Severe acute respiratory syndrome and tuberculosis

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Severe acute respiratory syndrome (SARS) and tuberculosis (TB) are among the recent emerging or re-emerging infectious diseases that have become global public health threats. An emerging infectious disease is classified as a disease that has not been previously identified; a re-emerging disease is one that becomes resurgent after it has no longer been considered a human health risk. Factors contributing to the emergence and spread of infectious diseases include the increase in world population, globalization, international food trade, contact of humans with natural reservoirs or vectors of a disease, climatic changes, and insufficient resources for a truly global public health infrastructure. The World Health Organization (WHO), which operates under the auspices of the United Nations, has no regulatory status and therefore relies on the cooperation of individual countries. The potentially devastating world health and economic impact of failing to globally control infectious diseases became evident with both SARS and TB.

Severe acute respiratory syndrome

SARS is caused by a newly identified human pathogen now known as *SARS-associated coronavirus* (SARS-CoV). The first known cases occurred in the southern Chinese province of Guangdong in mid-November 2002. Later that month, WHO representatives who were involved in a flu vaccine conference in Beijing heard of a cluster of cases of pneumonia. The samples they tested were positive only for strains of influenza. In retrospect, this was the first missed opportunity to arrest the outbreak before it became an epidemic. Evidence indicates that there was suppression of information within China about the growing cluster of patients with pneumonia caused by an unidentified etiologic

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agent. Three months and many missed opportunities later, the Chinese government informed the WHO on February 11, 2003, of 305 cases of an atypical pneumonia that had resulted in five deaths. Even then, representatives of WHO and the Centers for Disease Control and Prevention (CDC) did not receive governmental access to data or patients until early March. By this time, a worldwide outbreak had begun. A SARS-infected physician from Guangdong province had traveled to Hong Kong on February 21, where he checked into room 911 of the Metropole Hotel. He was later hospitalized and died of SARS, but not before transmission of SARS to other guests at the hotel who subsequently seeded the infection in Hong Kong, Vietnam, Singapore, Canada, the United States, and Ireland (no local transmission). On March 12, and again on March 15, when it was clear that SARS had spread beyond China, the WHO issued a global health alert [1–4]. Through unprecedented international cooperation involving public health officials, scientists, physicians, and the media, combined with basic infection control measures, the disease was brought under control by July 5, 2003. There were 8098 probable cases and 774 deaths [5].

There are currently three identified groups of coronaviruses. Groups I and II are known to cause fairly mild upper respiratory diseases in humans. Group III is only known to cause animal disease [6]. Based on recent sequencing data, SARS-CoV does not clearly fit into any of these three groups. Although coronaviruses possess an RNA-dependent RNA polymerase that can switch template strands when a cell is infected with several coronaviruses, making it very prone to recombination, point mutations, and large deletions, SARS-CoV does not show evidence of being a recombinant of other known viruses. It is an enveloped, single-stranded RNA virus containing 29,727 nucleotides and is approximately 100 to 150 nm in size. A similar virus has been identified in a number of wild animal species found in the animal markets of Guangdong, China. Sequence data from animal isolates show an extra 29-nucleotide sequence not found in humans who have contracted SARS. Otherwise the sequence data is only different by 43–57 nucleotides over the entire genome [7–13]. The outer envelope is embedded with club-shaped spike glycoproteins that give the virus its characteristic crown-like appearance [14]. A rapid sequence evolution of the spike glycoprotein is believed to be responsible for the increased infectivity that developed (the infectivity rate went from 3% initially to 70% by February 2003) [15]. This may explain the occurrence of superspreading events characterized by a large number of transmissions by a relatively few number of source patients. A dramatic pictorial representation of the explosive spread of the disease in Singapore can be seen in Fig. 1 [16].

There are no laboratory tests that are rapid, sensitive, and specific early in the course of disease, so SARS is considered suspect or probable based on clinical and epidemiologic criteria (Box 1). It is confirmed through laboratory testing showing an acute rise in SARS-CoV antibody titers within 4 weeks of developing the disease.

Current data suggest that after exposure to SARS, individuals are not contagious until they become symptomatic. This is generally within 4 to 6 days
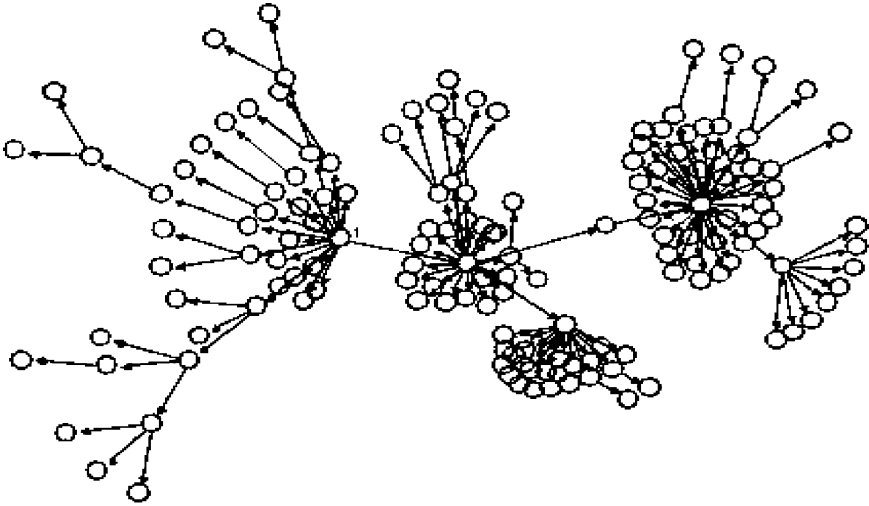
Fig. 1. Probable cases of severe acute respiratory syndrome by reported source of infection (Singapore, February 25–April 30, 2003). Case 1: Source patient for subsequent spread of SARS in Singapore. Excludes 28 cases with either no or poorly defined direct contacts or who were translocated to Singapore with no further secondary transmission. (*Reprinted from* Centers for Disease Control and Prevention. Severe acute respiratory syndrome—Singapore, 2003. MMWR 2003;52:405; with permission.)

of contact (range 2–10 days), though there are rare instances in which the contact may have occurred 14 days prior. With the caveat that respiratory symptoms are improving, infectivity ceases within 10 days of fever resolution. However, it is not clear what effect the use of steroids has on transmissibility, nor the duration of viral shedding. Transmission is through close contact, which is defined as living or caring for an individual who has SARS or having direct contact with respiratory secretions or bodily fluids of an individual who has SARS (eg, direct body contact, sharing eating or drinking utensils, talking to someone [within 3 feet], or exposure to large droplets of bodily fluid [from talking, coughing, sneezing, singing]). Airborne and fecal–oral modes of transmission have not been ruled out, necessitating a higher level of precaution when caring for patients who have SARS. Early symptoms include fever (95%–100%), chills/rigors (73%–90%), headache (20%–70%), and myalgias (20%–83%). This progresses within 2 to 7 days to include a nonproductive cough and shortness of breath. It is important to note that the fever may have resolved before the onset of respiratory symptoms. There is generally radiographic evidence of pneumonia within 7 to 10 days of symptom onset. The incidence of gastrointestinal symptoms varies widely (diarrhea, 10%–67%; nausea/vomiting, 10%–24%). This may be related to the mode of transmission. Those who became sick at the Amoy Garden Apartments in Hong Kong may have been exposed through a fecal–oral route and had a higher incidence of gastrointestinal symptoms than other patient populations. Accompanying laboratory findings include: lymphopenia, thrombo-

Box 1. Criteria for diagnosis of severe acute respiratory syndrome

Clinical criteria

Suspect case

Mild to moderate illness: temperature >100.4°F (>38°C)
    One or more of the following clinical findings: cough,
        shortness of breath, difficulty breathing
Epidemiologic criteria for exposure
Not yet laboratory confirmed
Death of individual with above criteria
Does not meet exclusion criteria

Probable case
As above, and:

Severe respiratory illness, which is classified as mild to moderate respiratory illness with one or more of the following: radiological evidence of pneumonia, acute respiratory distress syndrome (ARDS), pneumonia or ARDS on autopsy

Epidemiologic criteria

Possible exposure

Travel to an area with recent transmission
Close contact with a person with above travel history and who meets clinical criteria

Likely exposure

Close contact with a confirmed case
Close contact with an ill contact of a confirmed case

Laboratory criteria

SARS serum antibody (EIA) positive
SARS-CoV isolation in cell culture
Reverse-transcriptase polymerase chain reaction positive for SARS-CoV RNA

Exclusion criteria

   Alternate diagnosis that fully explains illness
   SARS-CoV antibody negative more than 28 days after onset of
      symptoms
   Case reported based on contact with person who has been ruled
      out for SARS [17]

cytopenia, prolonged activated partial prothrombin time, and increased liver function tests and creatine phosphokinase. Infiltrates on chest radiograph usually begin as focal infiltrates in the periphery of the lower lobes. They may progress to include multiple lobes and both lungs. Advancing age, coexisting disease, and possibly pregnancy are all adversely associated with the severity of illness [18]. The overall mortality from the outbreak was 9.6%. Age adjusted mortality are as follows [2,6,17]:

   20–29: 0.9%
   30–39: 3.0%
   40–49: 5.0%
   50–59: 10%
   60–69: 17.6%
   70–79: 28%
   80+: 26.3%

   The CDC has published an algorithm for the evaluation and management of suspect SARS (Fig. 2) [19]. Work-up should include a review of symptoms consistent with SARS as well as questions that would elicit an etiologic link to the source of infection. Anyone presenting with respiratory symptoms should be put on droplet precautions (standard face masks on the patient and those in close contact with the patient; avoidance of droplet contact with mucous membranes; hand hygiene). Patients who meet the criteria for suspect SARS should immediately be placed in a private respiratory isolation room that has been specially engineered to contain negative pressure in relation to the outside hallway and have a minimum of 12 air exchanges per hour. If this is unavailable, the patient should be in a closed room with a high-efficiency particulate air (HEPA) filter that generates the appropriate number of air exchanges. During the outbreak in 2003, hospitals cohorted patients because the number of infected patients overwhelmed the capacity of individual isolation rooms. If chest radiograph confirms pneumonia, the health department should be notified and the following tests should be performed: complete blood count with differential, pulse oximetry, blood cultures, sputum Gram stain and culture, testing for other respiratory pathogens (influenza A and B, respiratory syncytial virus, legionella, and pneumococcus). If an alternative diagnosis that fully explains the patient's disease has not been identified within 72 hours, testing for SARS-CoV should

Radiographic evidence of pneumonia requiring hospitalization?

Yes

If no, treat as clinically indicated

Continue droplet precautions and treat as clinically indicated for community-acquired pneumonia

The clinician should ask the patient about the following:
A. Recent travel (within ten days) to mainland China, Hong Kong, or Taiwan or close contact with ill person with a history of travel to such areas
B. Employment in an occupation at particular risk for SARS-CoV exposure, including a healthcare worker with direct patient contact or a worker in a laboratory which contains live SARS-CoV
C. Close contact with others who have been told they have pneumonia

Yes to one of three questions.

No to three questions.
Treat as clinically indicated.

1. Notify the health department
2. Evaluate for alternative diagnosis as clinically indicated. This work-up may include the following:
    A. CBC with differential
    B. Pulse oximetry
    C. Blood cultures
    D. Sputum Gram stain and culture
    E. Testing for viral respiratory pathogens such as influenza A and B, respiratory syncytial virus
    F. Specimens for legionella and pneumococcal urinary antigen
3. The health department and clinicians should look for evidence of clustering of patients with radiographically-*confirmed* pneumonia *without alternative diagnoses* (e.g., while traveling, exposure to other cases of pneumonia, clusters of pneumonia among healthcare workers).
4. NOTE: If the health department and clinician have a high suspicion for SARS-CoV infection, consider SARS isolation precautions (http://www.cdc.govÉ)

After 72 hours, alternative diagnosis?

Yes

No

Treat as clinically indicated

If part of a cluster of pneumonia (or there are other reasons to consider at higher risk for SARS-CoV disease), consider SARS-CoV testing in consultation with health department
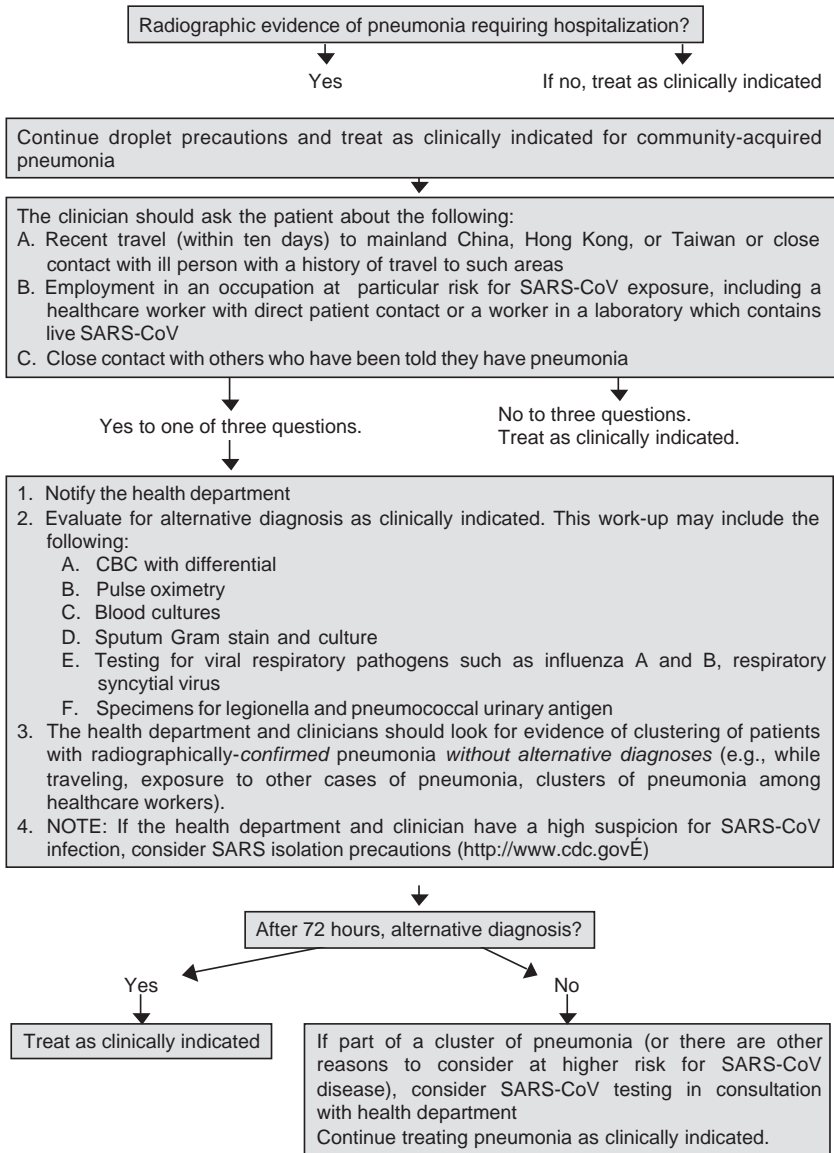Continue treating pneumonia as clinically indicated.

Fig. 2. Algorithm for evaluation and management of patients hospitalized with radiographically confirmed pneumonia in the absence of SARS-CoV disease activity worldwide. (*Adapted from* Centers for Disease Control and Prevention. Public health guidance for community-level preparedness and response to severe acute respiratory syndrome (SARS), Supplement C. Available at: www.cdc.gov/ncidod/sars/guidance2003).

proceed. Patients who do not have radiographic evidence of pneumonia initially should be re-evaluated with a chest radiograph after 72 hours. Only if there is still no evidence of pneumonia should discontinuation of SARS respiratory precautions be considered.

The SARS virus may be detected in sputum, bronchi-alveolar lavage, pleural fluid, nasopharyngeal washes and aspirates, naso- and oropharyngeal swabbings, serum, blood, and stool. Samples from multiple sites and at different times during the course of the illness should be collected for real-time reverse-transcriptase polymerase chain reaction testing for evidence of viral antigen (Table 1). A negative reverse-transcriptase polymerase chain reaction result does not rule out SARS, because there is a window of time during which the virus is present in any given specimen type, and this may be missed [12]. A positive result indicates true infection, assuming no contamination of the sample before or during testing and that there is no cross-reactivity between SARS-CoV and other coronaviruses (not yet fully delineated).

Antibody to SARS-CoV may be identified using one of three tests: immunofluorescent antibody, enzyme-linked immunosorbent antibody (EIA or ELISA), or a neutralization test. A positive antibody test may indicate prior exposure, acute disease, or cross-reactivity with another virus [20]. Antibody cross-reactivity is an ongoing area of investigation. Many workers in the markets of southern China have tested positive for SARS-CoV antibody (40% wild animal traders, 20% wild animal butchers, 5% vegetable traders) without ever having evidence of SARS infection [21]. SARS is confirmed in patients that have an acute illness consistent with SARS and convert from negative to positive SARS-CoV IgG, or have a fourfold increase in titers to SARS-CoV in acute versus convalescent serum [2,17,22].

There are no specific recommendations for treatment of SARS other than supportive care. Many countries that were seriously affected during the initial outbreak treated patients with a combination of steroids and antivirals such as ribavirin. There is no in vitro evidence in support of this regimen, and the CDC does not currently recommend it. Many potential antiviral agents are under investigation, as is the use of SARS hyperimmune-globulin and SARS-CoV vaccination.

Table 1
Reverse-transcriptase polymerase chain reaction positivity in respiratory specimens, stool and urine

Sample (% positive)	Days from illness onset				
	0–2	3–5	6–14	15–17	21–23
NPA/TNS (n = 392)	31	43	57–60	35	13
Stool (n = 50)	0	57	86–100	33	43
Urine (n = 20, n = 19)			50 (day 10)	35 (day 16)	21 (day 21)

Abbreviations: NPA, nasopharyngeal aspirate; TNS, threat and nose swabs.
Adapted from Peiris et al. Coronavirus as a possible cause of severe acute respiratory syndrome. Lancet 2003;361:1319–25, and Dr. Margaret Chan.

Infection control measures in the hospital setting are based on the mechanisms with which the disease is known to be transmitted (close contact, droplet) and those that are potential routes (airborne, fecal–oral). Precautions include respiratory isolation, use of personal protective equipment, hand washing, and disinfection of environmental surfaces.

Personal protective equipment

Respirators

Disposable, fit-tested N-95 or greater respirators that have been approved by the National Institute of Occupational Safety and Health should be used when coming in contact with patients. A surgical mask placed over the nose and mouth of the patient is sufficient to trap the large particles generated through coughing or sneezing. However, these masks are incapable of filtering the virus once the expectorated material dries and the virus becomes airborne as a droplet nucleus. N-95 masks attain a filter efficiency of more than 95% through mechanisms including electrostatic filtration, sedimentation, and diffusion [23–28].

Eye protection, gowns, gloves

Goggles, disposable gowns, and gloves should be worn when entering a patient's room and during patient contact. When leaving the patient room, gowns and gloves should be removed, avoiding self-contamination [24–28].

Hand washing

Hands should be washed with soap (antimicrobial or plain) and water after patient contact regardless of whether or not gloves have been worn. Alcohol-based hand rubs may be used if there has been no visible soiling [24–28].

Patient care equipment and environmental surfaces

When possible, patient care equipment should be left in the patient's room. Equipment and environmental surfaces should be disinfected with an agent that has been approved by the Environmental Protection Agency (such as a quaternary ammonium or phenolic compound) that is recommended for the particular item. Disinfectants that have proven to be effective include 75% ethanol, 2% phenol, hypochlorite (500 ppm available chlorine), and household detergent [24–28].

Recommendations for practice

Patient triage

Anyone who suspects that they have SARS is advised to contact the health care facility before their arrival. Patients should put on surgical masks and be isolated from other individuals at the earliest opportunity.

Patient transfer

SARS patients should only be outside their room for required medical procedures. Elective procedures should be postponed until the patient is no longer deemed to be infectious. While outside their room, patients should wear a surgical mask. Transport personnel should use full barrier protection.

Operating room

When surgery is required, efforts should be made to limit exposure of personnel and other patients. This includes performing the procedure when the least number of people are present in the operating room (OR) and limiting personnel in the patient's OR to only those who are essential for the procedure. ORs generally have positive pressure in relation to the outside hallways to decrease surgical infection risk. If available, ORs with antechambers are preferable for cases in which the patient may expose personnel to infection risk. All unnecessary equipment should be removed from the room to prevent contamination. Patients should be transferred directly to the OR in which the surgery will be performed. Everyone in the OR should use the full precautions discussed earlier. Bacterial/viral filters should be used on both the inspiratory and expiratory limbs of the anesthesia machine. There are no recommendations regarding anesthetic technique. Care should be taken to avoid contamination of the anesthesia machine and cart. This may be accomplished by double-gloving and changing the outer pair of gloves after each patient contact. After the procedure, the patient must be recovered in isolation. This may require that recovery occur in the OR itself, or the patient's isolation room. All personal protective equipment should be removed before leaving the OR, because it may have become contaminated. New personal protective equipment should be put on for transport of the patient when leaving the OR. There is controversy as to whether or not N-95 masks should be reused. If adequate supplies are available, it is preferable to dispose of the masks after use, as they are potential fomites for the transfer of infection. If there is a shortage of masks, one recommendation is to wear a surgical mask over (not under—this defeats the purpose of a tight seal that only allows air that is filtered inside the mask) the N-95 mask. This would decrease the gross soiling of the mask. The OR should remain vacant for a sufficient period of time to allow for 99.9% air turnover. For a room with five air changes per hour (ACH), 83 minutes would be required. At 10 ACH, this drops to 41 minutes, and only 28 minutes for 15 ACH. All surfaces should be disinfected with an agent that has been approved by the Environmental Protection Agency. The circuit and the gas sampling line should be disposed. All trash should be properly bagged and disposed of as per standard OR requirements. The tragically high infection rates of health care workers at the early stages of the epidemic makes it clear that these recommendations must be strictly adhered to in order to protect oneself and other health care workers [17,26,28–30].

The SARS outbreak was controlled by a combination of ancient infection control procedures (isolation, quarantine of contacts) and an unprecedented cooperation among governments, scientists, news agencies, and citizens. The

disease has clearly not been eradicated though. There have been cases of SARS in laboratory workers where the source of contact was easily identified. However, beginning in December 2003, a growing number of sporadic cases, where the source of contact has yet to be identified, have been occurring. A coronavirus that has 99.8% sequence homology with human SARS-CoV has been identified in many animal species sold in the markets of southern China for human consumption (eg, palm civets, raccoon, dog, ferret, badger, cyanomolgus macaque, fruit bat, snakes, wild pigs). It is not yet known whether any of these animals can transmit the disease to humans, but the Chinese government instituted an eradication campaign for all palm civets in captivity and the US Government has placed an embargo on importation of the animals [31]. Whether SARS can be eliminated will depend on whether there is an animal reservoir or if it has became endemic in the human population. It remains to be seen if it will re-emerge with seasonal outbreaks similar to influenza. Will the disease become more or less virulent over time? Will it be possible to develop a treatment or neutralizing vaccine that the virus doesn't circumvent through mutation?

As new information and answers to the many questions surrounding SARS are found, information is available on several public health Web sites, including:

Centers for Disease Control and Prevention (CDC): www.cdc.gov
World Health Organization (WHO): www.who.int/en/
International Society of Infectious Diseases (ISID): www.isid.org

Tuberculosis

TB, a scourge for many centuries, became a treatable disease after the discovery of effective chemoprophylaxis beginning in 1944 (streptomycin). *Mycobacterium* tuberculosis (MTB) develops drug resistance within months when treated with a single therapeutic agent, however. Multidrug therapy of adequate duration limits the probability that drug resistance will occur. Over the next two decades, many more drugs effective against MTB were identified: p-aminosalicylic acid (1949), isoniazid (1952), pyrazinamide (1954), cycloserine (1955), ethambutol (1962), and rifampin (1963). Between the mid-1950s and 1984 there was a steady decrease in the incidence of TB. It was thought to be a disease of the past. Resources (staff, funding, clinics, medication) for TB had dwindled. The World Health Organization (WHO) had only two full-time people assigned to work on TB. However, HIV, which increases the risk of developing active TB and subsequently the duration of infectivity, had begun to spread throughout the world. The conditions were ideal for re-emergence of TB. Between 1985 and 1992, surveillance for TB in the United States showed a 20% increase in the number of cases secondary to the HIV copandemic, poverty, medically underserved populations, congregate living situations (prisons, shelters, long-term care facilities), immigration from

countries with endemic TB (Haiti, India, Mexico, China, Korea, Vietnam), and a decrease in public health services. In the early 1990s, an estimated 1.7 billion people (one third of the world population) were TB exposed, there were nearly 8 million new cases per year, and 2.9 million deaths were attributed to TB. It became clear that nothing short of a global TB control program would be effective. A program known by the acronym DOTS (directly observed therapy short-course), which relies on increased governmental commitment, surveillance, diagnosis, availability of drugs, and verification of treatment compliance, was initiated. In the United States, this has led to an annual decline in TB of 5% to 6%. All 22 of the highest burden countries—which account for 80% of the global cases of TB—have adopted DOTS. The World Health Assembly has established targets of reaching 85% cure rates and 70% detection rates of infectious cases [32–37].

MTB is an aerobic rod measuring 2 to 4 μm by 0.3 μm that thrives at a pO_2 of 140 mm Hg. The bacilli are released into the air as droplets when a person with pulmonary or laryngeal TB coughs, sneezes, speaks, or sings. Droplets travel no more than 3 feet from the source. Particles larger than 10 μm are trapped and cleared by the cilia in the upper airway without causing disease. However, as the droplets desiccate, they form droplet nuclei that may stay suspended in air currents and spread more widely. Droplet nuclei may be inhaled deeper into the bronchioles, thereby evading the mucociliary defenses of the host and leading to infection. In addition to pulmonary TB, other tissues that may become affected include the kidneys, brain, bones, joints, and genitourinary tract [38]. When MTB disseminates, it is known as *miliary TB*. Although rare, TB infection can occur through vertical transmission. Congenital TB is usually disseminated and carries a 50% mortality risk [39]. There is an approximately 10% lifetime risk of developing active TB after exposure. The highest risk is in the first 1 to 2 years. However, certain conditions predispose an individual to progression. Individuals who have HIV coinfection have a 7% to 10% risk per year of converting to active TB [40].

At-risk populations should be screened for evidence of TB exposure with a mantoux skin test. Five units (0.2 mL) of purified protein derivative (PPD) are deposited subcutaneously. In the absence of anergy, induration will develop within 48 to 72 hours of testing if there has been exposure. Induration of 5 mm or more is a positive result in anyone who has HIV, chest radiograph consistent with active disease, duration of less than 12 weeks since exposure, or anyone who is immunocompromised. In all others, 10 mm or more is a positive response. There is cross-reactivity between Bacille of Calmette and Guérin (BCG) and PPD. The response to the BCG vaccine wanes with time, however, so a positive response to PPD testing is generally indicative of exposure to TB. The response to PPD may be attenuated if it has been a long time since TB exposure or previous testing. Periodic screening of at risk populations should use 2-step testing in anyone who has a negative PPD and if it has been more than a year since the previous test. The first test boosts the immune response and increases the positive predictive value of a second test performed 1 to 3 weeks later [24].

The Quantiferon-TB test, another screening test for latent TB infection, was approved by the US Food and Drug Administration in 2001. A whole blood sample is tested against antigen to PPD from MTB and *Mycobacterium avium*. It quantitatively measures the release of interferon γ in response, and can differentiate between these infections. A newer test is in development that can distinguish between MTB and previous vaccination with BCG.

Characteristic signs and symptoms of active TB include: cough (74%), weight loss (71%), fever (30%), malaise (30%), and hemoptysis (19%). Individuals who present with this constellation of symptoms should have sputum sampling (three samples collected 8–24 hours apart) for acid-fast bacillus staining and culture and a chest radiograph. Respiratory isolation precautions should be instituted until the patient is deemed not to be infectious (acid-fast bacillus–negative on three successive sputum samples). Chest radiograph evidence of an acute process correlates with infectivity in those who are not immunocompromised or on steroid treatment. Culture-positive samples should be tested for drug sensitivity. MTB rapidly develops drug resistance in circumstances of nonadherence to therapy or inadequate treatment regimens. The worldwide prevalence of resistance to at least one drug is 10.7% (range 2%–36%) and multidrug-resistant TB (MDR-TB), defined as resistance to at least isoniazid and rifampicin, is 1% (range 0%–14%). It is currently estimated that 3.2% of the world's new TB cases are MDR-TB. We recently had a patient at our hospital with a strain of TB resistant to nine drugs. Treatment should be initiated based on the current CDC recommendations (Fig. 3, Table 2). Because of the implications of coinfection with HIV regarding the choice of therapy and the duration of treatment, HIV counseling and testing is recommended for anyone that has been diagnosed with TB. Baseline laboratory values for aspartate aminotransferase, alanine aminotransferase, bilirubin, alkaline phosphatase, serum creatinine, and platelet count should be performed. Subsequent laboratory work should be based on known toxicities of the drugs used in treatment. If ethambutol is used, visual acuity and color vision should be assessed [40].

Prevention of transmission in medical facilities requires a combination of early identification, isolation, and treatment of infectious individuals with active disease, engineering controls, basic infection control measures, and the use of personal protective equipment. Elective surgery should be postponed in patients with TB until they are no longer contagious (three negative sputum smears, improving symptoms and chest radiograph). For surgeries that cannot be delayed, precautions should be used to minimize the risk of transmission. The patient should wear a surgical mask when outside of an isolation room. A surgical mask is adequate for trapping the droplets before they are released into the environment to become droplet nuclei. Unlike respiratory isolation rooms, ORs are never at negative pressure in relation to the outside hallways because of the risk it would carry for surgical site infections. However, choosing an OR with an antechamber or that is physically separated from other areas may reduce environmental exposure. Whenever possible, the case should be scheduled when the fewest health care workers risk exposure. The operating room doors should be
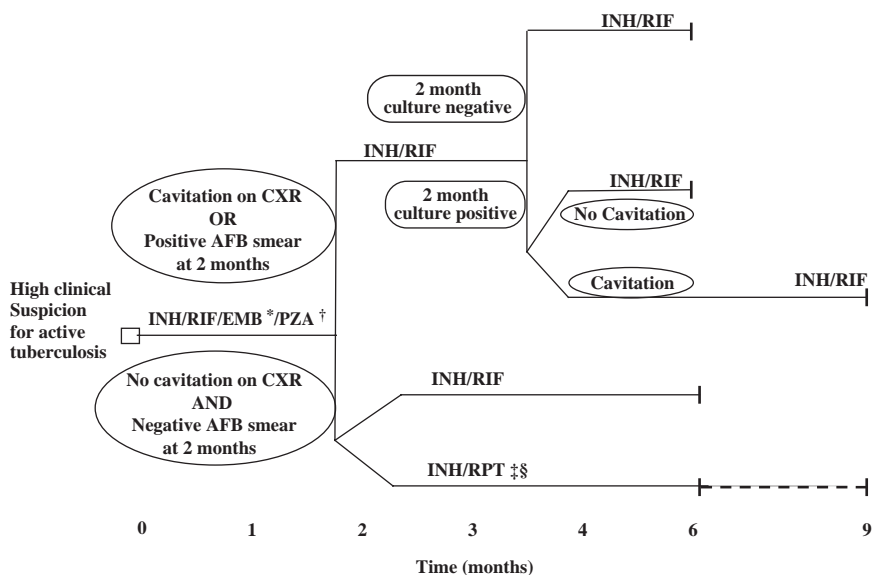
Fig. 3. Treatment algorithm for TB. Patients in whom TB is proved or strongly suspected should have treatment initiated with isoniazid, rifampin, pyrazinamide, and ethambutol for the initial 2 months. A repeat smear and culture should be performed when 2 months of treatment has been completed. If cavities were seen on the initial chest radiograph or the acid-fast smear is positive at completion of 2 months of treatment, the continuation phase of treatment should consist of isoniazid and rifampin daily or twice weekly for 4 months to complete a total of 6 months of treatment. If cavitation was present on the initial chest radiograph and the culture at the time of completion of 2 months of therapy is positive, the continuation phase should be lengthened to 7 months (total of 9 months of treatment). If the patient has HIV infection and the CD4^{+} cell count is less than 100/μL, the continuation phase should consist of daily or three times weekly isoniazid and rifampin. In HIV-uninfected patients having no cavitation on chest radiograph and negative acid-fast smears at completion of 2 months of treatment, the continuation phase may consist of either once weekly isoniazid and rifapentine, or daily or twice-weekly isoniazid and rifampin, to complete a total of 6 months. Patients receiving isoniazid and rifapentine, and whose 2-month cultures are positive, should have treatment extended by an additional 3 months (total of 9 months of treatment). *Ethambutol may be discontinued when results of drug susceptibility testing indicate no drug resistance. †Pyrazinamide may be discontinued after it has been taken for 2 months (56 doses). ‡Rifapentine should not be used with HIV-infected patients with tuberculosis or in patients with extrapulmonary tuberculosis. §Therapy should be extended to 9 months if 2-month culture is positive. CXR, chest radiograph; EMB, ethambutol; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin; RPT, rifapentine. (*Adapted from* Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf.)

kept closed, and personnel in the room kept to a minimum. Although there have been no reports of TB transmission from a contaminated ventilator, it is recommended that a HEPA filter be placed in the circuit between the patient and the ventilator. HEPA filters are rated to remove 99.97% of particles larger than 0.3 μm in diameter. When entering any area that could contain respiratory infectious particles, masks conforming to the National Institute for Occupational Safety and Health N95 standard should be used. For proper protection, fit testing for the specific brand of mask is required. The mask must make an airtight seal

Table 2
Doses of antituberculosis drugs for adults and children

Drug	Adults/children	Doses				Adverse drug reactions
		Daily	1×/wk	2×/wk	3×/wk	
First line drugs						
Isoniazid	Adults (max.)	5 mg/kg (300 mg)	15 mg/kg (900 mg)	15 mg/kg (900 mg)	15 mg/kg (900 mg)	Hepatoxicity, peripheral neurotoxicity, drug interactions
	Children (max.)	10–15 mg/kg (300mg)		20–30 mg/kg (900 mg)		
Rifampin	Adults[a] (max.)	10 mg/kg (600 mg)	—	10 mg/kg (600 mg)	10 mg/kg (600 mg)	Hepatoxicity, thrombocytopenia, gastrointestinal upset, drug interactions
	Children (max.)	10–20 mg/kg (600 mg)	—	10–20 mg/kg (600 mg)	—	
Rifabutin	Adults[a] (max.)	5 mg/kg (300 mg)	—	5 mg/kg (300 mg)	5 mg/kg (300 mg)	
	Children (max.)	Appropriate dosing for children is unknown	Appropriate dosing for children is unknown	Appropriate dosing for children is unknown	Appropriate dosing for children is unknown	
Rifapentine	Adults (max.)	—	10 mg/kg (continuation phase) (600 mg)	—	—	
	Children	Not approved for use in children	Not approved for use in children	Not approved for use in children	Not approved for use in children	
Pyrazinamide	Adults	Based on weight	—	Based on weight	Based on weight	Hepatotoxicity, gastrointestinal upset, arthraglia
	Children (max.)	15–30 mg/kg (2.0 g)	—	50 mg/kg (2 g)	—	
Ethambutol	Adults	Based on weight	—	Based on weight	Based on weight	Ocular neuritis
	Children[b] (max.)	15–20 mg/kg daily (1.0 g)	—	50 mg/kg (2.5 g)		
Second-line drugs						
Cycloserine	Adults (max.)	10–15 mg/kg/d (1.0 g in two doses), usually 500–750 mg/d in two doses[c]	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration	Central nervous system: psychosis, seizure

	Children (max)	10–15 mg/kg/d (1.0 g/d)				
Ethionamide	Adults (max.)	15–20 mg/kg/d (1.0 g/d/), usually 500–750 mg/d in a single daily dose or two divided doses	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration	Gastrointestinal upset, hepatotoxicity, neurotoxicity, endocrine
	Children (max.)	15–20 mg/kg/d/ (1.0 g/d)	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration	
Streptomycin	Adults (max.)[d]					Ototoxicity, neurotoxicity, nephrotoxicity
	Children (max.)	20–40 mg/kg/d (1 g)		20 mg/kg		
Amikacin/kanamycin	Adults (max.)[d]					Ototoxicity, nephrotoxicity
	Children (max.)	15–30 mg/kg/d (1 g) intravenous or intramascular as a single daily dose		15–30 mg/kg		
Capreomycin	Adults (max.)[d]					Ototoxicity, nephrotoxicity
	Children (max.)	15–30 mg/kg/d (1 g) as a single daily dose		15–30 mg/kg		
p-Aminosalicyclic acid	Adults	8–12 g/d in two or three doses	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration	Hepatotoxicity, gastrointestinal upset, hypothyroidism, coagulapathy
	Children	200–300 mg/kg/d in two to four divided doses (10 g)	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration	
Levofloxacin	Adults	500–1000 mg daily	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration	Gastrointestinal upset, tremor rash
	Children[e]					

Table 2 (*continued*)

Drug	Adults/children	Doses				Adverse drug reactions
		Daily	1×/wk	2×/wk	3×/wk	
Moxifloxacin	Adults	400 mg daily	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration	
	Children[f]					
Gatifloxacin	Adults	400 mg daily	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration	
	Children[g]					

Dose per weight is based on ideal body weight. Children weighing more than 40 kg should be dosed as adults. For purposes of this document, adult dosing begins at 15 years of age.

[a] Dose may need to be adjusted when there is concomitant use of protease inhibitors or nonnucleoside reverse transcriptase inhibitors.

[b] The drug can likely be used safely in older children but should be used with caution in children less than 5 years of age, in whom visual acuity cannot be monitored. In younger children ethambutol at the dose of 15 mg/kg/d can be used if there is suspected or proven resistance to isoniazid or rifampin. It should be noted that, although this is the dose recommended generally, most clinicians with experience using cycloserine indicate that it is unusual for patients to be able to tolerate this amount. Serum concentration measurements are often useful in determining the optimal dose for a given patient.

[c] The single daily dose can be given at bedtime or with the main meal.

[d] Dose: 15 mg/kg/d (1 g), and 10 mg/kg/d in persons more than 59 years of age (750 mg). Usual dose: 750–1000 mg administered intramuscularly or intravenously, given as a single dose 5–7 d/wk and reduced to two or three times per week after the first 2–4 months or after culture conversion, depending on the efficacy of the other drugs in the regimen.

[e] The long-term (more than several weeks) use of levofloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. However, most experts agree that the drug should be considered for children who have tuberculosis caused by organisms resistant to both isoniazid and rifampin. The optimal dose is not known.

[f] The long-term (more than several weeks) use of moxifloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. The optimal dose is not known.

[g] The long-term (more than several weeks) use of gatifloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. The optimal dose is not known.

Adapted from Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf.

with the face to ensure that all inspired air is filtered through the mask. If the available N95 masks have an exhalation valve, a regular surgical mask must be worn over it to protect the surgical field from infection. Those individuals who cannot be successfully fit tested for an N95 mask should use a higher level of respiratory protection, such as a powered air purifying respirator. Recovery from anesthesia must take place with the same level of precautions. If there is no isolation room in the recovery room, this will generally mean the patient needs to recover in the OR or a respiratory isolation room. A room in which a patient with active TB has been present should not be entered unless necessary until there has been a 99.9% turnover of the air. The duration is dependent on the number of air exchanges per hour, but is generally in the range of 30 to 60 minutes for most ORs [24,30].

Summary

Bacterial, viral, prion, and possibly as yet unidentified etiologic agents continue to cause human health risks through their ability to circumvent the immune system and our capability to eradicate, treat, or effectively prophylax against them. Of current concern to world health are the avian influenza viruses. The H5N1 strain is easily transmitted to humans from its primary host and is highly lethal (>75% mortality). The poultry industry has been severely affected in many countries. Its global impact on human health has only been limited by its current lack of transmission from human to human. This could easily change through a recombination event between an avian and a human influenza virus. We will continue to be exposed to new disease-causing organisms through exposure to areas with no prior human habitation and increasing globalization. In addition, we are increasing the selection pressure on these organisms through agricultural pressure (farming conglomerates) and the widespread overuse of antimicrobial agents. Our ability to avoid global epidemics in the future depends on our intelligence in responding to what we have learned from our prior failures in controlling infectious diseases.

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