Drug-resistant and extensively drug-resistant tuberculosis in southern Africa
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Introduction
Concerns about drug-resistant Mycobacterium tuberculosis date as far back as to the early chemotherapeutical attempts [1]. Tuberculosis (TB) incidence, prevalence and mortality are targeted to be falling as one of the millennium’s development goals. Currently (2008 data), TB incidence is estimated to run at 8.9–9.9 million cases globally, with a prevalence of 3.3–9.6 million cases. TB deaths are estimated as 1.6–2.3 million per year, out of which 0.5–0.6 are attributable to TB deaths among HIV-positive individuals [2 C15]. Seventeen per cent of those are living in one single southern African country, South Africa [3].

TB drug resistance is rife in southern Africa. This has mainly been attributed to poor performance of control programs and low cure rates [3 C15]. Globally, there were an estimated 0.5 million cases of multidrug-resistant TB (MDR-TB) in 2007 [2 C15], and South Africa, with an estimated 150,000 cases, ranks fourth on the global scale of MDR-TB cases in absolute numbers. By the end of 2009, 57 countries had reported at least one case of extensively drug-resistant TB (XDR-TB), but the prevalence of XDR-TB cases seems to be highly variable and still needs to be determined in many settings [3,4].

Several reviews addressing the problem of drug-resistant TB (DR-TB) in various contexts and from various angles have been published recently [5–10 C15], some of them focusing timely on the pressing issue of understanding the close entanglement of the HIV/TB copandemic and the need to tackle both conditions in a joint effort [11–13 C15], and Whittaker and Kampmann [14] briefly looking into the issue of DR-TB in mothers and infants.

Purpose of review
Drug-resistant tuberculosis (TB) is of increasing global concern. One of the hardest hit regions is southern Africa. This study focuses on a concise update on recently published developments in the field.

Recent findings
There is mounting evidence from high-coprevalence areas that the TB and HIV pandemics must be viewed as an entity and tackled together. In that context, it has become clear that a shift may be required from standard hospital-based models of care towards community-based approaches. Innovative rapid diagnostics to detect TB drug resistance suitable for the use in resource-poor settings and novel drugs effective against drug-resistant Mycobacterium tuberculosis strains are currently developed.

Summary
In order to allow for a maximum impact of novel interventions on the problem of multidrug-resistant and extensively drug-resistant TB, public health systems and existing TB programs must be strengthened significantly.

Keywords
extensive drug resistance, HIV/AIDS, multidrug resistance, southern Africa, tuberculosis

Drug-resistant tuberculosis and the HIV copandemic: the magnitude of the problem
The magnitude of the problem of TB drug resistance in conjunction with high AIDS comorbidity became evident only in late 2006 when Gandhi et al. [15] reported on an outbreak of XDR-TB in HIV-1 and TB-coinfected individuals in a rural area in KwaZuluNatal (KZN), South Africa. Sputum was obtained in 2005 and early 2006 from...
1539 patients, and MDR-TB was detected in 221 patients, of whom 53 were identified as having XDR-TB. Forty-four (100%) of XDR-TB patients tested for HIV were coinfected, and 52 of 53 (98%) of the XDR-TB patients died. The median survival time was 16 days in those 42 individuals with known dates of death. Genotyping of isolates yielded related strains in 39 of 46 (85%) patients with XDR-TB, suggesting nosocomial transmission. Although a recent meta-analysis review failed to demonstrate an overall association between MDR-TB and HIV [16*], a correlation between coexistent high prevalence of HIV and TB fuelling the development of TB resistance is undoubted. In South Africa, the estimated coinfection rate of HIV/TB is 70% [3*], but it may well exceed even 95% in epicenters as is the case for Johannesburg [17].

**Source of infection: in-house (nosocomial) vs. exogenous (community-acquired)**

Nosocomial transmission of drug-resistant strains amongst inpatients has been identified as one of the most potent promoters of DR-TB in South Africa; yet shifting care as far as possible to an outpatient and community care system may not offer a solution unless infection control measures are vigorously implemented. This is highlighted by recent work from the Tugela Ferry Care and Research Collaboration that evolved from the initial work drawing the attention to the magnitude of the problem in South Africa, as briefly described above. By means of spoligotyping, Andrews et al. [18**] examined initial and follow-up isolates of 17 of 23 patients who developed MDR-TB and higher degrees of DR-TB after having been treated for drug-sensitive or less resistant TB. In all (100%) of those, the subsequent isolates differed from the initial ones, thus indicating external re-infection. Although the exact denominator remains undetermined, this clearly illustrates the magnitude of the problem of exogenous re-infection. This casts some doubt on whether a shift away from the ethically, logistically and economically complex model of prolonged in-patient care until sputum and culture negativity are achieved offers, in general, prospects for better outcomes in terms of lower TB incidence and DR-TB rates in the South African setting, at least unless basic infection control measures become feasible on a large scale outside of institutions and control programs implemented in circumscribed areas only. Such a paradigm shift, as it is currently intensely discussed in the wider context of DR-TB care improvement [19*,20*], curbing of the spread of DR-TB [21*] and HIV/TB program integration in southern Africa [22*,23*] and beyond [24*,25*], would, however, require a significant logistical and financial effort as well as community awareness and support on a large scale.

**Recent molecular insights into drug-resistant Mycobacterium tuberculosis**

Hypothesizing that the genetic diversity of the mycobacterial strains present within a particular epidemic setting may give rise to an array of pathogenicity characteristics, Van der Spuy et al. [26*] analyzed DNA fingerprinting changes in the population structure of *M. tuberculosis* strains cultured from patients in Cape Town, South Africa, over a period of 12 years (1993–2004). Whereas the incidence of non-Beijing clade cases remained stable over time, Beijing clade cases increased exponentially over time. With drug-resistant Beijing clade cases remaining stable within this period, only the number of drug-sensitive strains increased, possibly reflecting an enhanced pathogenicity.

Whereas recent data from other southern African countries are scarce, spoligotyping of the isolates from the initial XDR-TB report from KZN showed that most cases were infected with the same strain of dubbed F15/LAM4/KZN, which had developed in little more than a decade [27]. In an attempt to further elucidate the causes of evolution of drug resistance on a molecular level, Ioerger et al. [28*] determined DNA sequences of KZN XDR-TB strains from the originally reported outbreak as well as from subsequent isolates. With the latter being nearly identical to the earlier isolates, clonal expansion appears to be the driving force behind the XDR-TB spread in this area of South Africa, thus leading the authors to question whether there is either a diminished loss of fitness as one would generally assume, an offset of fitness due to yet unidentified mutations, or treatment-related factors leading to the selection of drug-resistant strains; alternatively, diminished host immunity due to HIV infections has been suggested to play a role.

Another study [29] looking at XDR-TB genotypes from South Africa, in general, demonstrated high genotypic diversity and wide geographical distribution, with 17 different spoligotypes found in 41 XDR-TB isolates. It has been hypothesized that mixed infections may accelerate the emergence of drug-resistant strains, and Stavrum et al. [30*] examined the distribution and diversity of MDR-TB and particular genotypes. Spoligotyping yielded 10 different lineages in 109 MDR-TB isolates, and there was evidence of a high frequency of mixed *M. tuberculosis* subpopulations; yet multiple drug resistance could not be tied to a single strain but could only be linked to a history of previous TB treatment.

**Groups with a particular risk to develop (drug-resistant) tuberculosis**

Basu et al. [31*] sum-up the information on the up-to-10-fold increased TB incidence and the excessively high
rates of DR-TB amongst miners in southern Africa in the face of a high HIV prevalence. They point out that there is ample room for improvement in terms of better healthcare on an individual level and prevention/control measures extending to the afflicted communities both locally and abroad, as a significant proportion of the mining workforce originates from, and migrates back and forth to, their home communities throughout southern Africa.

There is a well established strong correlation between heavy alcohol use, alcohol use disorders and TB, as highlighted in a recent meta-analysis [32*]. The pooled relative risk across three cohort and 18 case–control studies (including one with data from Malawi) with the alcohol exposure cut-off level having been set at 40 g/day or above, and after accounting for possible confounding, was 2.94 [95% confidence interval (CI) 1.89–4.59]. Rehm et al. [33*] summarize the evidence of a strong association between alcohol consumption and TB in terms of an increase in incidence as a worsening of outcome, not surprisingly due to deleterious interactions of alcohol with the immune system facilitating mycobacterial disease, altered pharmacokinetics of antituberculosis drugs, higher rates of treatment defaults and re-infection rates, in part, due to biological as well as to social factors.

On a global scale, approximately 10% of TB cases were estimated to be alcohol-attributable. Confounding-adjusted conservative estimates for South Africa run at an alcohol-attributable fraction of about 23% for men and 7% for women, figures only topped by Russia, Nigeria and Thailand in an eight-country, four-continent analysis. Regarding a possible link between excessive alcohol consumption and the development of drug resistance in TB, ‘hard’ data appear to be lacking so far; yet it appears to be generally accepted that a wealth of biological and social factors, as mentioned above, all contribute substantially to a lack of appropriate drug accessibility and/or intake and reduced effectiveness of antituberculosis drugs, thus facilitating the spread of TB drug resistance.

Whereas the interactions between TB and alcohol are clearly established, there are only few voices so far who postulate a clear role for alcohol abuse containment to contribute significantly to curbing the TB problem in the southern African regions, and efforts to include antialcohol abuse measures into the TB/HIV prevention portfolio must be urgently stepped up.

**Determinants of treatment outcome**

Pepper et al. [34*] conducted a prospective, observational study to look into the nature of clinical deterioration of South African patients on TB therapy. This group identified new AIDS-defining illnesses and drug-resistant *M. tuberculosis* and TB-immune reconstitution inflammatory syndrome (IRIS) amongst the lead courses for deterioration.

As reviewed by Chan and Iseman [35*], outcomes of MDR-TB treatment vary widely depending on a whole range of variables. Sheikh et al. [36*] looked into the long-term treatment outcomes of MDR-TB patients in the Western Cape region of South Africa. During 1992–2001, 239 of 491 (49%) MDR-TB patients who had received appropriate treatment were considered ‘cured’ or completed treatment at least; 68 (14%) patients died, with the majority of the remaining ones having defaulted from treatment. Over time, the proportion of those with a successful TB treatment outcome declined further. One would hope that these data, in times of a well defined MDR-TB standard treatment regimen and alternative drugs at hand for those patients who need to change regimens due to adverse effects, are ‘historical’ by now, and that the cure rates are on the rise. Seung et al. [37*] assessed early treatment outcomes in a cohort of patients registered in the Lesotho national MDR-TB program. Of the 76 patients enrolled, half a year after the 1-year recruitment period had ended, 56 (74%) were HIV-positive, 22 (29%) had died, and in 52 of 54 (68%) surviving patients, a culture conversion was documented. A recent meta-analysis of treatment outcomes of MDR-TB patients worldwide (from 34 clinical reports with a mean of 250 patients) found that in patients who were treated for at least 18 months under strict DOTS (daily observed therapy, short course) conditions, the pooled success proportion reached 69% [38*]. A similar analysis by Johnston et al. [39*] found 62% of patients from 36 studies and 21 countries to have successful treatment outcomes, with 11% of the patients having succumbed to their condition.

To date, a fair dozen of studies from all over the world, including the earlier cited work of Gandhi et al. [15] regarding the KZN outbreak reported in 2006, have provided data on XDR-TB treatment outcomes so far. Sotigui et al. [40**] reviewed those systematically and concluded that under optimal treatment conditions and in the absence of HIV co-infection, successful treatment rates may be up to 65%. However, methodologically, a meta-analysis proved to be impossible due to the large heterogeneity of definitions and reporting styles.

**Improved diagnostic tools and novel treatment approaches**

With current TB control efforts in southern Africa failing [41*], the success of (re)gaining global control over TB, in general, and DR-TB, in particular, will largely depend on the broader and more successful implementation of already available control tools and the reinforcement of established, viable strategies, and on integrating those with anti-HIV programs at least in areas of high co-endemicity. However, novel diagnostic tools for rapid and reliable diagnosis of infection, disease and drug resistance
as well as highly effective and efficacious new drugs and combinations to reduce treatment duration, while sporting favorable adverse events profiles in the face of often complex comcodinations, are urgently needed.

Bwanga et al. [42] performed a timely literature review and meta-analysis of four direct susceptibility testing methods for MDR-TB, including two (in-house) phenotypic and two (commercially available) molecular methods, namely a nitrate reductase assay (NRA), microscopic observation drug susceptibility (MODS) and two related line probe assays (GenoType MDR-TB and Genotype MDR-TBplus assays; Hain Life Sciences, Nehren, Germany) detecting drug resistance-conferring polymorphisms in the rpoB (for rifampicin) and katG genes and the inhA promoter region (for isoniazid). All four assays performed with satisfying sensitivities and specificities compared with the standard. Of note, the NRA and MODS assays appeared to be by no means inferior to the more sophisticated and costly molecular methods, which may facilitate their rapid, large-scale introduction to laboratories in comparably resource-poor settings.

A group from South Africa [43] recently looked, by means of mathematical modeling, into what possible impact point-of-care use of rapid diagnostic tools (the Genotype MDRTBplus kit in this particular case; Hain Life Sciences) could have on halting the spread of MDR-TB in communities with high M. tuberculosis prevalence. Taking all the limitations of mathematical modeling into account, the simulations yielded that the incidence of drug-resistant cases in such communities would decline rather than rise steeply, but only provided that TB screening would be widely implemented, thus under-scoring the need for strengthening the public health systems and existing TB programs must be strengthened significantly.

Ma and Lienhardt [44] provide an excellent, concise overview on the history of TB drugs, the current drug pipeline and challenges in TB drug development. The good news is that for the first time, there is a TB drug pipeline, with newer fluoroquinolones (gatifloxacin and moxifloxacin) in phase 3 clinical trials aiming at an improvement of combination therapy of drug-sensitive TB (DS-TB) and rifapentin in phase 2b studies. However, although it is of utmost importance to shorten the DS-TB treatment duration in the first place, there is a need to develop agents capable to improve treatment outcomes of DR-TB patients. Nitroimidazoles (PA-824 and OPC-67683) constitute a novel class of antimycobacterial agents that have now entered phase 2 trials. The novel compound that is most advanced in its clinical evaluation is TMC-207, a diarylquinoline, representing a novel drug class of proton-pump inhibitors targeting mycobacterial ATP synthase (ATPase). Diacon et al. [45] reported early (week 8) results from a South African multicenter stage 1 of a two-stage, phase 2, double-blind, randomized, placebo-controlled clinical trial involving 47 individuals in total. Patients who received TMC207 (400 mg daily for 2 weeks, followed by 200 mg three times a week for 6 weeks) had, while the drug was well tolerated, a statistically significantly shorter sputum culture conversion time than those patients receiving placebo in addition to a five-drug standard regimen, as well as an increased proportion of patients with conversion of sputum culture (48 vs. 9%). Although the follow-up of this group continues, recruitment into the second stage (with TMC207 administration over 24 weeks) of the trial including centers outside Africa has been accomplished, and further clinical trials are underway.

Conclusion
Progress has been made in the understanding of how DR-TB has evolved in southern Africa, and the publications reviewed here reflect the lively discussion about how to optimize control of the HIV/TB copandemic and how to clamp down on the further increase of drug-resistant strains. Innovative rapid diagnostics suitable for the use in resource-poor settings and novel drugs are currently developed. However, in order to allow for a maximum impact of novel interventions, public health systems and existing TB programs must be strengthened significantly.

Acknowledgement
I do not have any conflict of interest to declare.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 286).


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6 Ben Amor Y, Nemser B, Singh A, et al. Underreported threat of multidrug-resistant tuberculosis in Africa. Emerg Infect Dis 2008; 14:1345–1352. A review of the MDR-TB estimates from all over Africa, showing that re-treatment failure rates were the most predictive indicator for the development of MDR-TB.


14 Shrivastava S, Brouwer ES, Van Rie A. Is HIV infection a risk factor for multidrug resistant tuberculosis? A systematic review. PLoS One 2009; 4:e5561. A meta-analysis looking into the association between HIV and development of drug resistance in TB. Although no clear correlation was found between time and geographic locations, only relatively few studies were eligible for review.


16 Suchindran C, Brouwer ES, Van Rie A. Is HIV infection a risk factor for multidrug-resistant tuberculosis? A systematic review. PLoS One 2009; 4:e5561. A meta-analysis looking into the association between HIV and development of drug resistance in TB. Although no clear correlation was found between time and geographic locations, only relatively few studies were eligible for review.


23 Penuma R, Padayatchi N, Steenkwater E. The whole is greater than the sum of the parts: recognising missed opportunities for an optimal response to the rapidly maturing TB-HIV co-epidemic in South Africa. BMC Publ Health 2009; 9:243. One out of the recent several essays motivating for tying HIV/TB programs closely together, with a focus on South Africa.


33 Rehm J, Samokhalov AV, Neuman MG, et al. The association between alcohol use, alcohol use disorders and tuberculosis (TB). A systematic review. BMC Publ Health 2009; 9:450. This article analyzes the current knowledge on the relationship between alcohol abuse and TB, hypothesizes briefly that there may be an (indirect) contribution to the development of DR-TB, and suggests a considerable proportion of TB cases being attributable to alcohol intake in South Africa.


One of the two recent meta-analyses of MDR-TB treatment outcome globally.


One of the two recent meta-analyses looking into MDR-TB treatment outcomes globally.


The first systematic review of XDR-TB treatment outcomes worldwide. A meta-analysis, however, was not possible due to data heterogeneity.


A study describing and analyzing failures undermining the South African National TB Program in an area of high HIV and TB coinfection rates and mounting rates of MDR-TB and XDR-TB.


Comparison of four methods for rapid TB drug resistance assessment.


Mathematical modeling by a South African group suggesting that the use of point-of-care rapid diagnostic tools, such as line probe assays, has the potential to contribute to the reduction of DR-TB incidence in communities with a high prevalence of M. tuberculosis infections.


An excellent state-of-the-art overview on the development of novel antimycobacterial agents.


A study on the outcome at week 8 of the first stage of a two-stage, double-blind, randomized, placebo-controlled trial of TMC207 in MDR-TB patients, with contributing centers from South Africa. At week 8, a statistically significantly reduced sputum culture conversion time in overall 47 participants was demonstrable in those individuals receiving the intervention drug on top of a standard MDR-TB regimen.