My thanks are due to the organizers of this conference for inviting me to be the discussant to Karin Weyer's talk, but more importantly, for having the foresight to address drug-resistant TB as one of the Urgent Issues in the Developing World - which it most certainly is.

I will address the implications of extensively drug-resistant tuberculosis (XDR-TB) for the global control of TB and, in particular, try to convince you of the seriousness of the threat; what needs to be done to address XDR-TB (and what should be avoided); and what steps are urgently required, right now.

The problem of XDR-TB was first defined by the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) in March of 2006 reporting data from a survey of TB reference laboratories in WHO's Supranational Reference Laboratory Network\(^1\). Of nearly 18,000 isolates, 20% were shown to be multidrug-resistant (MDR) and were then tested for susceptibility to 2nd line drugs. Ten per cent of the MDR isolates were extensive drug-resistant tuberculosis (XDR-TB).

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isolates were found to be resistant to 3 or more of the 6 2nd line drug classes, at that time the working definition of XDR-TB.

The level of resistance in XDR-TB seriously reduces treatment options, resulting in high rates of treatment failure and consequent mortality.

This above slide shows the cure rates of different levels of resistance in Latvian TB patients. In this setting 65% of cases of MDR-TB were cured, and less than 10% died, but less than 5% were HIV infected. The revised definition of XDR-TB (which is MDR-TB plus resistance to the fluoroquinolones and resistance to at least one of the injectable drugs, amikacin, kanamycin and capreomycin) yields cure rates that are significantly worse at 27%. However, Latvia is pretty well resourced and has developed excellent expertise in diagnosing and managing drug resistant TB. In contrast, most African countries do not have a laboratory capable of carrying out first line drug susceptibility tests, let alone for 2nd line drugs, which is technically more demanding. South Africa, alone, has more DST capable laboratories than the rest of sub-Saharan Africa put together.
Globally, WHO has estimated that in 2005 there were about 8.8 million cases, and 1.6 million deaths from TB.

Matteo Zignol and colleagues from our department have estimated that each year there are about 420,000 cases of MDR-TB with 116,000 deaths, and around 27,000 cases of XDR-TB, with 16,000 deaths (next slide). From the 17 countries known to have XDR-TB cases in March 2006, we now have 28 countries that have published cases, and/or reported cases to WHO.

I should emphasize that the little evidence we have suggests that this is not so much spread of resistant strains, but the creation of similar patterns of resistance in different strains around the world, because the drugs used are more or less the same everywhere, and unfortunately, so are the defects in the performance of TB control.

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The bulk of the problem of XDR-TB is likely to reside in those countries with high numbers of MDR-TB cases, and two thirds of MDR is in just 3 countries, China, India and the Russian Federation.

Worsening drug resistance demands a number of responses. We must strengthen basic TB control, in order to prevent MDR-TB, and also HIV management because of the high levels of susceptibility of those with HIV infection. The supervision and follow-up of all cases of TB needs to be assured - and it looks, at this point, that this is where problems arose in KwaZulu Natal; regular supplies of high quality drugs, without stock-outs, need to be properly organised. TB programs everywhere must now also initiate, if they have not already done so, and strengthen, efforts to manage drug resistant cases and prevent MDR from becoming XDR - as prescribed in the new Stop TB strategy of WHO and the Stop TB Partnership. How this should be done is in the Guidelines for the Programmatic Management of Drug Resistant TB. XDR-TB has exposed a number of weaknesses in the global response to TB, of which one of the biggest is the insufficient number and poor performance of TB laboratories. These need urgently to be strengthened and WHO is preparing a strategic plan for doing so. Drug resistance surveillance should, ideally, be part of routine recording and reporting, but where resources are still insufficient for this, then rapid surveys to understand the extent of XDR-TB are the priority. Messages of the importance of XDR-TB need to be communicated to decision-makers, health workers, civil society and the general public, but without causing undue alarm. Financial resources are needed and cannot be expected to come from government budgets where annual GDP is around $200 per annum. The

International Standards of Care\(^6\), published last year, represent the level of performance TB control programmes should aspire to, and to which they can be held to account. Research is imperative: into new diagnostics, so that the diagnosis can be made before the patient is buried, new drugs to avoid the long courses of toxic drugs that are currently essential to cure XDR-TB, and, ultimately a vaccine to prevent all forms of TB.

Another of the neglected areas in global TB control is infection control, which has been weak or non-existent in most developing countries.

The infection control guidelines from 1999\(^7\) are being revised, thanks to CDC, and an addendum addressing infection control in high HIV settings has just been finished - and is available on both CDC and WHO websites\(^8\). The goal now has to be to institute adequate controls in every health facility that sees TB patients or suspects. For that, a working group is being set up within the Stop TB partnership, and training courses planned at regional and national levels, with national programs preparing their own country level plans.

On what not to do - threats of enforced quarantine, and coercive treatment are not going to encourage a useful response from the general population.

There first has to be an effective management system in place for drug

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resistant disease. However, it is true that there are rare circumstances in which quarantine can, and should, be enforced, and these are laid out in the WHO and South African Medical Research Council websites.

**Immediate Needs**

- Commitment to address drug resistance
  - Governments and TB and HIV Programs
  - TB partners
- Co-ordinated planning
- Training
- Human resources
- Financial resources

Right now, governments, and their TB and HIV programs, need to step up to the plate, as do all the partners within the Stop TB Partnership. Global, regional and national level planning is needed. At the global level the XDR and MDR response plan is currently being circulated for consultation with numerous partners. Training in all aspects of drug resistant TB is needed, but we start from a very weak position. Today, Africa has less than one seventh the global average of physicians per head of the population, and less than one third of the average for nurses. Efforts to address drug resistant TB must be coordinated with those working on this health workforce crisis (next slide).

In financial terms this is what is needed: approximately $42 million for global and regional coordination, planning and technical support, and $604 million in countries, to scale up to the levels of diagnosis and treatment of MDR and XDR-TB required to reach Universal Access. If these resources are not found, we face, over the next few years, the replacement of the current global epidemic of mostly drug susceptible TB, with multi or

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11 Revision of the Stop TB Partnership's Global Plan to Stop TB, 2006-2015, in progress
extensively drug resistant disease, and the need to solve a human catastrophe, at vastly greater expense than if we address it now with all the skills and dedication of which we are actually capable.

In conclusion, XDR-TB is a wake up call for both strengthening basic TB, and HIV, care, prevention and control, and scaling up the management of drug resistant TB. I think that success in this will also require us to put the concerns of individual patients right at the centre of the way in which we address TB control - but that is the topic of another talk. The world needs about $650 million to be spent to respond to this call.

I would like to give my co-workers on this presentation the recognition they deserve. I leave you with the headline from the Lancet, which says it better than I can.

- Dr Paul Nunn
Co-ordinator, Stop TB Department, WHO