	10	Discharge
14	10/08	55	M	PTB, suspected	HIV-related infectious disease	Positive	Unknown	Not pneumonia	AFB+ Cx no growth	B	6	Discharge
15	11/08	60	F	Pneumonia; PTB suspected	Pulmonary TB	Negative	No	No CXR	AFB+ Cx n/d	B	3	Transfer to different hospital
16	4/10	62	M	PTB, not specified	Pulmonary TB	Negative	No	Pneumonia, alveolar	AFB+ Cx +	A (H1N1)pdm09	9	Discharge
17	6/10	24	M	HIV disease	Other	Positive	Yes	Pneumonia, alveolar	AFB+ Cx n/d	A (H1N1)pdm09	2	Transfer to different hospital
18	8/10	45	M	Fever of unknown origin	Influenza	Negative	Unknown	Not pneumonia	AFB-Cx +	A (H3N2)	3	Discharge
19	9/10	56	M	PTB, not specified	Pneumonia	Negative	Yes	Pneumonia, alveolar	AFB+ Cx +	A (H3N2)	6	Discharge

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Table 1. (Continued)

No.	Admit date (month/year)	Age (years)	Sex	Admission diagnosis	Discharge diagnosis	HIV status	Smoker	CXR findings	TB status	Influenza virus	Length of stay (days)	Disposition
20	8/11	40	F	PTB, not specified	PTB, not specified	Negative	No	No CXR	AFB+ Cx +	A (H3N2)	3	Discharge
21	8/11	39	F	PTB, not specified	PTB, not specified	Negative	Unknown	Pneumonia, interstitial, cavity	AFB+ Cx +	A (H3N2)	14	Discharge
22	9/11	10	M	PTB, not specified	PTB, not specified	Negative	Unknown	Pnuemonia, alveolar, cavity	AFB+ Cx n/d	A (H3N2)	14	Discharge
23	9/11	44	M	PTB, not specified	PTB, not specified	Negative	Yes	No CXR	AFB+ Cx n/d	A (H3N2)	2	Discharge

TB, tuberculosis; PTB, pulmonary tuberculosis; HIV, human immunodeficiency virus; AFB, acid-fast bacilli; Cx, culture; n/d, not done; CXR, chest radiograph.
''PTB, previously diagnosed'' means the original surveillance forms showed pulmonary TB had been diagnosed prior to the admission. ''PTB, suspected'' means the admission diagnosis on the original surveillance form showed that the admitting clinician suspected but had not confirmed TB at the time of admission. ''PTB, not specified'' means ''pulmonary TB'' was listed as the admission diagnosis without data to suggest TB diagnosis prior to admission. Discharge means patient was discharged from the inpatient ward.

Our findings contrast with two reports from South Africa using data from the 2009 H1N1 influenza pandemic, which found TB disease in 10% of deaths among H1N1-infected patients and 19% of deaths among H1N1-infected pregnant women,[6] and in 11% of patients admitted to the ICU.[7] However, without a direct comparison with overall TB and influenza mortality or TB prevalence among non-fatal H1N1 cases during that period, it is difficult to determine whether concurrent TB and influenza increased risk of severe disease or death. Furthermore, influenza/TB case mortality may differ substantially between South Africa and Thailand because of a number of factors, including differences in access to care, and the higher HIV and TB prevalence and mortality in South Africa.[9]

Our study has some important limitations. First, most patients hospitalized with ALRI were not tested for TB, so our results may not be generalizable or comparable to other countries. Among those tested, TB is likely underdiagnosed as we relied on sputum smear microscopy which has a lower sensitivity compared to culture.[13] However, it is also possible that not all AFB positives were MTB. After routine culture began in 2008, 229/245 (93%) of AFB smear-positive cases were confirmed to be MTB, suggesting that up to two of our AFB cases might not be MTB. Our sample size for influenza/TB patients is small, which limits our ability to draw conclusions when comparing them to the larger group of influenza patients or TB patients. We did not have access to the medical charts, so we were unable to assess more thoroughly for HIV status or prior TB diagnosis and treatment. Because few children were tested for TB, our findings cannot be extrapolated to children. Lastly, because of changes in enrollment criteria and HIV and TB testing guidelines throughout the period of the surveillance, we cannot infer temporal trends in the data.

Our study describes a small population of patients with concurrent influenza and TB in Thailand and found few differences between influenza/TB patients and those with only influenza virus infection or only TB. Further study may help clarify the significance of concurrent influenza virus infection and TB on diagnosis, management, and outcomes. Our findings highlight the importance of including TB in the differential diagnosis for adults hospitalized with an acute, influenza-like respiratory illness, particularly for HIV-infected individuals and especially in high TB-burden settings. Conversely, influenza, especially during seasonal peaks, should be considered in TB patients hospitalized with respiratory symptoms and/or exacerbations.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Detailed methods.

Figure S1. Schematic of patients enrolled into pneumonia etiology study between August 15, 2003 and December 31, 2011.

Table S1. Demographic and clinical characteristics of persons hospitalized with influenza virus infection and microbiologically-confirmed tuberculosis (TB), influenza virus infection only and TB only, among those tested for both influenza and TB (n = 7180).

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