REVIEW

Cough and the Transmission of Tuberculosis

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Cough is a predominant feature of respiratory infection and, in tuberculosis, is of prime importance for transmitting infection. Tuberculosis is transmitted by the air, yet the process by which bacilli are aerosolized has received little attention. Features of cough may account for differences in transmission rates from source cases of pulmonary disease. We review the literature on the mechanisms and characteristics of cough in tuberculosis in the context of the dissemination of infection. Coughing is probably more important than other respiratory maneuvers, and characteristics of mucus may have an important role but data are scarce. Direct mechanisms of cough in tuberculosis are unknown, as are temporal and other patterns that correlate with the release of viable airborne bacilli. Other than antituberculous chemotherapy and masks, there are few methods of modulating cough in tuberculosis. This is an increasingly important area for research.

Keywords. tuberculosis; cough; airborne transmission; infectiousness.

Tuberculosis remains a significant global problem. The rise of antibiotic resistance is a particular threat to efforts to control the disease, and new approaches are required. One possibility is to modify the process of transmission of the infection. There has been only limited interest in the process by which source cases disseminate disease since effective regimens for tuberculosis were developed in the 1960s [1].

Tuberculosis is distinct among infectious diseases in that it is transmitted almost exclusively through the air [2]. This basic fact affects epidemiology and approaches to infection control. Variability in the spread of tuberculosis is high, as indicated from the results of source-case contact tracing, in which it is common that either all or no other members of a household are infected [3]. This must be due to characteristics of 1 or more of the source case, the pathogen, the environment, or the new potential host [4]. Exposing guinea pigs to hospital air shared with people with untreated pulmonary tuberculosis has shown that characteristics of the source case accounts for a large part of this variability in transmission, as small numbers of patients caused a large proportion of secondary infections [5, 6]. Although sputum bacillary load is the most widely used surrogate of infectiousness [4], only the minority of sputum-smear-positive cases seem to pass infection on to their contacts [3].

A necessary step in propagating infection is the expulsion of bacilli from the lungs of infected individuals and their release into the surrounding air in a form that can remain viable during aerial transit. Although coughing is assumed to be the main way in which *Mycobacterium tuberculosis* passes from a human host into the environment, this has not been proven conclusively, and breathing, talking, and other respiratory maneuvers may make important contributions [4]. Cough in respiratory disease in general is only beginning to attract significant attention as a focus of clinical research, and mechanisms of the cough reflex continue to be explored [7]. We are aware of no specific data describing the mechanisms of cough in tuberculosis. The temporal pattern of coughing presumably influences infectiousness, but to our knowledge this has only been investigated in 1 small study [8]. There appear to be few recent studies of the mechanics of cough that associate with the aerosolization of viable bacilli, such as lung airflow patterns, airway-wall shearing forces, and respiratory tract deformation and vibration characteristics [9]. The properties of airway mucus are probably also

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important, both in the formation of aerosol particles and for protecting airborne bacilli within, but similarly seem to have been little researched in this context [10]. The role of cough in the transmission of tuberculosis is therefore a large subject about which relatively little is known. In this article, we review the existing literature and highlight areas for research.

METHODS

We searched PubMed for English-language articles published between 1900 and 2014 with the terms "tuberculosis", "TB", "*Mycobacterium*", "cough", "droplet", "particle", "airborne", "aerial", "dissemination", "transmission", "infectiousness", and "infectivity". From the reference lists of relevant articles found in this way we identified additional articles. Further references were used from our own collections.

COUGHING, OTHER RESPIRATORY ACTIONS, AND PARTICLE PRODUCTION

Studies of guinea pigs exposed to human tuberculosis suggest that the inhalation of a single bacillus is a sufficient infecting dose and that most patients with untreated pulmonary disease release very few infectious particles into the surrounding air on a daily basis [11]. *M. tuberculosis* measures about 3 μm in length, although its irregular shape suggests its aerodynamic diameter may differ from this. To resist the effect of gravity and to move by Brownian motion, the aerodynamic diameter of a particle released into the surrounding air should not be much larger than this [12]. To reach the alveolus, the initiating site of *M. tuberculosis* infection, a particle should measure <5 μm in diameter [13]. The aerodynamic diameter of the large majority of aerosol particles containing viable *M. tuberculosis* has been shown to be 0.65–4.7 μm [14]. The behavior of airborne particles is influenced by many factors, including their dimensions, composition, and velocity, as well as ambient conditions, such as temperature, humidity, air quality, and air movement. For aerial microorganisms, this has been reviewed elsewhere [15].

Cough is a significant feature of pulmonary tuberculosis and results in the release of airborne particles into the environment. However, infectious particles may also be aerosolized during talking and breathing [4], and singing may also be important in some situations, such as tuberculosis outbreaks in choirs [16]. Although not generally associated with tuberculosis, sneezing could also have a role during coincident viral upper respiratory tract infections. By use of modern laser diffraction methods, the predominant aerodynamic diameter of particles released during coughing in healthy volunteers is <5 μm and is similar to that for talking but probably larger than the diameter of the great majority of particles produced during tidal breathing (ie, <1 μm) [17, 18]. Only a few attempts have been made to compare the quantities of aerosols produced during different respiratory maneuvers by using modern techniques, and again only in healthy volunteers, but coughing seems to produce more airborne particles than vocalizing or breathing over similar periods [18]. As tidal breathing generally occurs much more frequently than coughing, it might be expected to produce much larger quantities of aerosol on a daily basis, but the small particle size associated with breathing suggests it is of lesser importance for tuberculosis transmission. Expelling debris from the airways as aerosol requires shear forces of sufficient magnitude to overcome mucus viscosity [9]. Coughing is usually associated with higher forces than talking or singing, as illustrated by the higher peak expiratory velocity during coughing than breathing or speaking (approximately 15 m/second [55 km/hour] in men and 11 m/second [38 km/hour] in women when coughing, compared with 4 m/second [15 km/hour] and 2 m/second [8 km/hour], respectively, during speaking in one study of healthy volunteers [19]).

It is therefore a reasonable assumption that coughing is the predominant way by which *M. tuberculosis* is aerosolized from the lung and released into the environment. Other mechanisms, however, cannot be discounted, and further investigation of particle production during respiratory activities in disease states, rather than in healthy volunteers, is required.

THE ROLE OF MUCUS AND AIRWAY FLUID PROPERTIES

Along with the presence of viable microorganisms, other components of aerosolized particles will influence the potential for infection. This might be through effects on particle size [12] and movement, both through the air and within the respiratory tract of a potential secondary host. Alternatively, certain substances might support organisms contained within by preventing desiccation and protecting against ultraviolet light and the first lines of defense of the secondary host. In a rare study exploring one of these aspects, Zayas et al used a cough-simulator machine with mucus-simulant solution to demonstrate that increasing mucus cohesiveness reduced its potential for aerosolization [10]. This is consistent with an observation that salivary rather than mucoid sputum in tuberculosis is associated with the ability to culture *M. tuberculosis* from airborne particles [14]. Mucus composition varies with disease, smoking, and possibly genotype [20], and it is possible that *M. tuberculosis* directly affects host airway mucus characteristics to promote transmission. As well as airway mucus, the properties of airway lining fluid may be important. Edwards et al observed that experimentally altering airway surface tension with isotonic saline or surfactant, both in a cough-simulator machine and in healthy human volunteers, altered the size and quantity of exhaled aerosol particles [21]. The role of mucus and airway fluid in infectiousness appears to have been addressed infrequently and deserves further analysis.

MECHANISMS OF COUGH

Although the basic anatomy of the cough reflex has been elucidated from animal studies, specific mechanisms await further explanation, as illustrated by the current lack of effective cough suppressant medications [22]. Sensory afferents include rapidly adapting receptors and unmyelinated C-fiber receptors, which preferentially respond to mechanical activity and chemical stimuli respectively. These in turn communicate with the nucleus tractus solitarius via the vagus nerve to trigger the characteristic pattern of muscular activity [7]. Important mediators for cough receptors include bradykinin, prostaglandins, and adenosine triphosphate [7]. Input from the cerebral cortex has a modulatory role, as demonstrated by the ability to suppress and start coughing voluntarily.

Transient receptor potential (TRP) ion channels in the airways are probably important. TRPV1 is activated by heat, particles, and other irritants, including capsaicin, and channel numbers are increased in the airways of patients with chronic cough [7]. TRPA1 activates the cough reflex both directly and indirectly, responding to protussive substances that do not activate TRPV1, such as acrolein and cinnamaldehyde [23]. However, the exact role of these channels is unclear, as illustrated by the fact that TRPV1 antagonism reduces capsaicin-induced cough sensitivity of the reflex but does not affect daily cough frequency in patients with chronic cough [24]. Polymorphism in TRPV1 genotype may be important for coughing patterns. This has only been explored in a population study to date but showed an association between several single-nucleotide polymorphisms of *TRPV1* and cough symptoms [25].

Only a limited body of work has investigated mechanisms of cough in infectious disease, the majority of which involves viral upper respiratory tract infections. Capsaicin-induced cough reflex sensitivity increases during upper respiratory tract infection [26]. This may be due to increased numbers of cough receptors: TRPA1, TRPV1, and TRPM8 expression can be upregulated by rhinovirus infection of a human cell line [27]. Protussive inflammatory mediators may also become more abundant in the airways during respiratory infection: the release of substance P and neurokinin A has been induced experimentally by infecting guinea pig tracheal neurons with Sendai virus [28].

To our knowledge, no studies have looked at the mechanisms of cough in tuberculosis. There may be coincident factors unrelated to infection that increase the propensity to cough, such as smoking [29, 30] or preexisting lung disease. In the absence of these factors, presumably a combination of the direct presence of bacteria, substances they produce, and products of the host immune response both reduce coughing threshold and provoke cough directly. Prostaglandin E2 might be important, as it is known to activate the cough reflex in other contexts [7] and may be a significant mediator in the pathogenesis of tuberculosis [31]. It is possible that *M. tuberculosis* directly affects the afferent limb of the cough reflex. The process would be analogous to the reduction of local pain sensation in Buruli ulcer as a result of the modification of nerve transmission by *Mycobacterium ulcerans* [32]. Increased knowledge of these fundamental processes is required. This should come about through the further study of cough in healthy individuals and during other respiratory diseases, as well as during tuberculosis. Also helpful might be further understanding of the general pathogenesis of tuberculosis and, in particular, how virulence characteristics vary with mycobacterial strain [33], possibly with an influence on cough patterns.

PATTERNS OF COUGH AND INFECTIOUSNESS

Subjective Descriptions of Cough

Further understanding of cough in the transmission of tuberculosis requires methods of measuring cough. Patients can subjectively describe cough severity and effects on quality of life with tools such as visual analogue scales, the Leicester Cough Questionnaire, and the Cough-Specific Quality of Life Questionnaire [34]. These were originally developed in cases of isolated chronic cough and correlate moderately well with objectively measured cough frequency in that context [35]. Correlation between subjective scores and characteristics of cough relating to infectiousness might be less for tuberculosis, owing to the influence of other symptoms that impact quality of life. However, one study has shown an association between patient-reported cough severity and rates of coincident household *M. tuberculosis* infection [36]. More data are needed. A lack of correlation between subjectively and objectively assessed cough severity would be of interest in tuberculosis as people with limited appreciation of high cough rates might transmit more disease because of delays in seeking medical treatment and continued social contact.

Temporal Patterns of Cough

Various features of cough have the potential for measurement, including coughing frequency and the force or intensity of cough. Several methods for recording cough activity have been used, but the cough monitors involved in most published studies in this area are based on ambulatory recordings of cough sounds [37, 38]. Because of digitalization and advances in recording techniques, devices are now small and portable enough to be worn during normal activities and can monitor cough sounds continuously for ≥48 hours. Counting coughs from audio recordings of patients by ear is the accepted standard for objectively determining cough frequency [39], but this method is labor intensive. A fully automated cough monitor that maintains performance across a range of patient and disease types and all background conditions does not yet exist. Two semiautomated cough monitoring systems, however, are becoming ever more refined by their developers [37, 38].

The effect of cough frequency on tuberculosis transmission appears to have been studied only once. In a Texas hospital in the 1960s Loudon and Spohn measured cough frequency between 11:00 PM and 7:00 AM in patients yet to initiate treatment for pulmonary tuberculosis [8]. These cough rates were compared to the tuberculin skin test results of 130 household contacts aged ≤14 years. They demonstrated only a small and statistically insignificant effect of nocturnal cough frequency on the infectiousness of untreated pulmonary tuberculosis; source case sputum smear status was a better predictor of the tuberculin skin test result in contacts. The main limitation of this study was the short duration of (overnight) cough recordings, owing to the technology available at the time. Cough in other diseases is more prevalent during the daytime [40], and this also seems to be the case for tuberculosis [41].

Recent developments in cough monitors should lead to further data on temporal patterns of cough in tuberculosis. For aerosolizing *M. tuberculosis*, it may not be only the overall frequency of cough that is important—other temporal characteristics, such as the extent of clustering of coughs into bouts, may also play a role. Coughs that are closely spaced may together be more efficient at moving material from distal airways and lung cavities.

Physical and Acoustic Characteristics of Coughs

The force of coughing, in terms of the velocity of chest wall movement, intrathoracic pressure changes, and resultant expiratory flows, is presumably important for the transmission of infection, as already discussed, and one study has associated subjectively assessed force of coughing with the production of culturable aerosols in tuberculosis [14]. However, we are aware of no study that has attempted to measure the intensity of force of normal involuntary coughs over a prolonged period in an ambulatory setting. This might be possible with electromyography, the measurement of esophageal pressures [42], or perhaps through inferences from acoustic properties of cough sounds.

Analysis of cough sounds has been performed with variable success in the ability to distinguish between diseases [43]. This does not appear to have been done specifically for tuberculosis. A cough can be split into 3 phases (Figure 1) corresponding to the opening of the vocal cords, the passage of air through them, and their subsequent reclosure [34]. Variation in the relative lengths of these phases or in the sound frequency components of each may be associated with the efficiency with which the respiratory tract acts as an atomizer of airway secretions.

Anatomical variation between individuals undoubtedly influences characteristics of cough. Thoracic volumes, relative airway calibers, and airway deformity are relevant for producing airflow forces high enough to overcome mucus viscosity and surface tension for aerosolizing secretions [9]. These characteristics will vary during disease, owing to the presence of edema, inflammation, and mucus. The shape of the oral cavity and position of the tongue and lips presumably also affect airflows, hydration of mucus, and the atomization of particles [15]. These factors appear to have been little studied in recent years [9].

Measures of Infectiousness

The direct measurement of the human-to-human transmission of tuberculosis is complex and a problem for research [4]. The guinea pig air-sampling model has been one of the most instructive methods of observing the release of *M. tuberculosis* into the environment by hospitalized source cases [11, 44], but it is complex and not adaptable to measuring transmission in the community. Because coincident cases of active tuberculosis are usually low in number, the method used by most

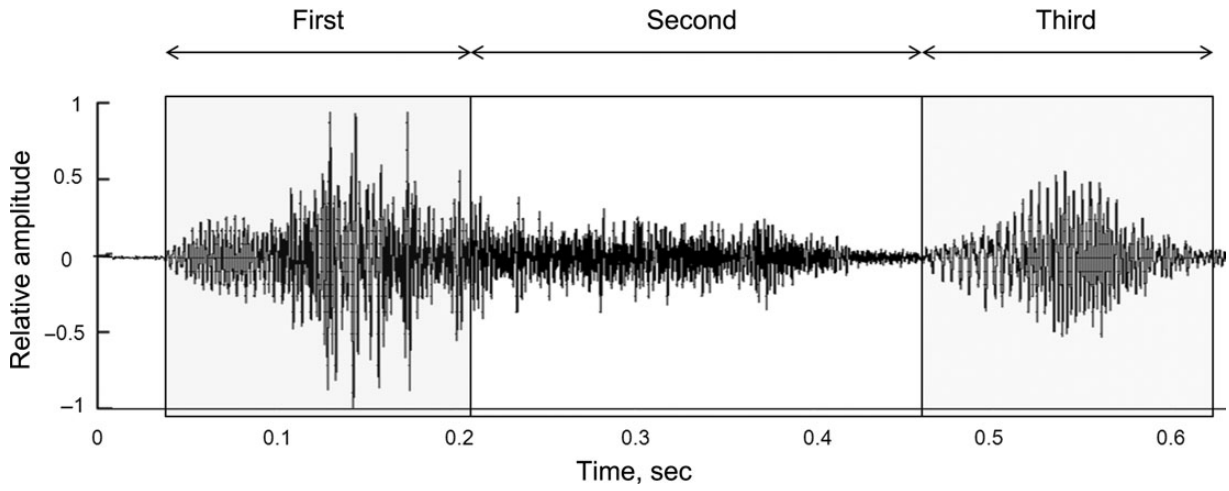

Figure 1. Phases of the cough sound, corresponding to opening of the vocal cords (first phase), air flow through the open larynx (second phase), and reopposition of the cords (third phase).

studies for transmission within a particular location is an estimation of overall tuberculosis exposure by tuberculin skin testing or interferon γ–release assay response. As well as limitations of these tests themselves, the other problem is the inability to confirm the origin of any presumed cases of latent *M. tuberculosis* infection.

A recently refined approach is the analysis of airborne particles produced by coughing. Fennelly et al have used an apparatus that selects expectorated particles in the airborne size range for mycobacterial culture [14, 45]. Fewer than 50% of individuals with sputum smear-positive pulmonary tuberculosis produced positive aerosol cultures, although a few had received treatment for several days [14]. *M. tuberculosis*–positive cultures of aerosol specimens from index cases were associated with higher rates of new household infection [45]. The technique could be useful to study host factors, cough variables, and particle characteristics associated with the aerosolization of viable bacteria. However, the apparatus is limited by the requirement of the patient to cough into a mouthpiece on demand. This may not reproduce usual airflow patterns created during involuntary normal coughs. Also, it only measures the potential for producing airborne *M. tuberculosis*; usual coughing frequency needs to be considered to illustrate what might happen in practice.

MODULATING COUGH

The definitive approach to treating cough and limiting new infection is treatment of the underlying cause [46, 47]. However, for several reasons it is often desirable to prevent, by other means, the release of aerosols produced during coughing: there may be a period of diagnostic doubt before definitive treatment is initiated, the minimum duration of treatment required to render an individual noninfectious is difficult to ascertain (although very recent data have revisited this [47]), and the selected treatment may not be effective, because of undiagnosed drug resistance. Possibilities for limiting the release of infectious aerosols include cough hygiene measures, the use of masks, modulation of characteristics of airway mucus, and antitussive treatment.

At one time the widest application of cough-suppressant medication was probably for symptom relief in tuberculosis [22]. Acute cough due to upper respiratory tract infection or chronic cough, explained or unexplained by secondary respiratory diseases, are now the usual indications for antitussives. Currently used drugs include dextromethorphan and codeine. However, good-quality evidence for their efficacy is limited, and side effects restrict the use of morphine, probably the most effective cough suppressant [48]. Further understanding of the mechanisms of the cough reflex and developments in measuring cough frequency should lead to the development of much-needed new agents [22].

We are aware of no attempts to pharmacologically alter the cohesiveness of mucus to reduce its ability to form airborne particles. Although masks and cough hygiene measures are widely used to protect the environment from individuals with transmissible respiratory disease, there are surprisingly few data directly demonstrating their efficacy. Covering the mouth with a hand, tissue, or sleeve diverts rather than stops airflow from the mouth while coughing [49] and may not limit the release of smaller particles into the environment [50]. The same probably applies for surgical face masks [50]. However, Dharmadhikari et al demonstrated convincingly that surgical masks worn by inpatients with multidrug-resistant tuberculosis reduced the likelihood of new infection in guinea pigs exposed to the ward air [44]. Masks, and perhaps other physical barriers, must therefore prevent tuberculosis transmission by blocking larger droplets, particularly those moving at high speeds with greater inertia, which would otherwise normally shrink in ambient air with evaporation to produce infectious airborne droplet nuclei [2, 12].

CONCLUSION

Coughing is advantageous to *M. tuberculosis* as a means of spreading to new hosts. It is possible that the cough reflex in tuberculosis is triggered more frequently than is physiologically required for protecting and clearing the airway. Human tuberculosis has probably existed for >70 000 years. Over this period of coevolution between *M. tuberculosis* and its host, mechanisms may have arisen through which the pathogen provokes cough for promoting the aerosolization of infectious particles with the ability to survive transit through the environment for reaching new hosts. The exact nature of these mechanisms, the patterns and types of cough that most efficiently aerosolize airway secretions, and the optimum composition of airborne particles for the transmission of disease are poorly defined. A broader understanding of cough from preclinical and clinical studies, the wider measurement of temporal patterns of cough with cough monitors, a better appreciation of the relationship between objective and subjective severity of coughs, and the study of the aerosolization of respiratory secretions should lead to important advances in knowledge of the role of cough in the transmission of tuberculosis. This should allow easier identification of superspreaders and the development of specific interventions to help limit the dissemination of the disease, particularly if antituberculous treatment is ineffective due to drug resistance. Studying cough and disease transmission in tuberculosis, the archetypal airborne disease, would also serve as a model for cough in other infectious diseases in which airborne transmission occurs but is less important [2].

Note

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

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