Tuberculosis Transmission—Rogue Pathogen or Rogue Patient?

In spite of dramatic successes in the implementation of directly observed therapy and a virtually uninterrupted decline in the incidence of tuberculosis in developed countries, outbreaks or "microepidemics" of tuberculosis continue to frustrate even the most ardent tuberculosis control programs. With the renewed attention to tuberculosis, numerous studies have focused on the nature of these microepidemics. Despite the availability of new tools such as DNA fingerprinting, social network analysis, and geographic information system mapping, these outbreaks are difficult to trace and extinguish. The secret to success lies—as it has for half a century—in the traditional contact investigation and old-fashioned shoe leather epidemiology. A frequent theme is initiation and spread among the disenfranchised with risk factors being poverty, homelessness, substance abuse, human immunodeficiency virus (HIV), and alcoholism. Most analyses have focused on urban centers in industrialized countries and comprehensive investigation of microepidemics (i.e., identification of the first and last cases) is frequently confounded by migration to and from these urban centers.

Restriction fragment length polymorphism (RFLP) typing has been useful in chronicling several spectacular microepidemics of tuberculosis. For example, in 1994–1996 an outbreak that took place in a community on the Kentucky–Tennessee border and that was associated with a single factory worker resulted in 21 active cases and 311 tuberculin reactors from a strain known as CDC1551 (1). Other outbreaks have been associated with bars, rooming houses, prisons, and homosexual social networks.

In this issue of *AJRCCM* (pp. 1165–1170), Caminero and coworkers report on a microepidemic of tuberculosis in the Canary Islands from 1993 to 1996 (2). The report includes several new and provocative twists. First, the island of Gran Canaria is a western European community with relatively restricted population migration, hence differentiating it from continental cities. Second, the initiation of the microepidemic can be pinpointed to the arrival of a single Liberian refugee in 1993 who subsequently spawned 75 new cases of tuberculosis and accounted for 27.1% of all RFLP-typed strains in 1996 on Gran Canaria. The particular isolate imported by the Liberian refugee has been shown rather definitively to have been absent from the island in surveys in 1991 to 1992. And an extensive contact investigation resulted in 68% of the RFLP types from this cluster being linked epidemiologically. The strain imported by the refugee showed extensive similarities to an isolate known as the "Beijing" strain. While the Liberian refugee was known to be poorly compliant and to have laryngeal tuberculosis as well as cavitary pulmonary disease, the authors also point out that this strain has demonstrated an impressive degree of worldwide proliferation.

These results prompt the question of where to place blame for microepidemics—the host or the pathogen? Are such outbreaks due to biological host factors (location and type of disease) coupled with social host factors such as homelessness and substance abuse? Or could it be that certain *M. tuberculosis* strains, such as the Beijing strain, have unique traits that differentiate them from garden variety isolates? The issues implicit in these questions go well beyond epidemiologic curiosity and touch on fundamental properties of the pathogenesis, evolution, and future perpetuation of tuberculosis.

The question is now being considered from a new angle, namely genomics. On the pathogen side, we now have a base-by-base comparison between an outbreak strain, CDC1551, and a classic type strain, H37Rv (3, 4). Although there has been controversy over whether CDC1551 is more virulent in animals than other type strains, alterations in the cytokine profile elicited by CDC1551 in comparison with other laboratory strains have been observed (5–7). The genome sequence of CDC1551 now available on the web, however, fails to identify a genetic smoking gun to explain the extent of the Kentucky–Tennessee outbreak. Comparison of the two sequences reveals about 40 insertions unique to CDC1551, about 35 insertions unique to H37Rv, and slightly more than 1,000 single nucleotide polymorphisms (SNPs); a disproportionate amount of the variation occurred in a few hot spots that encode hypothetical proteins with no clear-cut function. Although the CDC1551 strain may be hypertransmissible, the genetic basis for the human outbreak remains elusive, and we are left with the possibility that perhaps the index factory worker may have been an unusually good disseminator (a host attribute) or have had undiagnosed laryngeal TB.

A second genomic approach is to use microarrays to probe the bacterial chromosome for deletions that may correlate with disease pattern. While expensive, it is possible to survey clinical isolates by microarray genotyping in much the same way that traditional RFLP DNA fingerprinting is conducted. In a study using a 118,180 spot *M. tuberculosis* oligonucleotide-based microarray, Salamon and coworkers identified a correlation between the number of genetic deletions and the risk for cavitary tuberculosis among residents of San Francisco (8). Similarly, a Houston outbreak strain known as HN878 associated with hypervirulence elicits altered cytokine profiles in murine tuberculosis compared with standard strains (9), and the possibility of altered lipid antigens in this strain is being explored. The results suggest that bacterial genotype may predict disease phenotype.

Skeptics, however, point to human and mouse polymorphisms associated with susceptibility to tuberculosis (10, 11). They also point out that as a recently emerged pathogen with limited time to develop an extensive repertoire of genetic polymorphism, *M. tuberculosis* is unlikely to vary in its ability to be transmitted (12). After all, it is a microorganism that essentially does not inhabit ecologic niches other than the human body; if there were hypertransmissible strains, why are there so many different DNA fingerprint types of *M. tuberculosis*? Last, seasoned tuberculosis control experts know clearly that risk of transmission is proportional to burden of cavitary disease and is dramatically amplified by the presence of laryngeal disease. Perhaps we place too much blame on the bug, when in fact TB transmission could be directly proportional to macroscopic host variables such as extensive laryngeal or endobronchial disease, which may strictly predict the quantity of bacilli expelled for potential transmission.

The answer to this important question of whether host versus pathogen is the responsible agent for microepidemics may come, not from genomics, but rather from a reinvestigation of animal models. In view of the great difficulty of monitoring tuberculosis transmission among humans, future research efforts might be well advised to focus on animal models of transmission. Many new disciplines have been recruited to the growing tuberculosis research program, whereas aerobiology and quantitative studies of infectivity of exhaled aerosols have remained relatively neglected. Programs to revisit tuberculosis transmission in higher animals (beyond mice and guinea pigs, which do not transmit tuberculosis readily) offer promising avenues for

further research. Quantitative studies of disease in animals that develop cavitary, transmissible TB may be key in determining whether the host or the pathogen plays the rogue in TB transmission.

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