Carpe diem (‘Seize the day’): Building on the findings of the 2015 World Health Organization evaluation of the multidrug-resistant tuberculosis (MDR-TB) programme to make the most of shortened MDR-TB treatment in South Africa

South Africa (SA) has a high burden of multidrug-resistant tuberculosis (MDR-TB), i.e. TB resistant to isoniazid and rifampicin, the most effective TB drugs. The current MDR-TB regimen requires the use of multiple, toxic, poorly efficacious and expensive second-line drugs for 18 - 24 months. As a consequence of the often severe side-effects and lengthy unpleasant treatment, adherence is poor and failure to complete treatment common. Overall, treatment is successful in only half the patients treated.

Until 2008 SA, together with many countries in the world, adopted an inpatient model of care in which patients were hospitalised for the initial 6-month injectable phase of treatment in a centralised specialised hospital to facilitate daily injections and allow close monitoring of adverse events and adherence. Following discharge, for the remaining treatment period (18 months) patients were expected to return to the centralised hospital for monthly outpatient visits. However, by 2008 the escalating burden of MDR-TB and limited bed capacity resulted in long waiting lists, high mortality while patients waited to access treatment, and nosocomial transmission.

Furthermore, as the facilities to which patients were discharged were unfamiliar with MDR-TB management, continuity of care was poor and many patients were lost to follow-up.

To address these problems, alternative models of care for MDR-TB patients were introduced and in August 2011 a policy framework on decentralised and deinstitutionalised management of MDR-TB was launched by the National Department of Health (NDoH). In late 2015, the World Health Organization (WHO) led a review to assess the performance and outcomes of the MDR-TB programme and the implementation of alternative models of care. The review applauded recent efforts by the NDoH to address the TB and MDR-TB burden in SA, but also highlighted areas in which MDR-TB programme performance could be improved.

For the first time in the modern history of TB control, a shortened regimen and new drugs have been become available for the treatment of MDR-TB. These advances have revived hope for improved patient outcomes and for stopping ongoing transmission of MDR-TB. In 2013, the WHO recommended the use of a new drug, bedaquiline, for MDR-TB, followed by a similar recommendation in 2014 for the use of delamanid and clofazimine is being encouraged. These new drugs are primarily reserved for MDR-TB patients who have additional resistance to second-line drugs or respond poorly to the current treatment regimen. However, treatment outcomes are also poor for MDR-TB patients without second-line resistance. For these patients, hope comes in the form of a shortened standardised treatment regimen, conditionally recommended by the WHO in May 2016. Subsequently, the NDoH announced that this shorter 9 - 12-month regimen using existing drugs and repurposed clofazimine will be available in SA in the first half of 2017.

Given concern about the development of resistance to new drugs and logistical issues in the introduction of new regimen approaches, the tendency will be to centralise the provision and management of both these initiatives. However, given the burden of MDR-TB in SA together with the previous poor performance of centralised care, both the new drugs and shortened treatment regimen need to be available at centralised and decentralised hospitals and deinstitutionalised treatment sites to ensure universal access to effective treatment.

Although MDR-TB is treatable and curable, its programmatic management has long been characterised by multiple problems and inefficient health systems that fail the patient. To ‘seize the day’ and capitalise on the window of opportunity afforded by the introduction of the shortened regimen and new and repurposed drugs, these interventions must be optimally implemented. In this editorial we identify the key findings and recommendations from the WHO review that need to be addressed to ensure optimal implementation of the shortened regimen and new drugs.

Summary of the WHO review findings

While the WHO review of decentralised and deinstitutionalised MDR-TB treatment was wide ranging, several key issues were identified pertinent to implementation of the shortened regimen and new drugs.

The review found that, for a number of reasons, the extent and co-ordination of decentralised MDR-TB service implementation varied across the provinces. Firstly, the MDR-TB programme was not closely aligned to the TB programme or recent NDoH initiatives such as re-engineering of primary healthcare (PHC) services or the ‘ideal clinic’ initiative. Secondly, different policy and strategy documents do not always ‘talk to each other’, and MDR-TB management and the decentralisation policy framework are not consistently referred to. Importantly, as the framework was not costed, districts were expected to implement the framework with no extra resources. As a result, implementation and co-ordination of decentralised services varied, the framework was seldom included in district operational plans, and staffing was often inadequate. Finally, district and provincial level support and supervision for framework implementation were inadequate.

Quality of clinical care is important both for individual patient care and for stewardship of second-line drugs. The review found that clinical management was good and had improved over time. However, inadequate linkages to care and unclear referral pathways contributed to a loss of patients between different levels of care, and suboptimal integration of MDR-TB and HIV services compromised treatment. Monitoring of adverse events was inadequate, and in 29% of the medical records reviewed, patients were not regularly asked about adverse events. Adherence support was inadequate, with up to 90% of patients reviewed missing doses in both the injectable and continuation phases. Ongoing staff training with proper and regular supervision was often lacking, and there were no policies for patients failing to respond to treatment.

Several inadequacies in monitoring and evaluation of the MDR-TB programme were highlighted in the review. The electronic data management system used to monitor the programme is a vertical system and data bypass districts. With limited opportunities for data validation or feedback at facility and district levels, there is little ownership of the data at facilities and data quality is poor. The low use of ID numbers as unique identifiers compromises attempts to monitor patients between different levels of care, facilities and laboratory services.

Laboratory service support for the MDR-TB programme was well managed. The introduction of the GeneXpert MTR/RIF diagnostic test reduced the time of MDR-TB diagnosis to <48 hours in >90% of the
cases reviewed. However, the capacity for second-line drug sensitivity testing is limited, and drug sensitivity testing for moxifloxacin, the key fluoroquinolone in both the current and shortened regimens, was not conducted.

While the shortened regimen is expected to reduce the proportion of patients who do not adhere to treatment, support for patients throughout the 9–12 months of the shortened regimen is still essential. Among patients interviewed during the review, 25% interrupted treatment for socioeconomic or treatment-related reasons. Community-level support was undermined by poor alignment of the decentralisation programme with the PHC re-engineering initiative.

**Recommendations in light of the introduction of the shortened MDR-TB regimen**

Based on the review, a number of recommendations relevant for effective implementation of both the shortened regimen and more widespread use of new and repurposed drugs were proposed. The key recommendation for programme management and co-ordination was acceleration of decentralised and deinstitutionalised MDR-TB care through a more patient-centred approach. Recognising that different models of care are required to provide universal access to MDR-TB treatment, the review recommends that different packages, based on needs and local context, be piloted and scaled up. For each model of care, resource requirements at each level need to be clearly articulated, detailed costs determined and mechanisms to fund implementation determined.

The review recommended integration of the MDR-TB programme into other aspects of the health system. Integration of the MDR-TB programme with PHC re-engineering will facilitate patient support in the community from community health workers working in ward-based outreach teams. At a PHC level, MDR-TB management must be integrated into all guidelines. And, to ensure correct implementation of guidelines, human resource needs to be defined and facility-level staff trained, supported and guided by clinicians and district and provincial TB co-ordinators. Some but not all provinces have provincial MDR-TB clinical management teams to provide clinical expertise, guidance and oversight on the clinical management of patients. With the introduction of new therapies, these teams need to be functioning optimally in all provinces to provide clinical oversight and support.

Implementation of the shortened regimen will require rapid identification of second-line drug resistance status with rapid feedback to clinicians. For optimal clinical care and adherence, the shortcomings in referral pathways, adverse event monitoring and pharmacovigilance need to be addressed. To improve data quality, management and provision of services, the review recommended the alignment and incorporation of the MDR-TB data management system into the District Health Information System (DHIS) and implementation of a unique patient identifier system.

**Conclusion**

The WHO-led review highlighted a range of measures to improve patient care and health system functioning. Central among these are strategies to accelerate decentralised and deinstitutionalised MDR-TB care. However, the management of MDR-TB is not simple, and the introduction of a new regimen and new and repurposed drugs brings additional complications. There is a risk that implementing new inter-

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