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Dealing With Threat of Drug-Resistant Tuberculosis: Background Information for Interpreting the Andrew Speaker and Related Cases

Not since the threat of a potential SARS (severe acute respiratory syndrome) pandemic (in 2003) has medical news captured as much national media attention as in the recent few weeks. Tuberculosis (TB) has been in the public eye since news broke that Andrew Speaker, a 31-year-old US citizen and attorney from Atlanta, Ga, was a passenger on international commercial airline flights while infected with a very resistant strain of TB and that he has since been placed in isolation by US health authorities.

This case has focused attention on important public health issues: the global TB epidemic and the risk of spread of infectious agents either knowingly or unknowingly via air travel.

The purpose of this editorial is to provide background information on the epidemiology of TB in the world, the problem of drug-resistant TB, the risks of acquiring infections from air travel, and the role of health authorities in minimizing risk to the public.

Scope of TB Worldwide

Among infectious diseases, TB is second only to the human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome as the greatest contributor to adult mortality, causing approximately 2 million deaths per year worldwide. The World Health Organization (WHO) estimates that one third of the world's population is infected with *Mycobacterium tuberculosis* and that 1 in 8 deaths in the world today is due to tuberculosis.[1] After the discovery and introduction of antituberculosis medications in the late 1940s, there was hope that TB would soon be eliminated. However, after decades of steady decline, the number of reported TB cases began to increase in the late 1980s and early 1990s in the United States. This resurgence was fueled by several factors: the deterioration of the TB public health infrastructure, the onset of the HIV epidemic, increases in immigration of persons from countries where TB was common, and outbreaks in congregate settings such as hospitals and correctional institutions.

Multidrug-Resistant TB

Another important factor resulting in increasing numbers of TB cases is the increase in transmission of multidrug-resistant (MDR) strains of TB (Table 1). In the early 1990s, several outbreaks of MDR-TB occurred in hospitals and correctional facilities in Florida and New York, involving more than 250 MDR-TB cases.[2,3] Most patients in these outbreaks were coinfected with HIV. The mortality rate was approximately 80%, and the interval between TB diagnosis and death was short, ranging from 4 to 16 weeks. In addition to hospitalized patients and inmates, transmission of MDR-TB to health care workers and prison guards occurred; at least 9 of these workers developed active MDR-TB, and 5 died. Globally, 400,000 new cases of MDR-TB occur each year.[4] Currently, drug-sensitive TB can be treated with first-line drugs for 6 to 9 months, and 95% of patients can be cured with these regimens. In contrast, MDR-TB requires treatment for 18 to 24 months with second-line drugs (Table 2)[5] that are inherently less effective, often poorly tolerated by patients, and much more expensive. Under optimal conditions, the cure rate is 70% to 90% but is closer to 50% in diverse clinical practice.

Extensively Drug-Resistant TB

Coincident with the increasing use of second-line drugs to treat the growing numbers of MDR-TB cases, the resistance pattern of TB continued to evolve, and TB that is resistant to both first- and second-line agents, termed *extensively drug-resistant TB* (XDR-TB), was born. In early 2005, physicians from KwaZulu-Natal in South Africa reported an outbreak of TB with an alarmingly high mortality rate.[6] Of 221 patients with MDR-TB, 53 were found to have what is now known as XDR-TB; 52 of the 53 patients died, and the median survival was only 16 days from the time the first sputum sample was collected.

Extensively drug-resistant TB is defined as TB that is resistant to isoniazid and rifampin (ie, MDR-TB) in addition to being resistant to any fluoroquinolone and at least 1 of the 3 injectable drugs: capreomycin, kanamycin, and amikacin[7] (Table 2). Recent reports suggest that XDR-TB is a global problem (Figure 1).[8] It has been identified in all regions of the world but is most frequent in the countries of the former Soviet Union and in Asia.[9,10] Estimates from the United States, the Republic of Korea, and Latvia show that 4%, 15%, and 19%, respectively, of MDR-TB isolates were XDR strains. Many developing nations lack the ability to test for drug resistance, and hence the number of cases reported thus far may represent only the tip of the iceberg.

In the United States between 1993 and 2006, a total of 49 cases of XDR-TB were identified.[9] Of these 49 patients, 17 (35%) have completed treatment, 12 (24%) have died

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TABLE 1. **Definitions of Multidrug-Resistant Tuberculosis (TB) and Extensively Drug-Resistant TB**

Mutidrug-resistant TB
TB resistant to at least rifampin and isoniazid
Extensively drug-resistant TB
TB resistant to isoniazid ***and*** rifampin ***plus*** resistant to any fluoroquinolone plus resistant to at least 1 of 3 injectable second-line drugs: amikacin, kanamycin and capreomycin

TABLE 2. **Drugs for Tuberculosis Currently Used in the United States**

First-line drugs	Second-line drugs
Isoniazid	Cycloserine
Rifampin	Ethionamide
Rifabutin	Levofloxacin
Rifapentene	Gatifloxacin
Ethambutol	Moxifloxacin
Pyrazinamide	*p*-Aminosalicylic acid
	Amikacin or kanamycin
	Streptomycin
	Capreomycin

Data from *MMWR Recomm Rep*.[5]

during treatment, and an alarming 12 patients (24%) were lost to follow-up.

Multidrug-resistant TB and XDR-TB do not seem to be more contagious than other forms of TB. However, their danger lies in the fact that few or no drugs are available to treat these forms of TB. Persons who are infected with these strains and who develop active disease often undergo months to years of treatment with toxic medications plus possible surgical treatment, and they are at high risk of dying, especially if they have any form of immunosuppression.

M tuberculosis acquires resistance primarily from incomplete or inadequate treatment courses, and the development of XDR-TB essentially points to the worldwide weaknesses in TB management. Improper use of antimicrobial therapy for drug-susceptible TB inevitably leads to drug resistance. This improper use includes administration of inappropriate treatment regimens, failure to implement directly observed therapy, and incomplete adherence to or completion of the entire treatment course.

The issues with treatment are compounded by the fact that the diagnosis of TB and detection of drug resistance can be challenging. Patients in whom the diagnosis of XDR-TB is delayed spread the infection to close contacts who then acquire primary XDR-TB. Areas of the world that have high HIV rates are especially at risk for XDR-TB outbreaks because HIV infection predicts extreme vulnerability to TB.

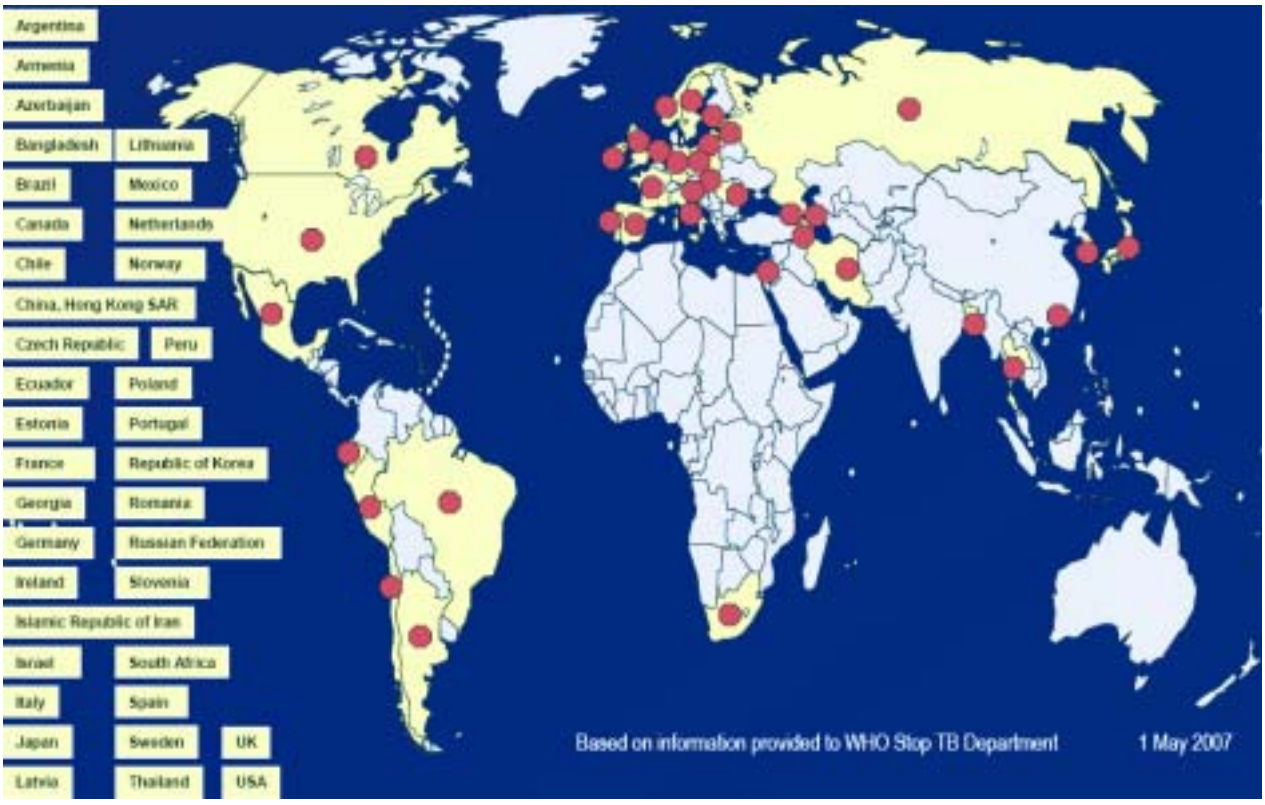

FIGURE 1. Countries with confirmed cases of extensively drug-resistant tuberculosis to date. From the World Health Organization,[8] with permission. All rights reserved.

Conventionally, TB is diagnosed by culturing the organism on liquid or solid media followed by identification of the species and then drug susceptibility testing. Since mycobacteria are slow growing, this process can take several weeks and can be technically challenging. This is highlighted in the case of Speaker, in whom the initial diagnosis of TB was made in late March. However, he was identified as having only MDR-TB on May 10, and it was not until May 22 that the extent of drug resistance was realized.[10] Recent advances in molecular biology and understanding of the molecular mechanisms of drug resistance in TB have led to newer diagnostic tools, some of which can provide information on susceptibility patterns in days.[11] A pilot study to evaluate some of these tests is currently under way in South Africa.[12,13]

Speaker was smear negative (ie, no tuberculosis bacilli were visible on microscopic examination of his sputum); hence, the risk of TB transmission from him is low but not zero. Subsequently, the Centers for Disease Control and Prevention has recommended that all his copassengers on 2 international flights be tested for TB.[14] This has caused a great deal of anxiety in the general public about the risk of infections related to air travel.

Air Travel and Infection Risk

Globally, more than 1 billion passengers travel by air annually. It is a common perception that airplanes are breeding grounds for microorganisms. Many people erroneously attribute upper respiratory tract symptoms after air travel to infections acquired on the airplane as a result of poor air quality.

In reality, from a microbiologic standpoint, the quality of air on modern commercial aircraft is carefully controlled and is much better than that in similar enclosed places on the ground.[15] Ventilation rates provide a total of 20 to 30 air exchanges per hour (the recommended rate for hospital isolation rooms for patients with TB is 6-12 exchanges per hour). Most modern aircraft have recirculation systems that recycle up to 50% of cabin air. However, this air is passed through high efficiency particulate air filters, similar to the ones used in hospitals, that remove 99.9% of particulate matter, bacteria, fungi, and viruses that are between 0.1 and 0.3 μm. The tubercle bacillus is approximately 0.5 to 1.0 μm and thus is removed by high efficiency particulate air filters.[16] Air enters and leaves the cabin at approximately the same seat row, and little front to back airflow occurs (Figure 2). This air circulation pattern means that essentially the cabin is divided into sections, and spread of airborne particles from a passenger is limited to the section in which he or she is seated. This is borne out by the fact that in reports of airborne disease transmission on aircraft, transmission has generally occurred to people close to a contagious passenger

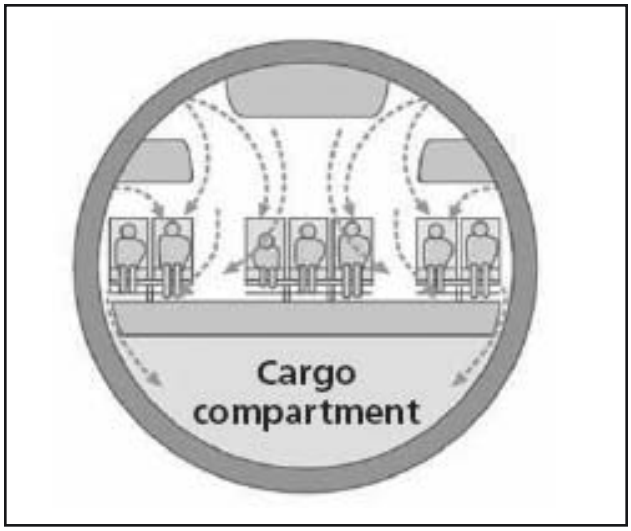

FIGURE 2. Airflow patterns in cabin of commercial aircraft. From the World Health Organization,[17] with permission. All rights reserved.

(within 2 rows) for a long time (>8 hours). Important exceptions are when flights are delayed, the aircraft is parked on the ground, and the aircraft ventilation system is not operating.[18] According to the US Department of Transportation, "if the ventilation system is not operating, passengers should not stay aboard the plane for more than 30 minutes."

Transmission of TB on Aircraft

Transmission of TB on board a commercial aircraft during long-distance flights has been reported several times,[19-22] but no case of active TB disease resulting from exposure on board has been identified subsequently. In all instances, transmission occurred to passengers seated within 2 rows of the index case. The WHO first published guidelines regarding TB and air travel in 1998 and revised them in 2006 in response to increased concerns about resistant forms of TB and improved international collaboration in dealing with infectious disease risks.[17] The latest guidelines can be accessed at http://whqlibdoc.who.int/hq/2006/WHO_HTM_TB_2006.363_eng.pdf. These guidelines provide specific recommendations for passengers, airline crews, health authorities, and airlines and are applicable to all domestic and international airlines worldwide. Instances in which the risk of TB transmission on airplanes may be increased are listed in Table 3.

Role of Isolation and Quarantine

Isolation and quarantine are public health strategies that aim to control exposure to infections. Isolation refers to the separation of persons who have a specific infectious illness from those who are healthy to stop the spread of that illness. In contrast, quarantine refers to the separation and

TABLE 3. **Factors That Influence Risk of Tuberculosis (TB) Transmission on Airplanes**

1. *Infectiousness of the patient with TB*—Smear positivity increases the risk of transmission
2. *Duration of exposure*—The total length of the flight, including time on the ground after boarding, flying time, and time on the ground after landing, must be taken into account. Evidence of transmission of TB has been found only when exposure to the person with TB exceeded 8 hours
3. *Proximity of an infectious passenger to other passengers*—Passenger-to-passenger transmission has been documented only among people seated in the same section as the person with infectious TB

Data from the World Health Organization.[17]

restriction of movement of persons who, although not yet ill, have been exposed to an infectious agent and therefore may become infectious. Local, state, and tribal jurisdictions are primarily responsible for isolation and quarantine within their borders. The federal government has the primary responsibility to prevent interstate spread of disease and to prevent the introduction of communicable diseases from foreign countries into the United States.[23] The communicable diseases for which federal isolation and quarantine are authorized by presidential order are infectious TB, cholera, diphtheria, plague, smallpox, yellow fever, viral hemorrhagic fevers, SARS, and influenza with pandemic potential. This federal quarantine provision was last invoked in 1963 to deal with a patient infected with smallpox, but local public health authorities exercise the right to enforce isolation more frequently. In fact, a person with XDR-TB is currently incarcerated in a Phoenix jail for failing to comply with a physician's instructions to wear a mask in public.[24]

SUMMARY

It remains unclear how Speaker became infected with XDR-TB. Additionally, it may never be known whether he understood the fact that he had a serious and potentially communicable form of TB and still chose to ignore medical advice or whether he simply did not understand all the implications of his diagnosis. His trans-Atlantic multicountry odyssey highlights the fact yet again that spread of infectious agents via global air travel remains a very real threat and that international cooperation remains vital to limit the spread of infections. Moreover, this case draws attention to the fact that TB remains a great threat to humanity worldwide; in the words of US Representatives Eliot L. Engel and Gene Green "We'll get nowhere on TB till we tackle it everywhere."[25]

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