Methods: We analysed data on drug resistance among new and previously treated TB cases reported by countries to WHO up to 2012. Data are collected in surveys of a representative sample of TB patients or from surveillance systems in which diagnostic drug susceptibility testing is routine practice, and quality-assured by the Supranational TB Reference Laboratory Network.

Findings: In 1994–2012, surveillance data on MDR-TB were reported from 136 countries worldwide. Global proportions of new and previously treated TB cases with MDR-TB were 3.6% (95% CI: 2.1–5.1) and 20.2% (95% CI: 13.3–27.2), respectively. The highest proportions are found in countries of the former Soviet Union (FSU), where in several countries more than 20% of new cases and more than 50% of previously treated cases have MDR-TB. Estimated MDR-TB incidence rates (MDR-TB cases per 100,000 population) are highest in FSU countries and in southern Africa. Extensively drug-resistant TB (XDR-TB) has been reported by 92 countries. On average, an estimated 9.6% (95% CI: 8.1%–11%) of MDR-TB cases have XDR-TB. A significant positive association between HIV and MDR-TB has been shown in 12 countries. Between 1994 and 2012, data on time trends in drug resistance were available from 88 countries and 10 territories worldwide for a total of 870 country-year data points. Rates of MDR-TB in the general population increased in Botswana, United Kingdom, and in Oblasts of the Russian Federation and declined in Latvia, Estonia, and the United States of America.

Conclusion: Better data from continuous surveillance or surveys are required, especially from Africa and India. Trends in MDR-TB are still unclear in most settings. Surveys should be repeated more frequently using molecular technologies to monitor the MDR-TB epidemic more effectively.

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Type: Invited Presentation

New developments in rapid diagnostics for drug resistant tuberculosis

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There has been considerable recent advance in the development of rapid tests for diagnosis of drug-resistant tuberculosis. These advances are primarily due to a fundamental change from a phenotypic to genotypic approach to testing. The two most commonly used genotypic tests for resistance to first-line drugs are line probe assays and Xpert MTB/RIF. Line probe assays detect resistance to rifampicin and isoniazid in cultured isolates of M. tuberculosis, as well as directly in smear-positive (and possibly smear-negative) sputum specimens. These assays are highly sensitive and specific for detection of resistance to rifampicin, but less sensitive for detection of isoniazid resistance. Xpert MTB/RIF may be used for immediate, direct detection of rifampicin resistant M. tuberculosis in sputum specimens, including the majority of smear-negative specimens. Early reports showed high sensitivity and specificity for detection of resistance, however the predictive value of this assay for resistance may be impaired in patients at low risk for rifampicin-resistant tuberculosis. More recent assay versions appear to have substantially improved specificity. After rifampicin-resistant tuberculosis is detected by one of these initial tests, there is a need to rapidly determine susceptibility to second-line drugs. At present, there are no highly accurate genotypic tests for prediction of resistance, and prolonged culture-based phenotypic testing is required. A line probe assay for detection of resistance to fluoroquinolones, injectables and ethambutol in smear-positive sputum specimens is available; however there is geographic variation in the distribution of different resistance mutations and lack of predictable cross-resistance to different drugs in a class. This assay is therefore specific for detection of XDR-TB, but lacks sensitivity. New developments in the field include highly multiplexed real-time PCR tests for detection of resistance and the use of whole genome sequencing for broad detection of resistance mutations. The field is, at present, limited by incomplete understanding of genotype-phenotype relationships and by the need for robust bioinformatics pipelines to facilitate sequence analysis and infer resistance patterns from sequence data.

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Newer and novel insights into the pathogenesis and treatment of drug-resistant tuberculosis

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Drug-resistant tuberculosis (MDR and XDR-TB) is a burgeoning global health crisis with a high mortality irrespective of HIV-status. In South Africa, despite comprising less than 3% of the total caseload, DR-TB consumes almost half of the total national TB management budget - this is unsustainable and threatens to destabilise national TB programs. MDR-TB has been eclipsed by the spectre of resistance beyond XDR-TB (totally drug-resistant TB [TDR-TB] and XXDR-TB) i.e. resistance to all or nearly all conventionally used first and second line TB drugs. Given the limited availability of new drugs in a TB endemic setting, their preferred use in newer first line regimens, the finite nature of the drug pipeline, and the likely rapid evolution of drug-resistance, alternative or adjunctive therapeutic options are urgently needed. The traditional view is that drug-resistance arises because of non-adherence or pharmacokinetic mismatch resulting in killing of susceptible populations but overgrowth of resistant ones. However, several new concepts have challenged this understanding, including within person PK variability, induction of efflux pumps, immunopathology-driven intrapulmonary drug gradients, pathogen-related factors, including compensatory mutations which impact fitness cost and physiological pathways, and recognition of “super-spreaders” that transmit the majority of disease. Several new drugs have also emerged for the potential treatment of drug-resistant TB. Those already in clinical use or likely to be imminently available will be briefly discussed including bedaquiline, delamanid, and linezolid. Finally, given the serious mortality and limited therapeutic options in highly resistant strains the utility of novel immunotherapeutic approaches are briefly discussed.

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