Universal regimens or universal access to drug susceptibility testing for tuberculosis?

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A universal regimen. At times this appears to be the Holy Grail in tuberculosis treatment.[1] For decades, policy makers, public health specialists, and donors have argued that in order to control—and these days to "End TB"—a simplified approach that offers everyone the same regimen is our best bet.[2] They argue that countries, programmes, and the people who work in them, are incapable of managing complexity when it comes to tackling tuberculosis.[3] Fears abound that recommending anything other than a basic treatment algorithm will lead to mismanagement and a tuberculosis crisis worse that what we see now.[4] Never mind that such an approach erases patient individuality and unique human treatment needs.[5] "Keep it simple" remains the mantra in tuberculosis control to this day.

How has this strategy—focused on uniform care for all people affected by *Mycobacterium tuberculosis*—worked out? The numbers are telling. According to WHO, an estimated 10 million people became newly sick with tuberculosis in 2017, of whom 1·3 million died. Tuberculosis is one of the top ten causes of mortality globally and the leading infectious cause of deaths worldwide.[6] If current trends continue, it is estimated that tuberculosis will be responsible for more deaths due to antimicrobial resistance than any other single pathogen.[7] Our efforts to tackle tuberculosis are failing, and the reasons for this are complex. Inadequate access to effective diagnosis, however, is a singularly difficult challenge, as seen in the 4 million so-called missing cases of tuberculosis that occur each year: only 24% of newly diagnosed and 70% of previously treated patients had access to any form of drug susceptibility testing in 2017.[6]

The article by Kathrin Zürcher and colleagues[8] in *The Lancet Infectious Diseases* shows the importance not only of drug susceptibility testing but also of getting the results of such testing right. In their study, looking at mortality among people with tuberculosis living in various settings, the investigators compared phenotypic or genotypic drug susceptibility test results obtained from national laboratories with results of testing obtained from the same *M tuberculosis* strains done at a reference laboratory in Switzerland.

Discordant results were found between the two laboratories in about 20% of the specimens assessed. The study found surprisingly high mortality rates among individuals with all forms of tuberculosis, ranging from 6% (17 of 302) among those with fully drug susceptible strains concordant on testing to 44% (eight of 18) among patients with strains resistant to isoniazid, rifampicin, and either a fluoroquinolone, an injectable agent, or both. Of concern, people with isoniazid monoresistant tuberculosis—the most common form of drug-resistant tuberculosis globally—had higher mortality rates (seven [30%] of 23) than did those with rifampin-resistant tuberculosis (two [14%] of 14), although this difference was not significant (p=0·38). When under-treatment of the drug-resistant strains was taken into account, the mortality rate increased to 57%. More than half of people with misdiagnosed drug resistant tuberculosis who received inadequate therapy died of their disease.

This study has several potential limitations, including the exclusion of almost one out of four participants because of incomplete data, the small number of drugs tested at the reference laboratory, and the possible presence of multiple subpopulations of *M tuberculosis* in a single sample. Nevertheless, the results point to the crucial importance of accurate drug susceptibility testing to guide optimal treatment of people with tuberculosis. Critics of drug susceptibility testing might argue that the poor quality of the drug susceptibility tests reported in the study is reason enough to do away with this approach.[9] However, poor quality drug susceptibility testing is probably a result of the global community's refusal to invest in this technology while hoping that an almost mythical combination of drugs will save the day. The new WHO rifampicin-resistant tuberculosis recommendations emphasise the importance of drug susceptibility testing in guiding all treatment decisions.[10] Now the global community must desperately scramble to achieve this because of a past refusal to commit to this essential tuberculosis service.

If we are serious about ending tuberculosis, we need to do things differently. And this means simplicity cannot

be the goal. Rather, we need to offer everyone access to the best diagnostic services possible—including high-quality drug susceptibility testing—and treat them with individualised regimens containing the strongest and safest drugs to which their strains are susceptible and avoiding drugs to which there is resistance. Wishful thinking about a scenario in which drug susceptibility testing is not necessary for tuberculosis treatment has no place in the modern approach to tuberculosis. Universal access to drug susceptibility testing will, no doubt, require substantial work, but we must commit ourselves fully to achieving this goal. As the study by Zürcher and colleagues shows, people's lives depend upon it.

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Unrecognised Ebola virus infection in contact persons: what can we learn from it?

The epidemic of Ebola virus disease in west Africa in 2014–16 was the largest and most complex the world has ever seen. The four pillars of Ebola response include: case management, case finding and contact tracing, safe and dignified burial, and social mobilisation and community engagement. These four pillars are being implemented in the current outbreak in the Democratic Republic of the Congo (DRC), which is further complicated by its location in a conflict zone.[1] Increased understanding of disease pathogenesis and the evaluation of novel therapeutics and vaccine candidates has informed current control measures, while access to survivors and their contacts in west Africa has also provided a unique opportunity to research filovirus transmission.

In *The Lancet Infectious Diseases*, Mamadou Diallo and colleagues[2] report data from a large cross-sectional study of contact persons of an established survivor cohort in Guinea. They aimed to estimate the frequency of unrecognised Ebola virus infection in contact persons after excluding individuals who were vaccinated, and to identify risk factors for infection. Using a novel and previously validated Luminex assay[3] on dried blood spots and detailed retrospective exposure histories, they identified 57 Ebola virus infections among 1390 contact persons.

The authors showed increased seropositivity in contact persons who reported any symptom associated with Ebola virus disease (8·33%, 95% CI 5·01–12·80, described as paucisymptomatic contact persons) compared with Ebola virus infection in asymptomatic contact persons (3·32%, 95% CI 2·37–4·51; p=0·0002). Participation in burial rituals and contact with blood or vomit were independent significant risk factors for Ebola virus infection in asymptomatic contact persons in multivariate analysis, while older age and participation in burial practices were risk factors in paucisymptomatic individuals. Their findings concur with a recent meta-analysis of seroprevalence surveys[4] and the results of a study in Sierra Leone of 486 household members of Ebola virus disease survivors, which identified Ebola virus infection in


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