is known, how much do isolates vary between patients? Fourth, can patients be ruled in or ruled out as part of community outbreaks with thresholds of variation and how often do patterns suggest super-spreading?

The results are fascinating. Within-host diversity—both cross-sectional and longitudinal—was typically less than five single nucleotide polymorphisms per patient, which perhaps indicates that M tuberculosis had achieved a local fitness maximum. Overall, 109 (96%) of 114 paired isolates from individuals and households were separated by five or fewer mutations. This threshold can be used to rule in community isolates as belonging to a specific outbreak cluster. A threshold of greater than 12 single nucleotide polymorphisms was used to rule out isolates as belonging to a cluster, allowing the researchers to refine clusters previously defined on the basis of genotyping alone. Further investigation provided evidence for super-spreading in two of the 11 community clusters, suggesting that it is a common mode of transmission in this setting. The investigators were also able to identify instances of reactivation of latent infection leading to clusters that could have been avoided with prophylaxis of latent infection in the source case.

The work of Walker and colleagues provides an important quantification of how genomic data can be used in investigations of tuberculosis outbreaks that will prove invaluable to future analyses, allowing modern day John Snows to map transmission and devise locally appropriate interventions. Further similarly comprehensive studies are now needed in various settings to establish whether there are any so-called universal truths about tuberculosis transmission, and whether genomics can differentiate between reactivation and recent transmission. This knowledge will be crucial to establishing evidence-based control and prevention programmes applicable worldwide and moving the global health community one step closer to the ambitious goal of stopping tuberculosis.

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infrequently reported, dropout rates of up to 37% have been documented. The benefit of examination of three rather than two sputum specimens was noted to be small, and collection of two sputum samples in a day was subsequently reported to be of equivalent diagnostic accuracy to the collection of two samples on separate days. Davis and colleagues did not report evidence of any significant difference in sensitivity or specificity between front-loaded and standard microscopy strategies for those involving two or three sputum smears. Findings were consistent across several study sites, suggesting that they are probably very generalisable.

That the inclusion of a morning sputum specimen in the diagnostic pathway might not be necessary is controversial. Morning specimens have repeatedly shown greater bacillary load and higher sensitivity than have spot samples. Nevertheless, Davis and colleagues’ report challenges this idea. In a study by Cuevas and colleagues, spot specimens were more likely to have low smear grades than were morning specimens. However, the sensitivity of a spot-spot compared with a spot-morning scheme was non-inferior. When the proportion of patients correctly identified with these two schemes was modelled, no significant difference was noted. The reasons for this discrepancy need to be clarified. One probable factor is the use of WHO’s revised definition, classifying smears with at least one acid-fast bacilli as positive in more recent publications. Crucially, high specificity seems to be preserved, suggesting that this change in definition was appropriate.

Even under the best conditions, smear microscopy has substantial limitations: sensitivity is low and drug resistance is not detected. Rollout of same-day molecular tests such as Genotype MTBDRplus (Hain Lifescience, Nehren, Germany) or Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) will address these restrictions. These tests generate results within hours, and with provision of same-day microscopy, assessment of two sputum smears plus molecular testing within one visit will be possible.

However, at present most patients with tuberculosis have access to only smear microscopy. In 2010, of 36 countries with the greatest burden of tuberculosis and multidrug-resistant tuberculosis, 20 had less than one laboratory capable of doing culture for every 5 million people. More than 80% of the estimated 8·8 million people with incident tuberculosis live in high-burden countries. We estimate that less than 10% of patients with tuberculosis in low-resource settings had their disease proven with culture or molecular biology approaches. Therefore, assuming a conservative estimate of 20% default, more than 1·5 million people will have a missed or delayed diagnosis every year. In view of the vast numbers of patients involved, incremental improvements in smear microscopy will lead to substantial increases in the numbers of patients detected at little or no cost.

However, such improvements will only lead to improved clinical outcomes if accompanied by immediate communication of results and same-day initiation of treatment, together with broader interventions to strengthen health systems. These measures will also be useful once molecular diagnostics are widely available, because the principle of same-day treatment will be equally relevant.

Worries about nosocomial transmission resulting from increased waiting time will need to be addressed. Measures such as outdoor waiting areas and maximisation of natural ventilation are inexpensive and effective. Cattamanchi and colleagues’ findings of non-inferiority when a second smear was prepared from the same sputum sample rather than from a second sample are of particular interest because this approach might reduce the length of time patients spend in the clinic. Davies and colleagues’ report suggests that repeated visits to the clinic are not necessary. It provides evidence for a major shift in the way tuberculosis programmes sequence sputum-smear examinations, and thus reduce rates of patient default and minimise delays in the start of treatment. The authors should be commended because they returned to examination of sputum smears, which is a neglected basic cornerstone of tuberculosis diagnosis. Further assessment of the accuracy of same-day microscopy in HIV-positive patients, the accuracy of single-specimen examinations, and the effect of a 1 day strategy on treatment completion is needed to clarify how to best use this basic but indispensable test.

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An epidemiological view of microbial genomic data

Mark Achtman devised the acronym YATM for “yet another typing method” when assessing the huge growth in the number of approaches to classifying different microbe strains. This increase was triggered by both new technologies and by the tendency for new typing schemes to be developed for each new question. Achtman concluded that the contribution of these fragmented activities to scientific progress was low. By contrast, the scope for convergence of complementary disciplines, such as microbial evolution and epidemiology, has been described along with the capacity for this convergence to support basic scientific progress and its translation into public health benefits. Examples of this productive convergence include population genetic evolutionary analysis of whole-genome bacterial data to address epidemiological problems; and extensive databases of HIV sequences (originally collected to clinically monitor drug susceptibility), which can be used for estimation of key HIV transmission parameters and for hypotheses about the nature of the HIV transmission network.

Researchers are now able to sequence the genomes of many bacteria, and can do so rapidly in response to specific public health problems. This achievement is accompanied by improvements in bioinformatics and population genetics methods supporting the analysis of large genomic datasets. These developments, combined with other epidemiological data that describe the temporal and spatial dynamics of infection, reinforce models of evolutionary ancestry in epidemiological analysis and enable mapping of complex transmission pathways. Two further studies integrating genomic and other epidemiological data are published in the current issue.

Analysis of the genetic diversity generated by non-phylogenetic population genetic processes has shown that imported genes can provide epidemiologically useful information, such as a history of the host species in which an isolate’s ancestors lived. The public health application of this information is improved knowledge about the original host species of these zoonotic human infections. Thus, the increasing capacity for pathogen genome sequencing and the associated new technologies create potential for a new era of data sharing, analytical convergence across countries and disciplines, and scientific and public health benefits. However, the risk of data-rich chaos also exists, which could occur after a fragmenting YATM-type approach to the generation, storage, analysis, and presentation of genomic data. The need for leadership to ensure data are comparable and accessible to maximize public health and scientific benefits is being investigated.

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