Drug Quality, Drug Supply and Access to New Drugs

Uniting to scale up TB care in Central Asia

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Aims of TB Treatment

- Cure the patient and restore quality of life and productivity
- To reduce transmission of TB to others
- To prevent the development and transmission of drug resistance

To achieve these aims - treatment providers must have an **uninterrupted supply** of **quality assured** medicines

What drugs are we talking about?

Group	Drugs
1. First Line Oral Drugs	Rifampicin (R), Isoniazid (H), Pyrazinamide (Z), Ethambutol (E)
2. Injectable Drugs	Kanamycin (Km), Capreomycin (Cm) Amikacin (Am) Streptomycin (S)
3. Fluoroquinolones	Moxifloxacin (Mfx), Levofloxacin (Lfx), Ofloxacin (Ofx), Gatifloxacin (Gfx)
4. Oral bacteriostatic 2nd line agents	Ethionamide (Eto), Protionamide (Pto), Cycloserine (Cs), Teridazone (Trd), p-aminosalicylic acid (PAS), p-aminosalicylic sodium (PAS-Na)
5. Agents with unclear efficacy	Clofazimine (Cfz), Linezolid (Lzd), Amoxicillin/clavulanate (Amx/Clv), clarithromycin (Clr), Thioacetazone (Thz), Imipenem/cilastin (Imp/Cln)

As described in WHO, "Guidelines for the programmatic management of drug- resistant TB. Emergency Update 2008"

Quality Assurance (QA) - A definition

"a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use"

Good Manufacturing Practices for pharmaceutical products: main principles. (37th report, 2003)

What do we mean by Quality?

- The drug is safe, effective and does no harm
- Quality Assurance concept is the same for all medicines and should not be different standards for a drug manufactured in country compared to a drug imported
- It is related to both the manufacturer of the product and the unique product dossier

Mechanisms to Ensure QA sources

- WHO Prequalification Program
- Created in 2002
- Prequalification of medicines for HIV / AIDS, TB, Malaria, reproductive health (& H1N1) for procurement by UN agencies.
- End of 2010 – 252 products approved
- 31 TB drugs approved (7 for DRTB)
- 43 TB drugs under evaluation (19 for DRTB)

Mechanisms to ensure QA sources

- Registration / Marketing authorisation in countries with a **Stringent Regulatory Authority** (SRA)
- **Expert Review Panel (ERP)**
  - Part of QA Policy in Global Drug Facility (GDF) / Global Fund (GF)
  - Time limited approval based on an Expression of Interest for drugs with limited sources. (<3 QA sources)

Quality Assurance of DR TB drugs

What is available today for DRTB

Group	Classification	Drug	WHOPQ	SRA	USFDA tent approval	GDF / GF ERP	Total	WHO PQ pipeline
2	Injectable Drugs	Km		3			3	1
		Cm		1			1	1
		Am	1	2			3	
3	Fluoroquinolones	Lfx		1	13	2	16	2
		Mfx	1	1	2		4	1
		Ofx		3		1	4	2
4	Oral bacteriostatic 2nd line agents	Eto	1	1		1	3	
		Pto		1			1	1
		Cs	2	1			3	3
		Trd		1			1	
		PAS	1	1			2	
		PAS-Na	1				1	

Supply Channels – TB specific

In most cases patients access TB drugs through either the

- public sector – National TB programs, or
- private sector & NGO's.

For DR TB programs these may be either

- GLC approved *or*
- Not GLC approved

Drug Supply

Many actors involved in Supply Chain to assure Good Quality Medicines reach the patient

- Manufacturer
- National Drug Regulatory Agency (NDRA)
- National TB Programs
- Donors
- Procurement Agent
- Distributor
- Purchaser - NGO's, International Organisations (eg; PAHO, UNOPS, UNDP)
- Clinician / Prescriber
- Pharmacy / Dispenser

Drug Supply

National Drug Regulatory Agency (NDRA)

- Responsible to ensure the quality and safety of drugs available on the market
- Registration
  - Criteria for registration – bio-equivalence
  - Irrational Fixed Dose Combinations (FDC)
- Importation
- Quality Control
- Restrict availability of TB drugs in private sector
- Economical Pressures
  - Different requirements for registration of local production and international production
  - Political agenda rather than public health objective

National Drug Regulatory Agency (NDRA)

- Registration - Today there are mechanisms to identify products that are quality assured
- NDRA can use this endorsement to “fast track” registration in their countries – recognition of the existing mechanisms
- Facilitate importation of quality assured sources – as interim solution while waiting for registration process
- Regional initiative – EMEA . East African community
- Fast track customs clearance – many of the drugs used to treat DR TB have only a 2 year shelf life

Stock Management

- Stock Ruptures should be seen as a failure in the system
  - Terrible implications to a patient
  - Public health implications to community
- Forecasting of needs
  - Need good data coming up upstream – actual patients on treatment - + expected new inclusions
  - Important to consider in this drugs for children
  - DR TB - Include drugs for side effect management
  - Include buffer stock (must take into account importation / customs clearance procedures)

Availability of TB drugs in the private sector

- Ready availability encourages self medication and potential purchase of inadequate combinations and quantities of medicine
- The goals of the NTP will be hampered, drug resistance will increase along with the investment needed to counteract TB
- Change in pharmaceutical legislation and capacity to enforce it

New drugs on the horizon

- Most drugs we are using today for DR TB are old, with unfavourable side effect profiles and require up to 24 months of treatment
- Has been an investment on research into new drugs targeted for treatment of TB
  - 3 drugs in preclinical testing
  - 3 drugs in clinical development
    - 2 of these are completing Phase II
      - TMC207 – Tibotec / Johnson & Johnson
      - OPC 67683 - Otsuka
- Patients today are failing on the currently available drugs

Drug Resistant TB
- Compassionate Use

- Possibility to use (outside of clinical trials) a new drug under development for patients suffering from a life threatening disease and for whom conventional therapies have failed
- Never used for TB as no new drugs in pipeline – till now
  - Has been used for HIV / Aids, cancer
- Consultation by MSF – Campaign for Access to Essential Medicines to evaluate regulatory issues in countries
  - South Africa, Swaziland, Armenia, Georgia, Uzbekistan, India

What Are the Requirements in a country for using CU for TB

- Decision to be made at MoH / NTP level on the medical added value of doing CU in TB
- As per international standards for CU, usual requirements can be:

  - evaluation of CU projects by an Ethics Committee,

  - review of Phase II pharmaceutical data by MoH for each drug which is a candidate for CU,

  - informed consent procedure with patients,

  - requirements for the importation of drugs under CU.

Summary

- Registration – restrict QA sources
  - Fast track registration procedures
  - Facilitate importation
- Stock ruptures TB drugs –”zero tolerance”
- Address Private sector
  - Limit access to TB drugs
- Consider CU mechanisms to facilitate access to new drugs

Thank you