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EDITORIAL

Drug Resistant Tuberculosis

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The emergence of antimicrobial resistance against Mycobacterium tuberculosis, the leading cause of mortality due to a single microbial pathogen worldwide, represents a growing threat to public health and economic growth. The global burden of multidrug-resistant tuberculosis (MDR-TB) has recently increased by an annual rate of more than 20%. Tuberculosis (TB) is the leading cause of death attributed to a single microorganism worldwide. Without combatting antimicrobial resistance in Mycobacterium tuberculosis, the causative microorganism of this disease, achieving the goals of the End TB strategy of the World Health Organization (WHO) will not be possible.[1] The leaders of the G20 nations have recently highlighted that antimicrobial resistance represents a growing threat to public health and economic growth worldwide and that fostering research and development against TB, among other pathogens and diseases, should be an international priority.[2] Between 2009 and 2016, numbers of patients identified with MDR-TB, defined by resistance of M. tuberculosis against at least rifampicin and isoniazid, increased annually by over 20%.[3,4] Estimated numbers of MDR-TB increased in the same period from 250 000 to 490 000, partly also due to improvements in rapid diagnostics and molecular or phenotypic drug susceptibility testing (DST). In 2016, 8014 patients in 72 countries were identified with extensively drug-resistant TB (XDR-TB),[3] defined as MDR-TB plus resistance to at least one fluoroquinolone and a second-line injectable agent (amikacin, capreomycin or kanamycin). Actual numbers of patients with XDR-TB are likely much higher. Mathematical modelling predicts an increase in MDR-TB among incident TB cases and XDR-TB among incident MDR-TB patients in high-burden countries in the forthcoming decades.[5] More than 50% of recurrent TB in Europe were MDR-TB or XDR-TB. Only 54% of patients with MDR-TB and 30% of patients with XDR-TB completed treatment successfully according to the latest WHO report[3]; probably fewer were actually cured based on WHO definitions. Death rates from MDR-TB and XDR-TB are 16% and 28%, respectively, but the real rates are likely twice these estimates if one takes into account mortality in those lost to follow-up. Some patients with M/XDR-TB treatment failure may survive for many months and pose an ongoing threat of transmission of drug-resistant M. tuberculosis.[6] Despite these grim figures, dramatic improvements in the treatment outcomes have been reported for M/XDR-TB, where resources for novel diagnostics and medicines are available to individualize treatment regimens.[7,8].

The global burden of MDR-TB

Annually, the WHO estimates that of the approximately 600 000 newly emerging MDR-TB or rifampicin resistant TB (RR-TB) cases, only one fourth are detected and notified.[3] Assessments relying on the disease prevalence suggest a 16% and 80% higher frequency among estimated and notified MDR-TB patients.[9] Between 2015 and 2016, the number of reported MDR/RR-TB increased by more than 30% in 9 of the 30 high MDR-TB burden countries.[3] The geographical distribution of MDR-TB is highly variable, consisting of several hot spots in low- and middle-income countries, from Eastern Europe to Asia. In 2016, the largest number of MDR/RR-TB was reported from the European Region (49 442), followed by South East Asia (46 269).[3] In the Western Pacific region, 21 252 cases of MDR/RR-TB were notified. The highest relative burden for a single country is reported from Belarus, where 38% of new cases and 72% of retreatment cases are estimated to have MDR/RR-TB.[3] Currently, not more than one third of bacteriologically confirmed TB cases are evaluated with DST for first-line drugs and only 36% of MDR-TB patients benefit from DST for second-line drugs.[3] Similarly, not more than 20% of MDR-TB cases have access to MDR-TB

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treatment.[9,10] In a world challenged by unprecedented travel and migration, it is likely that the global MDR-TB map will undergo significant changes, leaving no country unaffected.

Key control considerations

Epidemiological and social perspectives Selection pressure from inappropriate clinical use of TB drugs accounts for initial emergence of drug resistance.[11] However, more recent molecular epidemiological data suggest that ongoing transmission of MDR- and XDR-strains is the dominant mode of spread in many endemic countries.[12,13] As clinical diseases only represent a small fraction of total infections, endogenous reactivation from the much larger latent pool of infection will continue to generate more drug resistant infectious sources in next few decades.[14] The TB epidemic in recent human history occurred in close temporal association with rapid industrialization, urbanization, poverty, poor nutrition and poor living condition.[15] These social determinants are associated with multiple downstream risk factors, affecting not only TB risk, but also access and adherence to appropriate treatment, often leading to programmatic failure that breeds drug resistance.[16] While interventions on many of these upstream social determinants require strong government commitments, international collaboration and sustainable economic development, they, together with collaboration among programmes on TB, HIV, smoking and diabetes mellitus, are expected to work equally for drug-susceptible and drug-resistant TB.[3,16] Programmatic perspective With the currently available tools, case ûnding followed by effective chemotherapy remains the primary strategy for controlling TB.[17] Early modelling exercises by Karel Styblo suggested a need for achieving 70% case detection and 85% treatment success to reduce TB burden progressively.[17] Endogenous reactivation of remote infection may further retard the decline.[18] To ensure programme sustainability, emergence of drug resistance must not be allowed to outpace new drug development. Recent in vitro hollow fibre experiments failed to demonstrate progressive acquisition of resistance by irregular drug exposure to a combination regimen.[19] However, such experiments did not incorporate the and social perspectives Selection pressure from inappropriate clinical use ofintrinsic pharmacokinetic variabilities[20] and bacillary heterogeneity within complex lesions of the human host,[13] which could add to or magnify the effects of treatment non-adherence. Clinically, emergence of drug resistance has been well associated with intermittent treatment in HIV-infected patients.[21] Nonadherence necessarily reduces effective treatment duration, and insufûcient duration of treatment has consistently been associated with poorer outcome.[22]

Improving diagnosis

In recent years, programmatic implementation of molecular tests worldwide has dramatically reduced the time to TB diagnosis.[23-26] These tests can be applied to various biological samples (sputum, cerebrospinal fiuid, pleural fiuid, urine, blood, stool).[27] Nucleic acid amplification tests (NAATs) also enable the prediction of resistance to important first- and second-line drugs on the basis of resistance-conferring mutations.[28]

Shorter MDR-TB regimen

In 2016, the WHO published new treatment guidelines for drug-resistant TB and reclassified the drugs recommended to treat MDR/RR-TB into groups from A to D (A=fluoroquinolones; B=second-line injectable drugs; C=other core second-line agents; D 1-3 = addon agents).[29] The previous 2011 guidelines conditionally recommended an intensive phase of 8 months for most MDR-TB patients and total treatment duration of 20 months in patients who had not been previously treated.[30] In 2010, Van Deun et al[31] reported an overall success rate of 87.9% in the treatment of a cohort of 206 MDR-TB patients who had never received second line drugs in Bangladesh, using a standardized regimen of 9-12 months at a fraction of the cost of traditional regimens (only 225/course). This regimen was subsequently tested in 507 adult MDR-TB patients in 9 African countries with similar, promising outcomes.[32] This led, in May 2016, to the WHO's conditional recommendation of this shorter regimen of 9-12 months for patients with pulmonary MDR-TB under programmatic conditions.[33] The regimen, which has since been used in 23 countries with notable success, consists of 4-6 months of a later generation fluoroquinolone, kanamycin, prothionamide, high-dose isoniazid, clofazimine, pyrazinamide and ethambutol, followed by 5 months of the fluoroquinolone, clofazimine, pyrazinamide and ethambutol alone.

Novel treatment regimens

The results of two early bactericidal activity (EBA) studies provided evidence that the newly developed antituberculosis compounds bedaquiline[34] and delamanid[35] have antimycobacterial activity in humans. Subsequently, the results of a phase 2(b) clinical trial with optimized backbone MDR-TB regimens and either bedaquiline or placebo documented significantly higher relapse-free cure rates in the bedaquiline arm (58% vs 32% in the placebo arm).[36]

Conclusion

Molecular methods for early detection of drug resistance are available in most parts of the world. Still, the link between potential resistance-conferring mutations and the corresponding minimal inhibitory concentration (MIC) is essential to fully rely on molecular tests in clinical routine. With the emergence of new drugs and novel diagnostic methods, including active case finding strategies, we have an opportunity to reduce the global burden of MDR-TB substantially. By practicing good antibiotic stewardship, including personalizing the treatment of patients with MDR-TB, we will leverage this window of opportunity to the fullest.

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