

Diagnosis of the MDR-TB



Case-Findings Strategies

W.H.O.

Second MDR-TB Consultant Course

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José A. Caminero, MD

The Union (IUATLD)
Canary Islands, Spain



Diagnosis of the MDR-TB



Case-Findings Strategies

- 1. Suspects of MDR-TB***
- 2. Clasification of MDR-TB Cases***
- 3. Support of the Conventional TB Diagnostic Procedures to the MDR-TB Diagnostic***
- 4. How to Approach Diagnosis of MDR-TB***
- 5. Confirmation of MDR-TB. Reliability of DST***

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Diagnosis of the MDR-TB. ***Case Finding and Confirmation***

***The Diagnosis of the Patient with
MDR-TB must start with the
Identification of the Suspects of
Resistances***

Suspects of Resistances



Suspects of Resistances

Classification by Probability of Resistance

1. High Probability of Resistance

- From a bacteriological point of view they should be MDR-TB

2. Middle to Low Probability of Resistance

- In some Settings can be associated with a middle rate of Resistance

3. Low to very Low Probability of Resistance

- Only in very exceptional circumstances can be associated with MDR-TB



Suspects of Resistances

1. High Probability of Resistance

1. Failures to the Standard Short Course of Chemotherapy (SCC)

- Failures of Cat. II and **Chronics**

- Highest Probability

- Failures of **Cat. I**

2. Exposure to a known MDR-TB case



2. Middle to Low Probability of Resistance ***In some Settings can be associated with a middle rate of Resistance (1)***

4. Failure of anti-TB Treatment in the Private Sector

5. Patients who Remain Sm+ at 2-3 m. of the Cat. I

6. Relapses and Return after Defaults

7. Exposure in Institutions that have MDR-TB out-breaks or a high MDR-TB prevalence



2. Middle to Low Probability of Resistance ***In some Settings can be associated with a middle rate of Resistance (2)***

- 8. Residence in **Areas** with **high MDR-TB** prevalence***
- 9. History of using antituberculosis drugs of **Poor** or **unknown Quality*****
- 10. Treatment in **programmes** that operate **poorly** (especially recent and/or frequent **drug stock-outs**)***





3. Low to very Low Probability of Resistances

Only in very exceptional circumstances can be associated with MDR-TB

11. Co-morbid conditions associated with malabsorption or rapid transit diarrhea

12. HIV in some settings

Suspects of Resistances

1. High Probability of Resistance

1. Failures to the Standard Short Course of Chemotherapy (SCC)

- Failures of Cat. II and **Chronics**

- Highest Probability

- Failures of **Cat. I**

2. Exposure to a known MDR-TB case





Suspects of Resistances

1. High Probability of Resistance

The Failures to the Standard Short Course of Chemotherapy (SCC) have the Highest Probability of Resistance

From a bacteriological point of view, All the Failures should be Resistant, because they are motivated by the Rapid Multiplication Bacilli (selection of the Natural Resistant Mutant)

Pharmacological Failure

- *This is when a patient does not achieve a negative sputum smear at the end of the 4th-5th month, or after achieving a negative one, it then becomes positive.*
- *It is caused by the **Continually Growing Bacilli**.*
- *It is accompanied by **Resistance** to Drugs used*
- *Sensitivity Tests should be performed.*



Bacillary populations

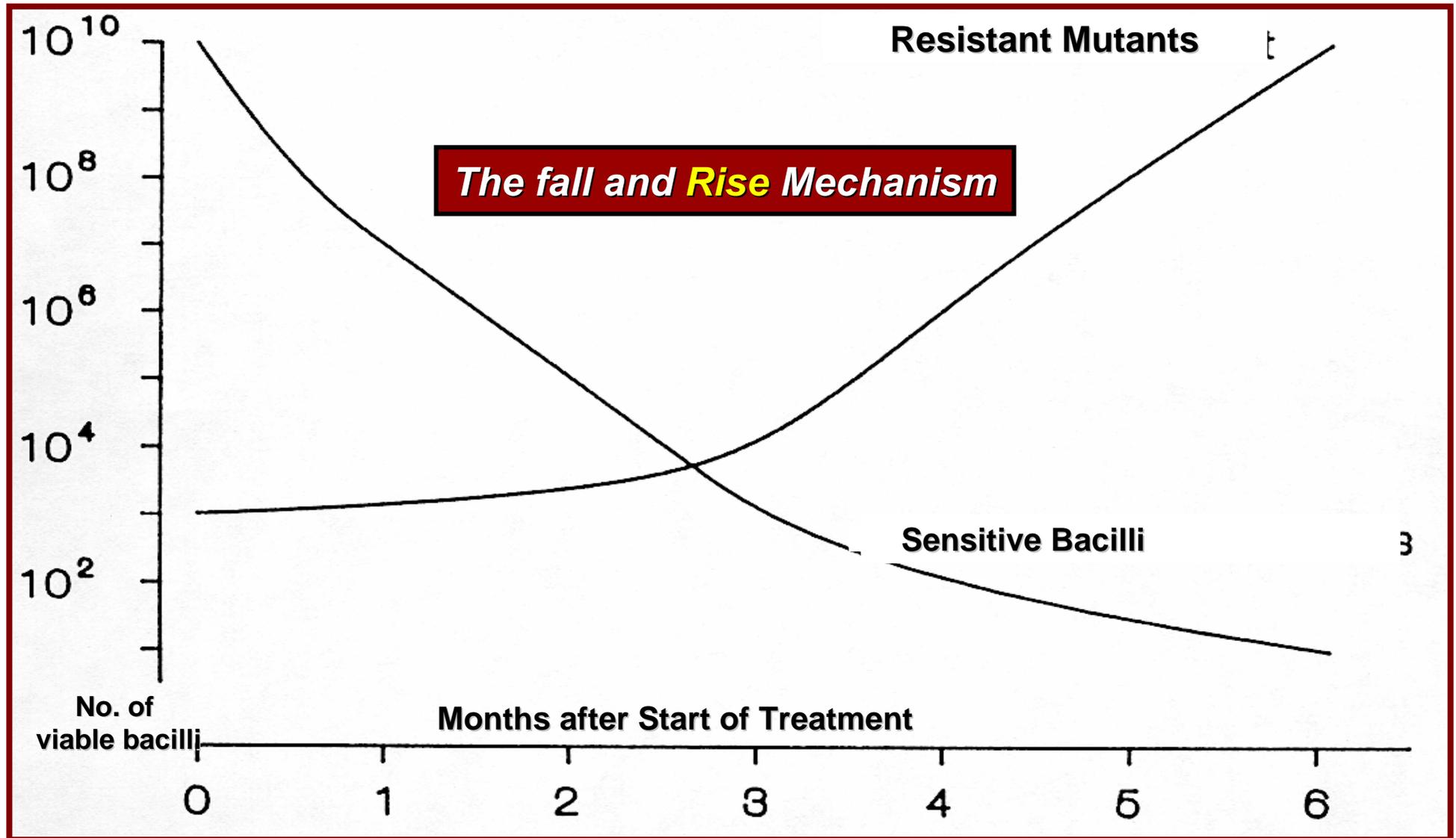
1. Continually Growing Bacilli

Failure

- Optimum medium: Extracellular. PH 6.5-7, maximum oxygenation (cavern wall)
- Large number of bacilli → High probability of spontaneous natural mutations



Appearance of resistance to INH administered in Monotherapy



1. The **Highest** Probability of **Resistance**

The Failure of re-treatment regimens
and **Chronic** TB cases



- **Chronic** TB cases are defined as patients who are still sputum smear-positive at the end of a **re-treatment** regimen
- Usually these patients have **failed** in **two** SCC treatments
- These patients have perhaps the **highest** MDR-TB rates of any group, often exceeding **80%**

Brazil: Rates of MDR-TB in Failures Category II (1986-1990)

Kritski AL, et al. Chest. May 1997;111(5):1162-1167.

Retreatment Group	Percentage of <i>MDR-TB</i>	Number of Patients
Failures of retreatment (most commonly HREZS, and on some occasions oflo, clof, rifabutin were included.	<u>65%</u>	49/78

Peru: Rates of MDR-TB in the Failures of Category II Re-treatment

Suarez PG, et al. Lancet. Jun 2002;359(9322):1980-1989.

<i>Retreatment Group</i>	<i>Percentage MDR-TB</i>	<i>Number of Patients</i>
<i>Failures of category II retreatment **</i>	<u>87%</u>	298/344

Nicaragua: Rates of MDR-TB in patients that fail **Category II**

Heldal E, et al. *Int J Tuberc Lung Dis.* Feb 2001;5(2):129-136

<i>Retreatment Group</i>	<i>Percentage of MDR-TB</i>	<i>Number of Patients</i>
<i>Failures of retreatment with Category II</i>	<u>89%</u>	<i>34 / 38</i>

High Probability of Resistance

2. Failures of Category I

- **Patients who while on treatment are sputum *smear-positive at month 5* or later during the course of treatment**
- **In the field, *Not all* patients who fail a Cat. I regimen has *MDR-TB*, and the percentage may depend on a number of factors, above all:**
 - **Including whether *rifampicin* was used in the continuation phase**
 - **Whether *DOT* was used throughout treatment**
 - **Some other Circumstances**



The Choice of the **Cat. I** and the possible of MDR-TB



Choice of Category I

- *HR 6 month regimens*
- *HE 8 Month regimens*
- *HT 8 month regimens*
- *Other*

Influences

***Case finding
and
Retreatment Strategy***

Frequent Case: Initial **INH Resistance**



Prudent approach

2 EHRZ / 6 EH

**Failure / relapse:
relatively frequent**



2 SEHRZ / 6 ERHZ



Failure = MDR

Relatively infrequent

Risky approach

2 EHRZ / 4 RH

**Failure / relapse:
relatively infrequent**



2 SEHRZ / 1 ERHZ / 5 ERH



Failure = MDR

Relatively frequent

Failures of failures: appropriate numerator

Rates of resistance in different retreatment groups. Evidences

<i><u>HE</u> based regimens</i>	<i><u>HT</u> based regimens</i>	<i><u>HR</u> based regimens</i>
<i>Malawi</i> <i>Vietnam</i>	<i>Benin</i> <i>Nicaragua</i> <i>Bangladesh</i>	<i>India</i> <i>Brazil</i> <i>Thailand</i> <i>Peru</i>

Malawi: Rates of **MDR-TB** in failures

Harries AD, et al. *Int J Tuberc Lung Dis.* Nov 2003;7(11):1040-1044.

Cat. I: 2 HRZE / 6 HE

Retreatment Group	Percentage MDR-TB	Number of Patients
Failures of Category I	<u>0%</u>	90 patients identified as failures, 30 had specimens sent for culture and DST, only 11 patients grew <i>M. tuberculosis</i> : 8 fully sensitive, 3 mono-resistance.

Vietnam: Rates of **MDR-TB** in different retreatment groups

Quy HTW, et al. Int J Tuberc Lung Dis 2003 7(7):631-36

Cat. I: 2 HRZE / 6 HE

Patient group	Percentage of <i>MDR-TB</i>	Number of Patients
<u>Failures</u> of Category I	<u>80%</u>	32/40
Relapse of Category I	8%	3/39

Benin: Rates of *MDR-TB* in the different re-treatment categories, 1994-1995

Cat. I: 2 HRZE / 6 HT

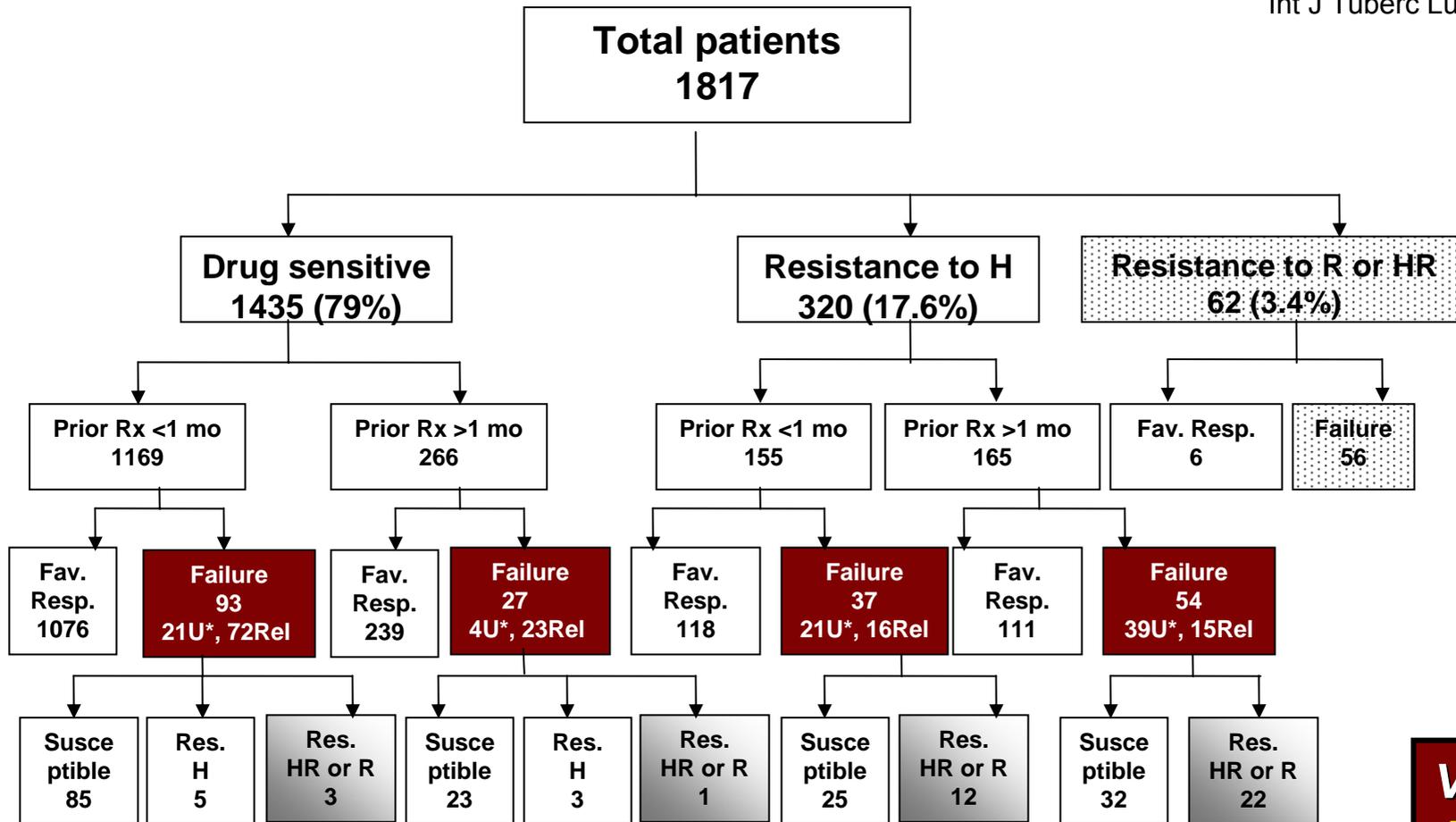
Trébuçq A, et al. *Int J Tuberc Lung Dis* 1999; 3: 466-470.

<i>Retreatment Group</i>	<i>Percentage of MDR TB</i>	<i>Number of Patients</i>
<i>Failures of Category I</i>	<u>22%</u>	2/9
<i>Relapse of Category I</i>	4%	1/23
<i>Return after default of Category I</i>	12%	3/25
<i>All retreatment groups</i>	10.5%	6/57

Treatment *outcome* with SCC in relation to prior treatment.

Clinical Trial. Tuberculosis Research Centre. India

Int J Tuberc Lung Dis. 2001 Jan;5(1):40-5



U* = unfavourable response during treatment
Rel = Relapse during follow up

 Initial HR Resistant
 Acquired HR Resistant

**Very Low Rate
MDR between
Failures and
Unfav. Resp.**

Brazil: Rates of MDR-TB in failures (1986-90)

Kritski AL, et al. Chest. May 1997;111(5):1162-1167.

Cat. I: 2 HRZ / 4 HR

Retreatment Group	Percentage of MDR TB	Number of Patients
Failures of Category I	33%	29/91
Relapse/Default of Category I	6%	2/37
Failures of retreatment (most commonly HREZS, and on some occasions oflo, clof, rifabutin were included.	65%	49/78

Thailand: Rates of **MDR-TB in the different retreatment categories for 59 cases with DST at the start of their first treatment and start of retreatment (29% were HIV positive)**

Yoshiyama T, et al. *Int J Tuberc Lung Dis.* Jan 2004;8(1):31-38.

Retreatment Group	Percentage of MDR TB	Number of Patients
Failures of Category I with HR in the continuation phase	<u>86%</u>	19/22
Relapse of Category I with HR in the continuation phase	11%	2/18
Return after default of Category I with HR in the continuation phase	5%	1/19

Peru: Rates of **MDR-TB** in Failures to Cat. I

Saravia JC, et al. *Int J Tuberc Lung Dis* 2005, 9: 421-9reviewers].

<i>Retreatment Group</i>	<i>Percentage MDR-TB</i>	<i>Number of Patients</i>
<i>Failures of Category I with H₂R₂ in the continuation phase</i>	<i><u>88%</u></i>	<i>125 consecutive failures from category I, 91 had DST and 80/91 had MDR-TB</i>

High Probability of Resistance Failures



In the field, **Not all** the Failures (even the failures to Cat. II) are **MDR-TB**

Why an **Operational** Failure can be Susceptible?

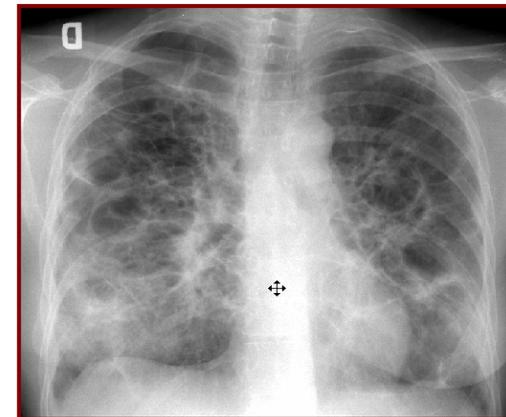
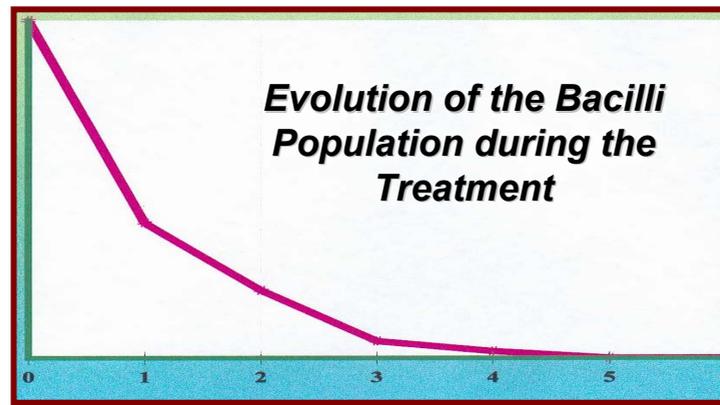
Why an Operational **Failure** can be **Susceptible**?

5 **POSSIBILITIES** (1)

1. Very **Late** Negativization (Later than 4° m.)

- It can occur in the **0.25-1%** of the Cohort, specially linked to some circumstances:

- Sm++++ and extensive cavitary lesions
- Acid media in some lesions → bad pharmacodinamic of the drugs



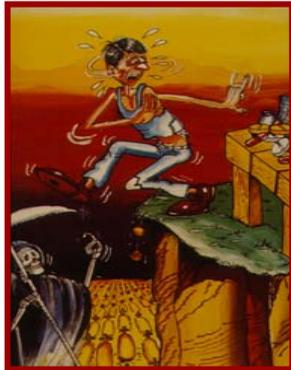
Why an Operational **Failure** can be **Susceptible**?

5 **POSSIBILITIES** (2)

2. **Bad Adherence** (Supervision) to the Treatment

- **WARNING**: High Risk of Resistance if:

- The patient take only a **single** drug
- The patient is **regular** in the bad **adherence**

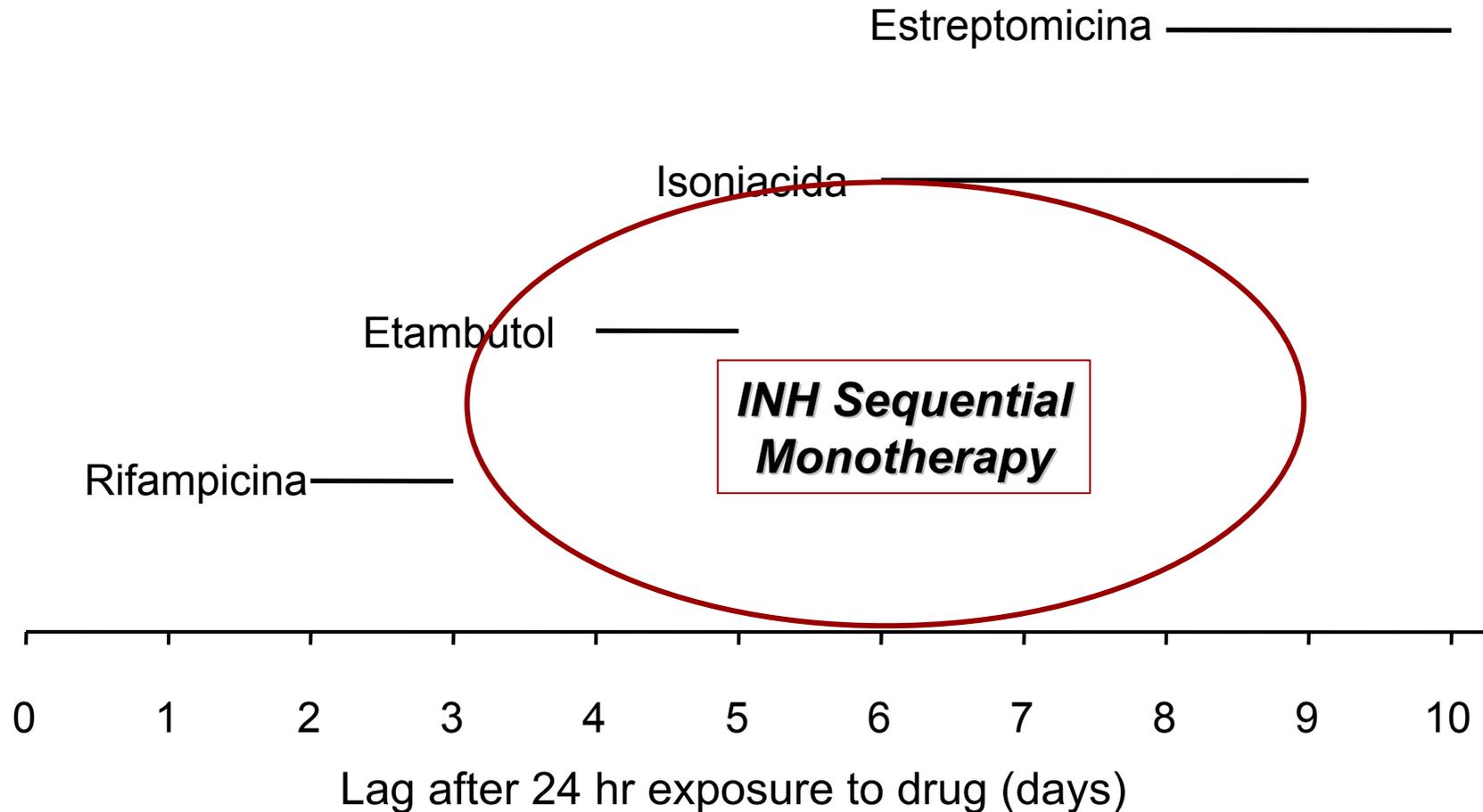


DOTS is Pivotal to avoid this risk of Resistance



Post-Antibiotic Effects with *M. tuberculosis*

Lag Periods before Commencement of Growth after Exposure in 7H10 Medium



Why an Operational **Failure** can be **Susceptible**?

5 **POSSIBILITIES** (2)

3. **Nontuberculous Mycobacteria**

- **In some Projects can be the 5-10% of the theoretical MDR-TB**



An adequate **Identification** (Lab. Network) is essential

Why an Operational **Failure** can be **Susceptible**?

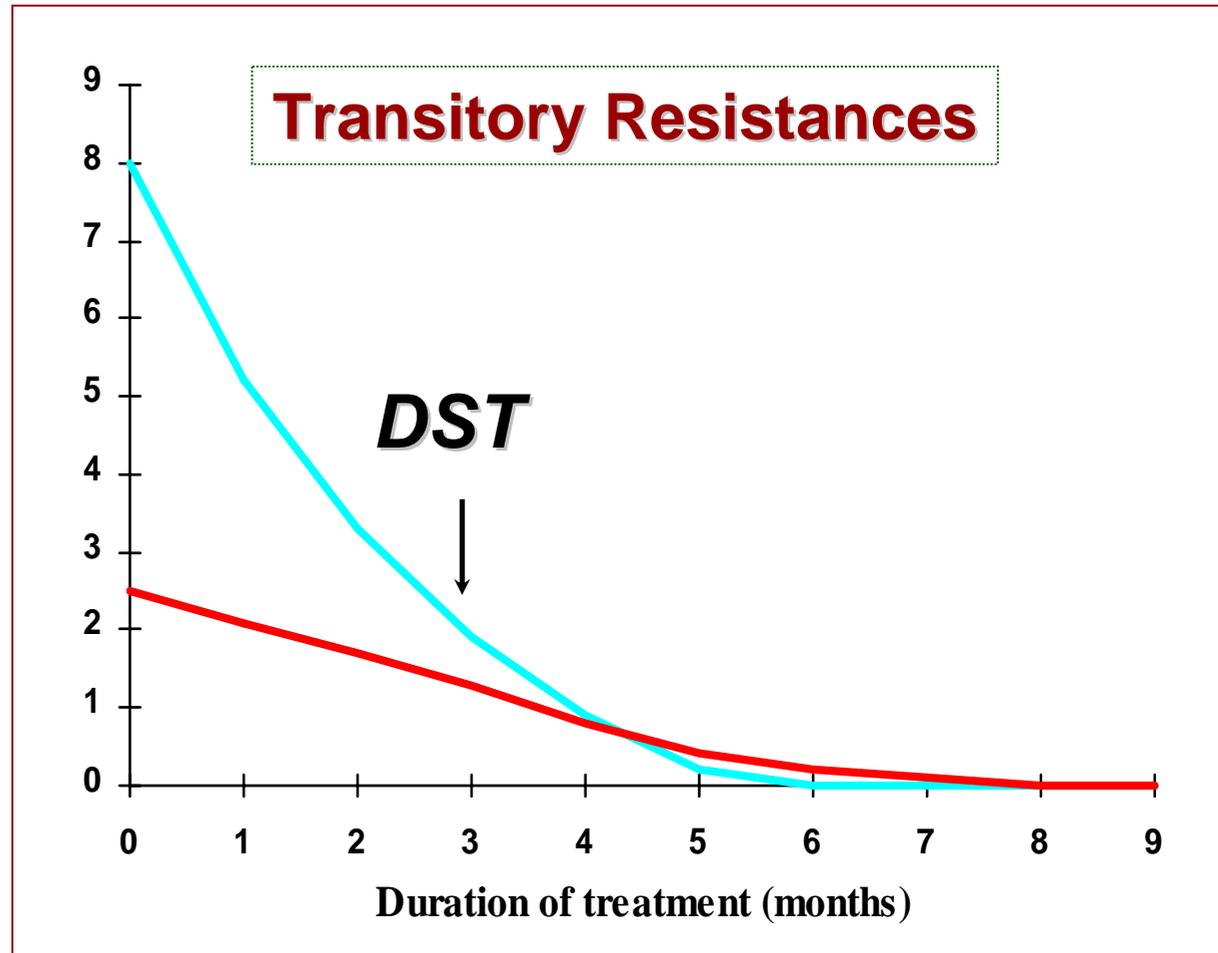
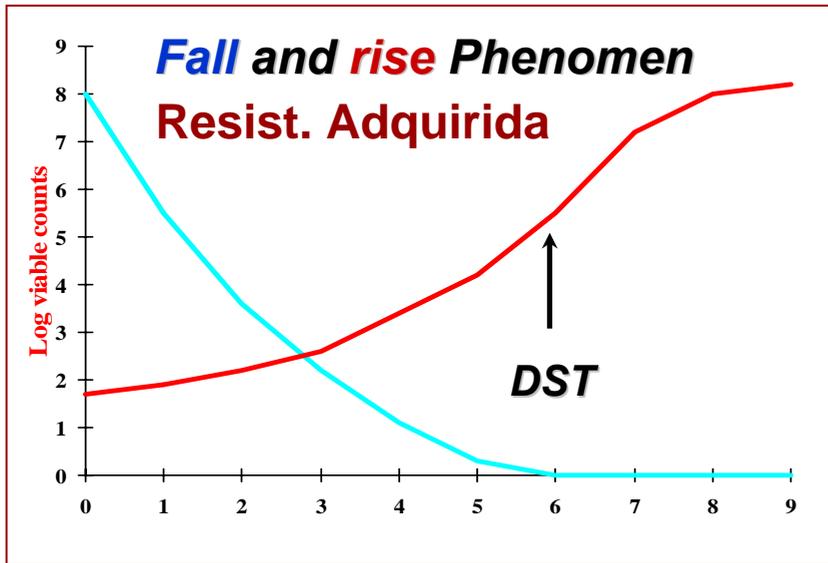
5 **POSSIBILITIES** (2)

4. **Bacillary Escapes**

- They are the patients who, after a good bacteriological evolution (negativitation of the cultures), it is appear a solitary Positive Culture at 4-5^o months, but only with **< 10-20 Colonies**
- Only is possible to detect by Culture (Sm-)
- It is the elimination of the last bacillus, with not significance if other cultures are negative
- Never perform DST → **Transitory Resistance**



Transitory Resistances in TB



The *Transitory* Resistances do not alter the outcome of the Treatment and, for this reason, it *should not be changed*

Why an Operational *Failure* can be *Susceptible*?

5 *POSSIBILITIES* (2)

5. *Died Bacillus*

- The treatments with INH-RIF are very *bactericidal* and it can kill a lot of bacillus (above in the Sm+++⁺) in the first months, and these bacillus can be observed in the smear, but they can not grow in the cultures because they are *died* bacillus
- It is not an unusual circumstance in the 1-2^o months of the treatment, but also is possible in the 4-5^o months

WARNING: The NTP are accepting Failure by the *Smear*

Suspects of Resistances

1. High Probability of Resistance

1. Failures to the Standard Short Course of Chemotherapy (SCC)

- Failures of Cat. II and Chronics

- Highest Probability

- Failures of Cat. I

2. Exposure to a known MDR-TB case



High Probability of Resistance

3. *Exposure* to a known *MDR-TB* case

Most studies have shown close *contacts* of MDR-TB patients to have very *high* rates of *MDR-TB*



Transmission of Tuberculosis to Close Contacts of Patients with Multidrug-resistant Tuberculosis

AFRANIO L. KRITSKI, MARIA J. OZORIO MARQUES, MARCELO F. RABAHI, MARIA A. M. SILVA VIEIRA, EDUARDO WERNECK-BARROSO, CARLOS E. S. CARVALHO, GERALDO DE NORONHA ANDRADE, ROBERTO BRAVO-DE-SOUZA, LAERTE M. ANDRADE, PAULO P. GONTIJO, and LEE W. RILEY

Serviço de Pneumologia, Hospital Clementino Fraga Filho, Universidade Federal de Rio de Janeiro; Instituto de Tisiologia e Pneumologia da Universidade Federal do Rio de Janeiro; and Hospital Evandro-Changas, Instituto Oswaldo Cruz, Rio de Janeiro, Brazil, and Division of International Medicine, Cornell University Medical College, New York, New York

Multidrug-resistant tuberculosis (MDRTB) has emerged as a major public health problem worldwide. To determine the incidence and risk factors associated with tuberculosis among contacts of MDRTB index cases, we studied human immunodeficiency virus-seronegative close contacts of 64 culture-confirmed MDRTB patients in Rio de Janeiro, Brazil. Between March 1988 and July 1992, tuberculosis developed in 17 (7.8%) of 218 previously healthy close contacts of 64 MDRTB index cases (1.6 cases per 1,000-person-months of contact). Among strains of *Mycobacterium tuberculosis* isolated from 13 contacts of 12 index cases, six (46%) had susceptibility patterns identical to those of their index cases, four (31%) had different patterns of resistance, and three (23%) were susceptible to all drugs. Tuberculosis developed more frequently in male contacts ($p < 0.05$), persons ≥ 15 yr of age ($p < 0.05$), nonwhites ($p < 0.001$), and persons not previously vaccinated with bacillus Calmette-Guerin (BCG) ($p < 0.05$). The association of BCG vaccination with decreased risk of disease was significant even when this variable was controlled (by Cox's regression analysis) for age, sex, race, purified protein derivative (PPD) status, and isoniazid prophylaxis. BCG vaccination appears to offer protection against tuberculosis during prolonged exposures to persons with MDRTB, which identifies a novel and specific indication of BCG use. Kritski AL, Ozorio Marques MJ, Rabahi MF, Silva Vieira MAM, Werneck-Barroso E, Carvalho CES, de Noronha Andrade G, Bravo-de-Souza R, Andrade LM, Gontijo PP, Riley LW. Transmission of tuberculosis to close contacts of patients with multidrug-resistant tuberculosis.



Infection and disease among household contacts of patients with multidrug-resistant tuberculosis

L. Teixeira,* M. D. Perkins,[†] J. L. Johnson,[‡] R. Keller,* M. Palaci,* V. do Valle Dettoni,*
L. M. Canedo Rocha,* S. Debanne,[§] E. Talbot,[†] R. Dietze*

* Núcleo de Doenças Infecciosas, Universidade Federal do Espírito Santo, Vitória, Brazil; [†] Department of Medicine, Duke University Medical Center, Durham, North Carolina, [‡] Department of Medicine, Division of Infectious Diseases, and [§] Department of Epidemiology and Biostatistics, Case Western Reserve University, Cleveland, Ohio, USA

SUMMARY

SETTING: Urban public teaching and referral hospital in Espírito Santo, Brazil.

OBJECTIVE: To assess whether rates of infection and progression to active tuberculosis (TB) differed between household contacts of patients with multidrug-resistant (MDR) and drug susceptible (DS) pulmonary tuberculosis.

DESIGN: Household contacts were assessed for evidence of TB infection and disease by purified protein derivative (PPD) skin testing, physical examination, chest X-ray, and sputum smear and culture.

RESULTS: Among 133 close contacts of patients with MDR-TB, 44% were PPD-positive (≥ 10 mm) compared to 37% of 231 contacts of the DS-TB cases ($P = 0.18$, χ^2 test, OR 1.2, 95%CI 0.8–2). In a multivariate logistic regression analysis, after allowance for between-household variation in PPD responses, PPD positivity among household contacts of patients with MDR-TB remained comparable to PPD positivity in contacts of

patients with DS-TB (OR 2.1, 95%CI 0.7–6.5). Respectively six (4%) and 11 (4%) contacts of the MDR- and DS-TB cases were found to have active TB at the time of initial evaluation or during follow-up ($P = 0.78$, χ^2 test). Five of six contacts of MDR-TB cases and nine of nine contacts of DS-TB cases who developed TB, and for whom drug susceptibility test results were available, had the same bacterial susceptibility profiles as their index cases. DNA fingerprinting analysis of *Mycobacterium tuberculosis* isolates was identical between household contacts with active TB and the index MDR or DS-TB case for all 14 pairs compared.

CONCLUSION: Our data suggest that the prevalence of tuberculous infection and progression to active TB among household contacts exposed to DS and MDR-TB cases is comparable, despite a longer duration of exposure of contacts to the index case in patients with MDR-TB.

KEY WORDS: tuberculosis; MDR-TB; PPD; transmission



Transmission of multidrug-resistant tuberculosis

H. SIMON SCHAAF, MMED (PED), ANNELIES VAN RIE, MD, ROBERT P. GIE, MMED (PED), NULDA BEYERS, PHD, TOMMY C. VICTOR, PHD, PAUL D. VAN HELDEN, PHD AND PETER R. DONALD, MD

Aim. To compare the *Mycobacterium tuberculosis* isolates of adult index cases with multidrug-resistant (MDR) tuberculosis to the isolates obtained from their child contacts.

Patients and methods. A 4-year prospective study in the Western Cape Province of South Africa. We evaluated 149 child contacts of 80 adult MDR pulmonary tuberculosis cases. This report includes those cases where a culture for *M. tuberculosis* was obtained from both the adult source case and the child contact. Isolates were compared by drug susceptibility pattern and restriction fragment length polymorphism analysis.

Results. Six adult-child pairs with cultures for *M. tuberculosis* were identified. Two children had contact with more than one adult tuberculosis case. One child received previous isoniazid prophylaxis. Drug susceptibility pattern and restriction fragment length polymorphism analysis were identical for five adult-child pairs. One child, with no other known source case, had a strain different from that of the identified source case, but the MDR *M. tuberculosis* strain with which he was infected was prevalent in the community in which he resided. All children responded well to treatment.

Conclusion. This study confirms that most of the childhood contacts of adults with MDR tuberculosis are likely to be infected by these MDR source cases despite their exposure to other drug-susceptible adults with tuberculosis in some instances. Child contacts of adults with MDR tuberculosis should be treated according to the drug susceptibility patterns of the likely source cases' *M. tuberculosis* strains unless their

own strain's susceptibility testing indicates otherwise. Contact tracing remains of fundamental importance in identifying children at risk.

INTRODUCTION

Drug-resistant *Mycobacterium tuberculosis* strains had been postulated to be less infectious and to be less likely to cause disease than their drug-susceptible counterparts¹ but recent studies have shown them to cause infection and disease as often as drug-susceptible organisms.²⁻⁴ It is further presumed that a person in contact with both drug-susceptible and drug-resistant source cases will be less likely to develop drug-resistant tuberculosis (TB).⁵ When young children develop drug-resistant TB, it is most likely primary resistance caused by transmission.^{6,7} Studies have compared the characteristics of *M. tuberculosis* strains from children in contact with adults with single and multiple (excluding rifampin) drug-resistant TB by drug susceptibility patterns only.^{2,3} These studies found a high degree of correlation between the susceptibility patterns of the source cases and the child contacts.

Restriction fragment length polymorphism (RFLP) analysis is a useful epidemiologic tool to trace the transmission of particular strains of *M. tuberculosis* during investigations of outbreaks mainly in large epidemiologic studies in adults.^{8,9} It has been used in a nosocomial outbreak of TB in pediatric wards¹⁰ and to prove adult to child transmission of drug-susceptible TB.¹¹ The aim of this study was to compare the isolates of adult index cases with multidrug-resistant (MDR) TB and their child contacts by drug susceptibility pattern as well as by RFLP analysis.

PATIENTS AND METHODS

This prospective study was conducted between April 1994 and March 1998 in the Western Cape



Evaluation of Young Children in Contact With Adult Multidrug-Resistant Pulmonary Tuberculosis: A 30-Month Follow-up

H. Simon Schaaf, MMed (Paed); Robert P. Gie, MMed (Paed); Magdalene Kennedy, Dipl Nurs; Nulda Beyers, PhD; Peter B. Hesselning, MD; and Peter R. Donald, MD

ABSTRACT. *Setting.* The Western Cape Province of South Africa, an area with a high tuberculosis (TB) incidence, where initial multidrug resistance (MDR) among adult TB cases was 1.1% during 1992–1993.

Objective. To determine the long-term prevalence of TB infection and disease in children in household contact with adults with MDR pulmonary TB, and to establish the efficacy of chemoprophylaxis in preventing disease in these children.

Method. Children <5 years old in contact with 73 MDR TB adults were evaluated. Disease was treated by prescribing at least 2 drugs to which the adult's strain was susceptible. The remaining children were classified as infected or noninfected and received chemoprophylaxis according to the index's strain susceptibility or were followed up and treated when indicated. All were followed up for 30 months.

Results. At the initial evaluation 125 children were seen, median age 27.5 months. Of these, 119 were followed up. Fourteen (12%) had disease, 61 (51%) were infected only, and 44 (37%) were noninfected. By 30-month follow-up, 29 (24%) had developed disease and 64 (54%) were infected only. Four adult-child pair *Mycobacterium tuberculosis* isolates were compared by DNA fingerprinting; 3 were identical. All children who developed TB disease were clinically cured. Two (5%) of 41 children who received appropriate chemoprophylaxis and 13 (20%) of 64 who did not, developed TB during follow-up (odds ratio: 4.97).

Conclusion. The study confirms MDR TB transmission to childhood contacts. Seventy-eight percent of children were infected or developed disease. Appropriate chemoprophylaxis may prevent disease in these children. *Pediatrics* 2002;109:765–771; tuberculosis, multidrug-resistant, children, contacts, follow-up, chemoprophylaxis.

Tuberculosis (TB) contact tracing has produced a significant yield of new TB cases and newly infected patients in the past.¹ Children in close contact with drug-susceptible adult pulmonary TB have a high risk of becoming infected and developing disease.^{2,3} It is generally accepted that 30% to 50% of household contacts of adults with infectious forms of pulmonary TB will become infected.³ The risk for young children with untreated infection to develop TB is up to 43% in children <1 year of age and about 24% for children 1 to 5 years of age.³ Little is known, however, about the long-term outcome of children in contact with multidrug-resistant (MDR) adult pulmonary TB cases. Although studies in guinea pigs suggested that isoniazid-resistant strains are less infectious and cause less disease than the drug-susceptible strains, this diminished infectiousness and pathogenicity was not confirmed in human studies.^{4,5} The management of adults or children in contact with infectious MDR pulmonary TB cases is still very uncertain and, although many suggestions for different regimens for MDR chemoprophylaxis have been made, there are no prospective studies to verify their effectiveness.⁶ Furthermore, the optimal duration of chemoprophylaxis with these drugs is uncertain.^{6,7} On the other hand, the implications of not being able to give adequate chemoprophylaxis to children infected with MDR strains of *Mycobacterium tuberculosis* are serious, because about 10% or more of infected children will develop TB disease in their lifetime, and they will have the potential to continue the transmission of MDR TB in future.⁸

Drugs used in the treatment of MDR TB cases are generally much more toxic than first-line drugs. In



Contact investigations as a means of detection and timely treatment of persons with infectious multidrug-resistant tuberculosis

J. Bayona,*† A. M. Chavez-Pachas,‡ E. Palacios,* K. Llaro,* R. Sapag,* M. C. Becerra†

* Socios En Salud Sucursal Peru/Partners In Health, Lima, Peru; † Department of Social Medicine, Harvard Medical School, Boston, Massachusetts, USA; ‡ Dirección de Salud V Lima Ciudad, Programa de Control de Tuberculosis, Lima, Peru

SUMMARY

SETTING: Two regions of metropolitan Lima, Peru.

OBJECTIVE: To determine the outcomes of two contact investigation strategies used in therapy enrollment cohorts of patients with multidrug-resistant tuberculosis (MDR-TB).

DESIGN: From 28 August 1996 to 31 December 1999, 91 index patients received individualized MDR-TB therapy (Group A), and from 1 October 1997 to 31 December 1999, another 101 index patients received a standardized MDR-TB regimen (Group B). We conducted a retrospective chart review and home visits to identify secondary cases among close contacts of both of these groups. Group A secondary cases with MDR-TB received therapy based on the drug susceptibility profile of their infecting strain, while Group B secondary cases received standard short-course therapy.

RESULTS: Among 945 close contacts, 72 secondary TB cases (8%) were found. Of 42 who had drug-susceptibility testing, 35 (84%) were MDR-TB, but only seven (17%) had the same drug susceptibility profile as the index case. Cure exceeded 80% in Group A secondary cases, while only half of Group B secondary cases were cured (RR 1.6, 95%CI 1.1–2.2).

CONCLUSION: Contact investigation protocols coupled with enrollment in MDR-TB therapy are a useful means of detecting and promptly treating persons with infectious MDR-TB. In settings with endemic MDR strains of *Mycobacterium tuberculosis*, effective therapy of contacts of MDR-TB patients requires knowledge of drug susceptibility for each contact with active disease.

KEY WORDS: contact investigations; multidrug-resistant tuberculosis; case finding; DOTS-Plus; Peru



Rates of **MDR-TB** among **Contacts** of MDR-TB patients

<i>Study</i>	<i>Country</i>	<i>Number of contacts</i>	<i>Percentage of patients with MDR-TB (# of TB case/total # with active TB)</i>
<i>Kritski et al. (1996)</i>	<i>Brazil</i>	218	<u>62%</u> (8/13)
<i>Schaaf et al. (2000)</i>	<i>South Africa</i>	149	<u>83%</u> (5/6)
<i>Texeira et al. (2001)</i>	<i>Brazil</i>	133	<u>83%</u> (5/6)
<i>Schaaf et al. (2002)</i>	<i>South Africa</i>	119	<u>75%</u> (3/4)
<i>Bayona et al (2003)</i>	<i>Peru</i>	945	<u>84%</u> (35/42)



2. Middle to Low Probability of Resistance ***In some Settings can be associated with a middle rate of Resistance (1)***

4. Failure of anti-TB Treatment in the Private Sector

5. Patients who Remain Sm+ at 2-3 m. of the Cat. I

6. Relapses and Return after Defaults

7. Exposure in Institutions that have MDR-TB out-breaks or a high MDR-TB prevalence



2. Middle to Low Probability of Resistance ***In some Settings can be associated with a middle rate of Resistance (2)***

- 8. Residence in **Areas** with **high MDR-TB** prevalence***
- 9. History of using antituberculosis drugs of **Poor** or **unknown Quality*****
- 10. Treatment in **programmes** that operate **poorly** (especially recent and/or frequent **drug stock-outs**)***



4. **Failure** of antituberculosis treatment in the **Private** Sector

- Antituberculosis regimens from the **private** sector can **vary** greatly
- A detailed **history** of drugs used is essential.
- If both isoniazid and rifampicin were used, the chances of **MDR-TB** may be high
- Sometimes **second-line** antituberculosis drugs may have been used, and this is important information for designing the re-treatment regimen.





Tuberculosis patients and practitioners in private clinics in India

M. Uplekar, S. Juvekar, S. Morankar, S. Rangan, P. Nunn*

The Foundation for Research in Community Health, Worli, Mumbai India, * Global Tuberculosis Programme, World Health Organisation, Geneva, Switzerland

SUMMARY

SETTING: Rural and urban areas of Maharashtra, a large state in Western India.

OBJECTIVE: To understand tuberculosis (TB) management practices among private medical practitioners (PPs) and the treatment behaviour of the patients they manage.

DESIGN: Prospective study of help-seeking patterns and treatment behaviour among 173 pulmonary TB patients diagnosed in private clinics, and the TB management practices of 122 PPs treating these patients.

RESULTS: The first source of help for 86% of patients was a PP. The diagnostic and treatment practices of PPs were inadequate; 15% did not consider sputum examination to be necessary, and 79 different treatment regimens were prescribed by 105 reporting PPs. Sixty-seven

percent of the patients diagnosed in private clinics remained with the private sector, and the rest shifted to public health services within six months of treatment. The treatment adherence rate among the patients in private clinics was 59%. There were discrepancies between the reported management practices of the PPs and what their patients actually followed.

CONCLUSION: The study identifies and highlights the need to educate PPs and their TB patients, and indicates ways in which PPs could be meaningfully involved in efforts to revitalise the national TB control programme.

KEY WORDS: India; tuberculosis; private practitioners; management practices; patient behaviour

A survey of prescribing patterns for tuberculosis treatment amongst doctors in a Bolivian city

J. E. Ollé-Goig,* J. E. Cullity,† R. Vargas‡

*German Leprosy Relief Association (DAHW), Santa Cruz, Bolivia, †London School of Hygiene and Tropical Medicine, Maternal and Child Epidemiology Unit, London, UK, ‡Universidad Católica Boliviana, Santa Cruz, Bolivia

SUMMARY

SETTING: A sample survey of knowledge about prescribing tuberculosis treatment among private physicians in the city of Santa Cruz, Bolivia.

OBJECTIVES: To study the anti-tuberculosis regimens prescribed by private physicians and to assess the number of tuberculosis patients treated by them.

DESIGN: Questionnaire survey of a random sample of 401 private physicians in Santa Cruz.

RESULTS: Of the 401 physicians, 165 (41%) could not be located or did not want to participate. Among the 236 completed questionnaires, 137 physicians (58%) stated that they did not see patients with tuberculosis, 16 (7%) referred them to other centres and 83 (35%) treated them in their practice. Among 80 prescribed regimens that could be evaluated there were 58 different regimens: 17 (21%) followed the National Tuberculosis Control Programme's standard regimen, but overall 35 regimens (60%) were incorrect—18 regimens (31%)

were non-curative and 17 (29%) could not be recommended. Frequent errors were the prescription of medications not available in the market (7%) or not included in the national regimen (34%), the prescription of insufficient medications (9%), or of only one in the continuation phase (16%), or for too short (9%), or too long (12%) a period. Eighty physicians estimated that they attended in their practice an average total of 404 patients with tuberculosis per month.

CONCLUSIONS: A significant number of physicians in private practice did not adhere to the standard norms for prescribing anti-tuberculosis treatment. This study also suggests that in the city of Santa Cruz, Bolivia, there is a not insignificant number of patients with tuberculosis treated outside the National Tuberculosis Control Programme.

KEY WORDS: tuberculosis; prescribing; treatment; physicians; Bolivia



5. Patients who remain sputum *Sm+* at month 2 or 3 of SCC

- **Many programmes may choose to do culture and DST on patients who remain sputum *smear-positive* at months 2 and 3**
- **This group of patients is at risk for *MDR-TB*, but rates can vary considerably**
- **Anyway, this situation should be considered a *Risk Factor* for Failure and MDR-TB**



Should we take a history of prior treatment, and check sputum status at 2-3 months when treating patients for tuberculosis?

D. Wilkinson,*†‡ S. Bechan,* C. Connolly,* E. Standing,§ G. M. Short†

*Centre for Epidemiological Research in Southern Africa, Medical Research Council, South Africa,

†Division of Tropical Medicine, Liverpool School of Tropical Medicine, UK, ‡Hlabisa Hospital, Hlabisa,

§Pinetown Municipality, Pinetown, and †Regional Office, State Health Department, Durban, South Africa

SUMMARY

SETTING: Pinetown, South Africa (1975-1983).

OBJECTIVE: To determine the value of previous treatment history and sputum smear examination at 2-3 months in predicting treatment failure and relapse in tuberculosis patients treated with four drugs given twice weekly for six months under direct observation.

DESIGN: Four cohort studies among 562 ambulant adults with culture positive pulmonary tuberculosis, designed to test the effectiveness of isoniazid 600-900 mg, rifampicin 600 mg, pyrazinamide 2-3 g, and streptomycin 1-2 g, given twice weekly. The same drug regimen was given to all patients irrespective of previous treatment history. Therapy was not changed if smears remained positive at 2-3 months.

RESULTS: Positive predictive values of a history of previous treatment for a positive smear at 2-3 months

(18.3%), treatment failure (5.2%), and relapse (9.4%) were poor. Although patients with positive smears at 2-3 months were more likely to fail therapy than patients with negative smears (relative risk = 4.5, 95% Confidence Interval [CI]: 1.6-12.8), positive predictive value for treatment failure was only 12.5%. Although relapse was more frequent in patients with positive smears than those with negative smears (9.7% vs 6.2%; $P = 0.4$), most patients who relapsed had been smear negative at 2-3 months (18/21).

CONCLUSION: A four-drug rifampicin-containing regimen can safely be given twice weekly under direct observation to both new and retreatment cases, and the 2-3 month smear examination can safely be omitted.

KEY WORDS: tuberculosis; treatment history; sputum smear examination



Identifying early treatment failure on Category I therapy for pulmonary tuberculosis in Lima Ciudad, Peru

A. M. Chavez Pachas,* R. Blank,^{†‡} M. C. Smith Fawzi,^{†‡} J. Bayona,^{†‡§} M. C. Becerra,^{†‡} C. D. Mitnick^{†‡}

* Programa de Control de Tuberculosis, Direccion de Salud V Lima Ciudad, Lima, Peru; † Partners In Health, Boston,

‡ Harvard Medical School, Boston, Massachusetts, USA; § Socios En Salud—Sucursal Peru, Lima, Peru

SUMMARY

SETTING: Ambulatory, public tuberculosis treatment facilities, central Lima, Peru.

OBJECTIVE: To identify risk factors for failure on directly observed Category I therapy.

DESIGN: Case-control study. All failures of Category I (2HREZ/4H₂R₂) therapy in 2000 (2.9% of smear-positive TB patients) were included as cases; two controls per case were matched on health center and approximate time of treatment initiation.

RESULTS: The study included 38 cases and 76 controls, all new smear-positive, pulmonary TB patients treated with Category I therapy in central Lima in 2000. Neither treatment irregularity nor incidence of adverse events predicted failure in the study group. Mean baseline body mass index was lower in cases than in controls ($P = 0.06$). Cases gained less weight during therapy ($P =$

0.01). Smear positivity at 2 months of therapy was strongly associated with failure (OR 11.7; 95%CI 2.4–57.5). No controls had positive smears at or after 3 months of therapy (OR [corrected] 144.9; 95%CI 8.4–2500). Nearly 75% of cases with isolates tested for susceptibility to first-line drugs had multidrug-resistant TB (MDR-TB).

CONCLUSION: A large proportion of failures on Category I therapy can be identified early. As three-quarters of patients with susceptibility results have MDR-TB, early referral for culture and drug susceptibility testing is critical for prompt initiation of appropriate therapy and improved outcomes.

KEY WORDS: treatment failure; smear conversion; multidrug-resistant tuberculosis



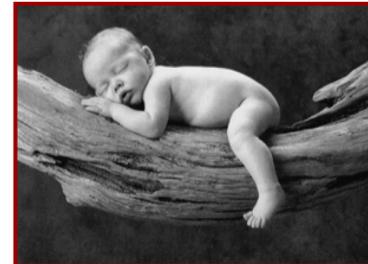
6. **Relapse** and return after **default** without recent treatment failure

- From a **bacteriological** point of view, the **Relapses** and Return after **Default** are **Susceptible**, because they are motivated by the Latent *Bacillus* (not division during the treatment)
- However, in the field, the Relapses and the Defaulters are **Amplifying** the Initial **Resistances**
- Certain histories may point more strongly to **possible** MDR-TB; for example, erratic drug use or early relapses.



Bacteriological Relapse

- ***This is when a patient has concluded treatment and has been **Cured** and then presents TB symptoms with positive bacteriology again.***
- ***It is caused by **Latent** Bacillary Population.***
- ***It may be **Early** (< 24 months) or **Late*****
- ***It is usually **Sensitive** to Drugs used.***
- ***Sensitivity Tests should be performed.***

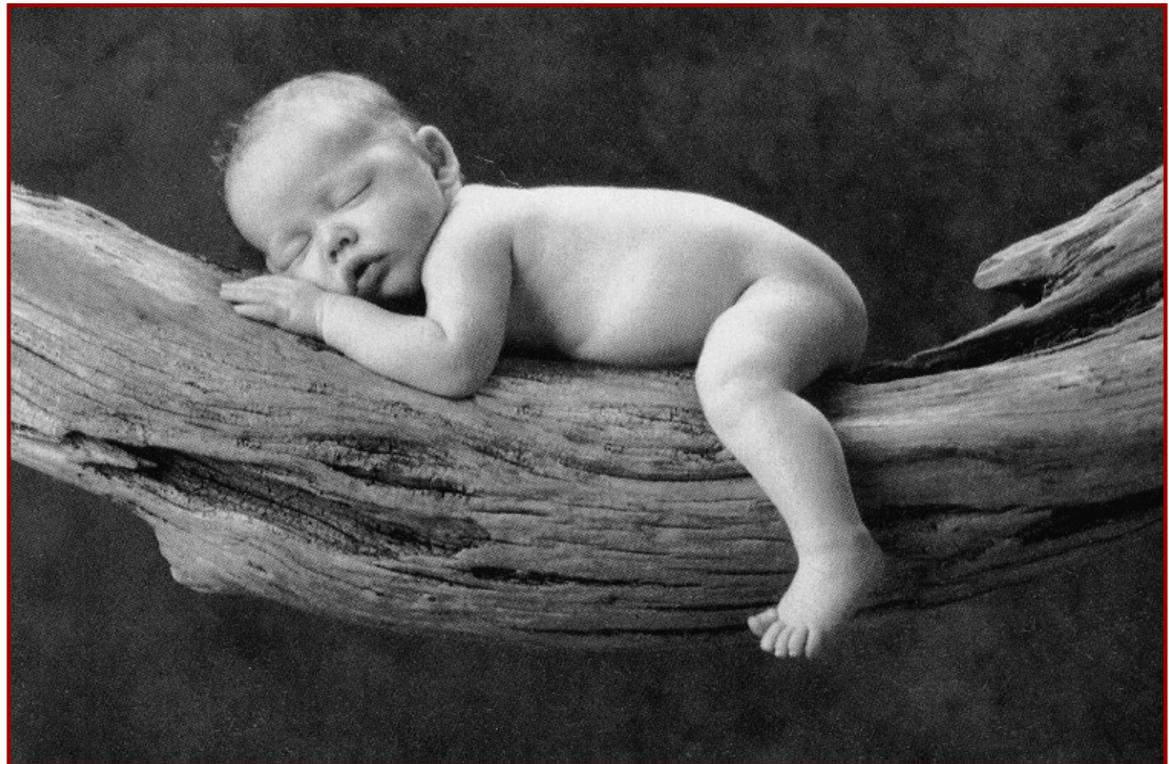


Bacillary populations

2. Slow multiplication Bacilli → **Relapses**

- *Intramacrophagic location. Acid pH. Population 10^5*

No Natural Resistant Mutants



Bacillary populations

3. Intermittent growth Bacilli → **Relapses**

- Unfavourable conditions. Solid caseum. Extracellular
- Population $<10^5$
- Relapse capacity

No Natural Resistant Mutants



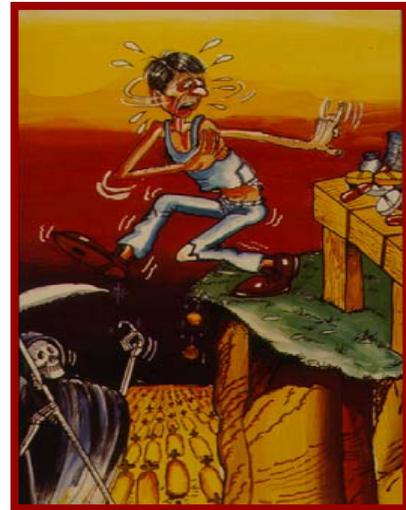
Treatment Default

- A patient is thus defined if he/she stops taking the medication for more than 1-2 months.

- Default in taking medication may be:

- Total: *Like a Relapse*
Probable Sensitivity to Drugs taken

- Partial: *Like a Failure*
Probable Resistance to the Drug taken



TB Re-Treatment and Selection of Resistances

- Theoretically:

- The **Relapses** and Total **Defaulters** have the same Initial pattern of Resistances
- The **Failures** and Partial Defaulters could Amplify Resistances

- However, in the Field:

- The **Relapses** and Total **Defaulters** increase the rate of Initial Resistances
- A lot of **Failures** are **Susceptible**



Vietnam: Rates of **MDR-TB** in different retreatment groups

Quy HTW, et al. Int J Tuberc Lung Dis 2003 7(7):631-36

Cat. I: 2 HRZE / 6 HE

Patient group	Percentage of <i>MDR-TB</i>	Number of Patients
<u>Failures</u> of Category I	80%	32/40
Relapse of Category I	<u>8%</u>	3/39

Benin: Rates of **MDR-TB** in the different re-treatment categories, 1994-1995

Cat. I: 2 HRZE / 6 HT

Trébuçq A, et al. Int J Tuberc Lung Dis 1999; 3: 466-470.

<i>Retreatment Group</i>	<i>Percentage of MDR TB</i>	<i>Number of Patients</i>
Failures of Category I	<u>22%</u>	2/9
Relapse of Category I	<u>4%</u>	1/23
Return after default of Category I	<u>12%</u>	3/25
All retreatment groups	10.5%	6/57

Brazil: Rates of MDR-TB in failures (1986-90)

Kritski AL, et al. Chest. May 1997;111(5):1162-1167.

Cat. I: 2 HRZ / 4 HR

Retreatment Group	Percentage of MDR TB	Number of Patients
Failures of Category I	33%	29/91
Relapse/Default of Category I	<u>6,4%</u>	2/37
Failures of retreatment (most commonly HREZS, and on some occasions oflo, clof, rifabutin were included.	65%	49/78

Thailand: Rates of **MDR-TB in the different retreatment categories for 59 cases with DST at the start of their first treatment and start of retreatment (29% were HIV positive)**

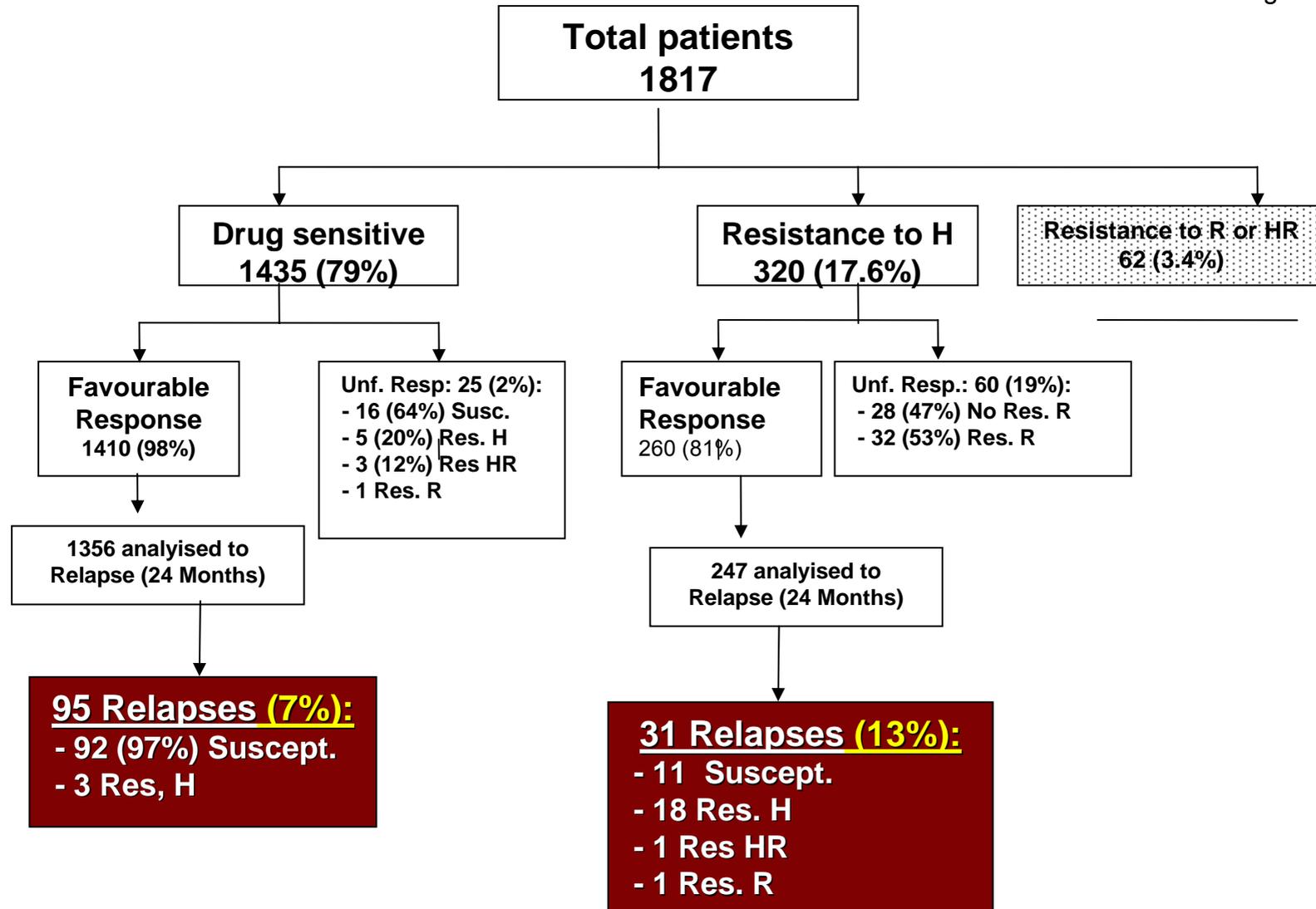
Yoshiyama T, et al. *Int J Tuberc Lung Dis.* Jan 2004;8(1):31-38.

Retreatment Group	Percentage of MDR TB	Number of Patients
Failures of Category I with HR in the continuation phase	86%	19/22
<u>Relapse</u> of Category I with HR in the continuation phase	11%	2/18
<u>Return after default</u> of Category I with HR in the continuation phase	5%	1/19

Treatment *outcome* with SCC in relation to prior treatment.

Clinical Trial. Tuberculosis Research Centre. India

Int J Tuberc Lung Dis. 2001 Jan;5(1):40-5



7. *Exposure in Institutions that have MDR-TB out- breaks or a high MDR-TB prevalence*



Patients who frequently stay in homeless shelters, prisoners in many countries and health-care workers in clinics, laboratories and hospitals can have high rates of MDR-TB

Outbreak of multidrug-resistant tuberculosis at a methadone treatment program

C. Conover,* R. Ridzon,[†] S. Valway,[†] L. Schoenstadt,[‡] J. McAuley,[†] I. Onorato,[†] W. Paul,[‡] and an investigative team[§]

* Epidemiology Program Office, and [†] Division of Tuberculosis Elimination, Centers for Disease Control and Prevention, Atlanta, Georgia; [‡] TB Control Program, Chicago Department of Public Health, Chicago, Illinois, USA

Multidrug-resistant tuberculosis outbreak among transvestite sex workers, Buenos Aires, Argentina

D. Palmero,* V. Ritacco,[†] S. Ruano,[‡] M. Ambroggi,[§] L. Cusmano,[‡] M. Romano,[‡] Z. Bucci,[‡] J. Waisman*

* Tuberculosis Multirresistente/SIDA, Hospital Muñiz, Buenos Aires, [†] Laboratorio de Micobacterias, Instituto Nacional de Enfermedades Infecciosas Administración Nacional de Laboratorios e Institutos de Salud (INEI ANLIS) Malbrán, Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Buenos Aires, [‡] Servicio de Promoción y Protección de la Salud, and [§] Laboratorio de Bacteriología de la Tuberculosis A Cetrángolo, Hospital Muñiz, Buenos Aires, Argentina



Outbreak of Multi-Drug-resistant Tuberculosis in a New York State Prison, 1991

Am J Epidemiol 1994;140:113-22.



Sarah E. Valway,¹ Sonia B. Richards,² Joan Kovacovich,¹ Robert B. Greifinger,³ Jack T. Crawford,⁴ and Samuel W. Dooley¹

Nosocomial Transmission of Multidrug-resistant *Mycobacterium tuberculosis*

A Risk to Patients and Health Care Workers

Annals of Internal Medicine. 1992;117:191-196.

Michele L. Pearson, MD; John A. Jereb, MD; Thomas R. Frieden, MD, MPH; Jack T. Crawford, PhD; Barry J. Davis, MSEHE; Samuel W. Dooley, MD; and William R. Jarvis, MD

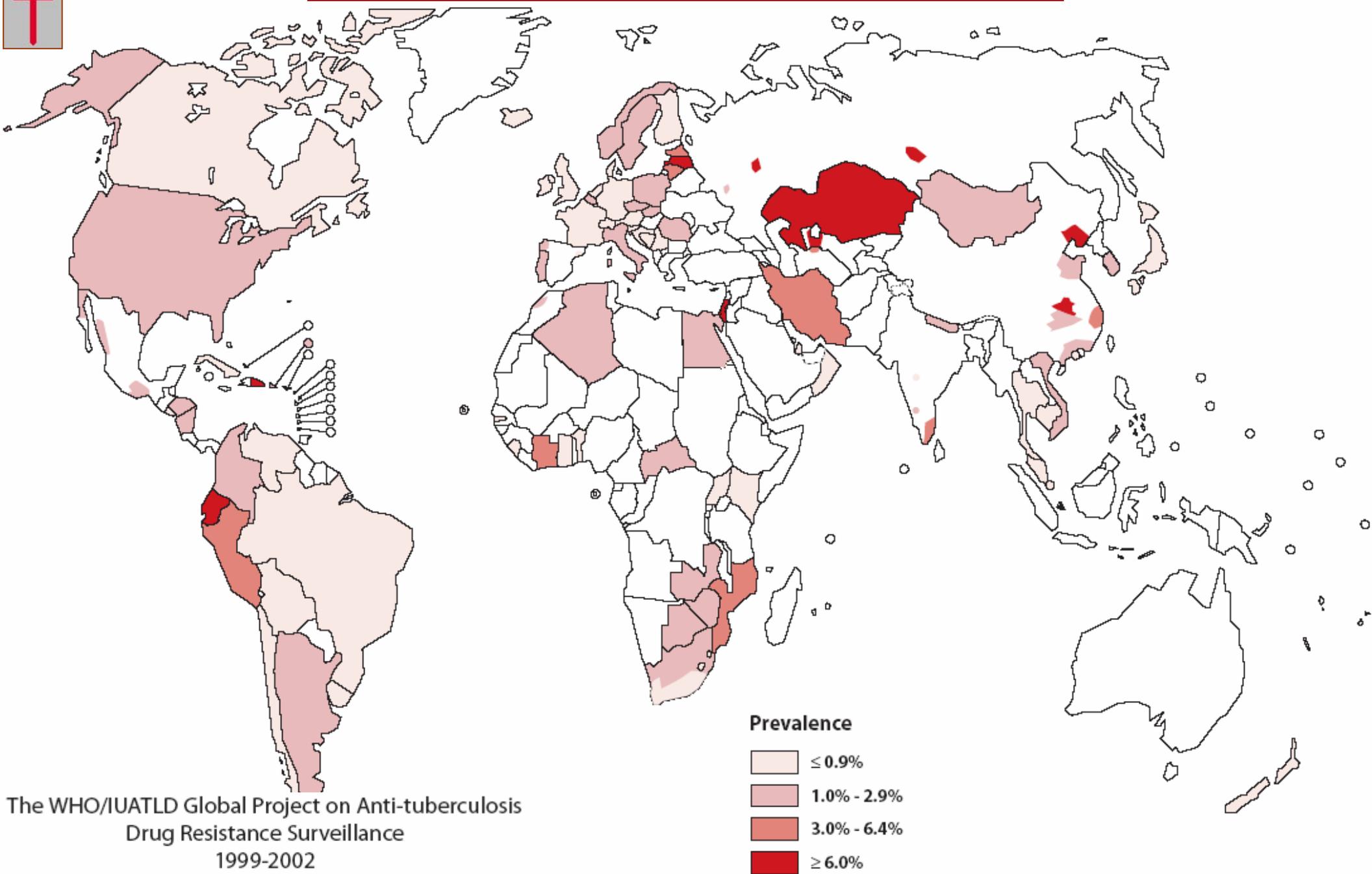
8. Residence in **Areas** with **high MDR-TB** prevalence

MDR-TB rates in New cases in many **areas** of the world can be **High** enough to justify routine **MDR-TB testing** in all new cases

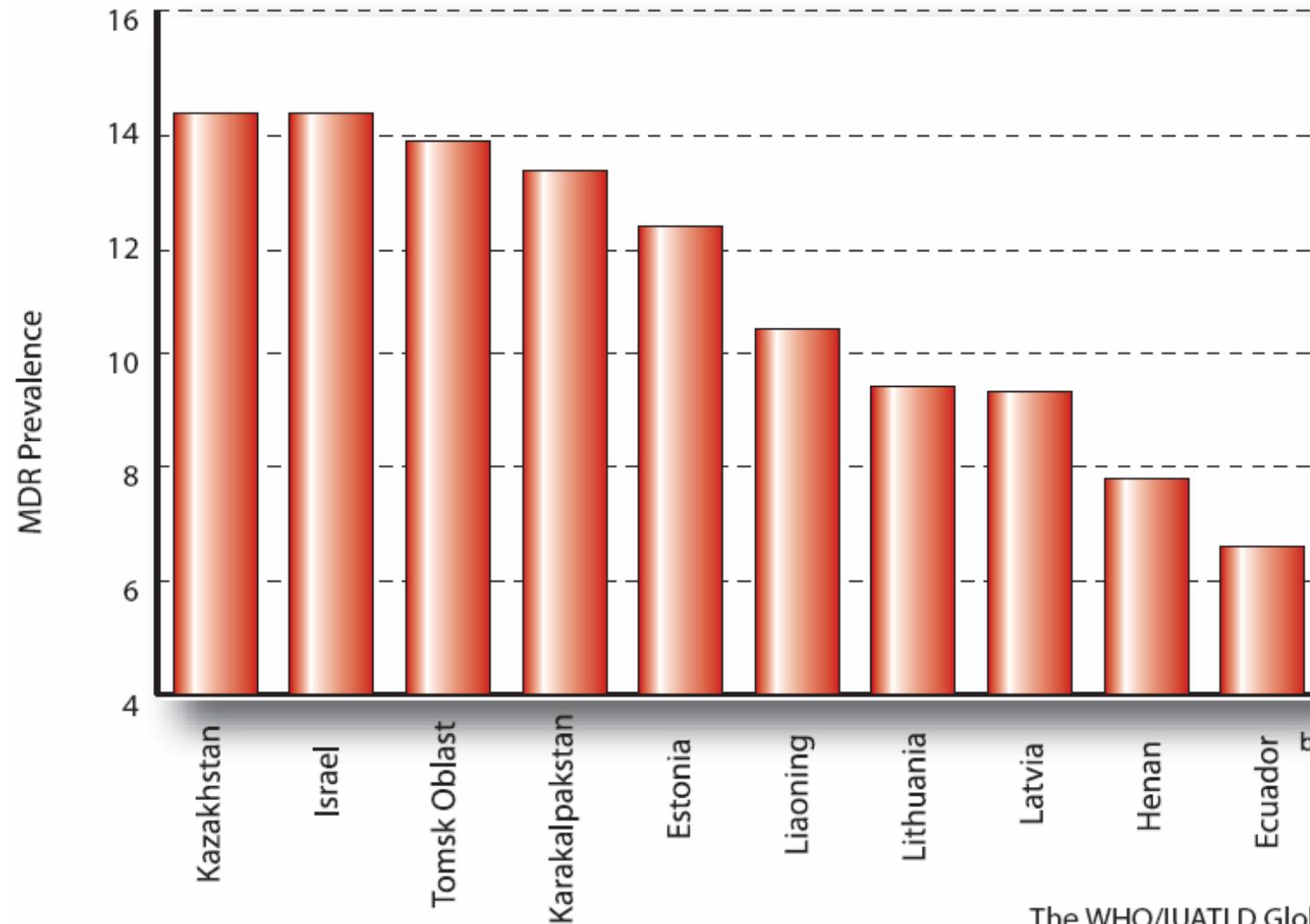




Prevalence of MDR-TB among new TB cases, 1994-2002



Countries/settings with MDR prevalence higher than 6.5% among new cases 1999-2002



The WHO/IUATLD Global Project on Anti-tuberculosis
Drug Resistance Surveillance
1999-2002



9. History of using antituberculosis drugs of *Poor or unknown Quality*

- **The percentage of *MDR-TB* caused by use of *Poor-quality drugs* is unknown but considered significant**
- **It is known that poor-quality drugs are *prevalent* in many countries**
- **All drugs should comply with *quality-assured WHO standards*.**



Quality control of anti-tuberculosis fixed-dose combination formulations in the global market: an in vitro study

Y. Ashokraj,* S. Agrawal,* M. V. S. Varma,* I. Singh,* K. Gunjan,* K. J. Kaur,* S. R. Bhade,* C. L. Kaul,* J. M. Caudron,† J. Pinel,† R. Panchagnula*

* Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research (NIPER), Mohali, Punjab, India; † Médecins Sans Frontières International Office, Brussels, Belgium

S U M M A R Y

OBJECTIVE: To determine the quality, and especially the dissolution properties of rifampicin, of fixed-dose combination (FDC) formulations of anti-tuberculosis agents manufactured by major market holders in the anti-tuberculosis sector and supplied for use in national tuberculosis control programmes.

METHODS: Dissolution studies were performed for four formulations supplied by four different manufacturers in four dissolution media (0.1N and 0.01N HCl, phosphate buffer [PB] and 20% vegetable oil in PB), at four different agitation rates using USP apparatus II. The formulations were subjected to 4-week accelerated stability studies (40°C/75% RH) and evaluated for physical, chemical and dissolution stability.

RESULTS: The formulations tested complied with phar-

macopeial quality control (QC) tests. The extent of rifampicin release was independent of dissolution medium; however, a slight decrease in the dissolution rate was observed in two products. More than 75% of drug was released in 45 min at all agitation intensities except 30 rpm, and 20% oil in the medium reflected fed state. Formulations were stable in the packaging conditions recommended by the manufacturer for at least 4 weeks.

CONCLUSIONS: The formulations tested passed the QC tests and were found to be stable. A decrease in the rate, although not the extent, of dissolution necessitated multiple point dissolution in gastric and intestinal pH conditions to ensure consistency in in vivo bioavailability.

KEY WORDS: dissolution; rifampicin; tuberculosis; fixed-dose combination (FDC); bioavailability



The physical and chemical stability of anti-tuberculosis fixed-dose combination products under accelerated climatic conditions

H. Bhutani, T. T. Mariappan, S. Singh

Department of Pharmaceutical Analysis, National Institute of Pharmaceutical Education and Research (NIPER), SAS Nagar, Punjab, India

SUMMARY

OBJECTIVE: To determine the physical and chemical stability of anti-tuberculosis fixed-dose combinations (FDC) of rifampicin (RMP), isoniazid (INH), pyrazinamide (PZA) and ethambutol (EMB) sold on the Indian market.

METHODS: The products were stored for 3 months under ICH/WHO accelerated conditions (40°C/75% RH), with and without the original packaging in the presence and absence of light.

RESULTS: The initial RMP, INH and PZA content was found to be within the range of 90–110% of the label claim. However, the products were found to have some chemical instability even initially; one of the tablets also showed physical instability. Under accelerated conditions,

the unpackaged products underwent severe changes, whereas both physical and chemical changes were also observed in the packaged formulations. The physical changes were stronger under lighted conditions. A significant finding is that PZA and perhaps EMB may play a catalytic role in the interaction between INH and RMP.

CONCLUSION: This study suggests that, unless they are packed in barrier packaging, anti-tuberculosis FDC formulations should be considered unstable, and due consideration should be given to their development pharmaceuticals, packaging and stability testing.

KEY WORDS: FDC anti-tuberculosis products; accelerated stability testing; isonicotinyl hydrazone; ICH; WHO

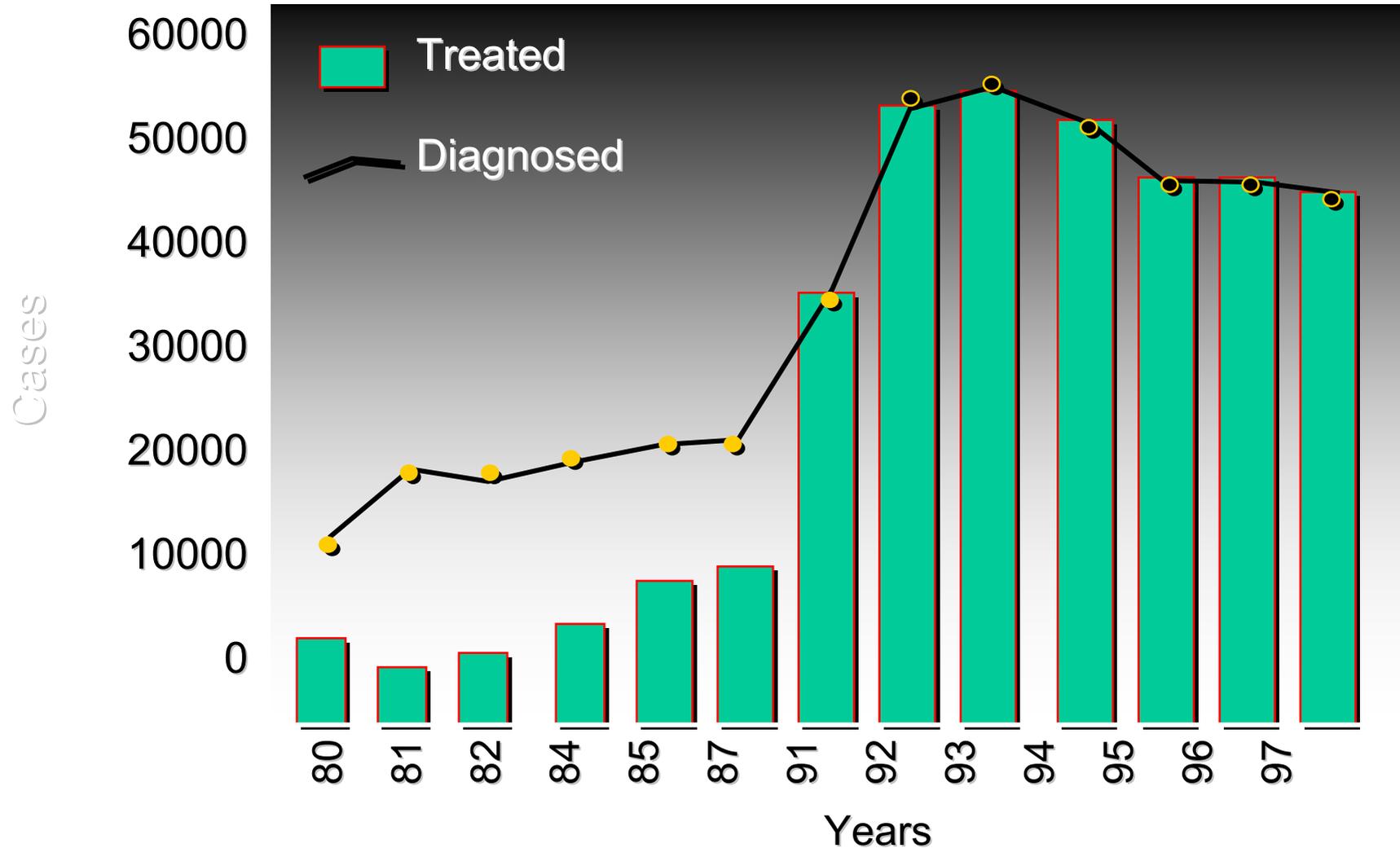


10. Treatment in *programmes* that operate *poorly* (especially recent and/or frequent *drug stock-outs*)

These are usually *non-DOTS* or *DOTS* programmes with *poor drug management* and distribution systems (especially recent and or frequent drug stock-outs)



TB Cases Diagnosed and *Treated* in Perú, 1980-97



Source : NTP Peru, Ministry of Health



3. Low to very Low Probability of Resistances

Only in very exceptional circumstances can be associated with MDR-TB

11. Co-morbid conditions associated with malabsorption or rapid transit diarrhea

12. HIV in some settings



11. *Co-morbid* conditions associated with *malabsorption* or rapid transit diarrhea

***Malabsorption* may result in selective *low* serum drug *levels* and may occur in either *HIV-negative* or *-positive* patients**



Malabsorption of Rifampin and Isoniazid in HIV-Infected Patients With and Without Tuberculosis

**Prema Gurumurthy,¹ Geetha Ramachandran,¹ A. K. Hemanth Kumar,¹
S. Rajasekaran,² C. Padmapriyadarsini,¹ Soumya Swaminathan,¹
P. Venkatesan,¹ L. Sekar,¹ S. Kumar,² O. R. Krishnarajasekhar,²
and P. Paramesh²**

¹Tuberculosis Research Centre (Indian Council of Medical Research)

and ²Government Hospital for Thoracic Medicine, Tambaram, Chennai, India

The absorption of rifampin, isoniazid, and D-xylose in patients with human immunodeficiency virus (HIV) infection and diarrhea, in patients with HIV infection and tuberculosis (TB), in patients with pulmonary TB alone, and in healthy subjects was studied. Percentage of dose of the drugs, their metabolites, and D-xylose excreted in urine were calculated. A significant reduction in the absorption of drugs and D-xylose in both the HIV infection/diarrhea and HIV infection/TB groups was observed ($P < .05$), and the correlation between them was significant. Our results indicate that patients with HIV infection and diarrhea and those with HIV infection and TB have malabsorption of rifampin and isoniazid.



Risk Factors for Rifampin-mono-resistant Tuberculosis

A Case-Control Study

LAURIE SANDMAN, NEIL W. SCHLUGER, AMY L. DAVIDOW, and STANLEY BONK

Division of Pulmonary and Critical Care Medicine, Department of Environmental Medicine, and Department of Pathology, New York University School of Medicine, New York, New York

Rifampin is the cornerstone of short-course chemotherapy for the treatment of tuberculosis (TB). Rifampin mono-resistance (RMR) is less common than resistance to isoniazid alone or in combination with other antituberculous medications. We conducted a retrospective case-control study to identify risk factors for RMR-TB. Complete records for 21 of a total of 26 RMR patients from 1990 to 1997 were available for review, and were compared with those of 48 patients with drug-susceptible TB, controlling for year of diagnosis. Cases more frequently had a history of TB than did controls (61% versus 22%, $p < 0.01$), and were more often human immunodeficiency virus (HIV) positive (81% versus 46%, $p = 0.02$). With control for HIV status, cases were more likely to have extrapulmonary involvement (47.6% versus 11.6%, $p = 0.05$). Four cases (19%) and one control (2.1%) died ($p = 0.02$) during hospitalization. Cases more often had a history of incarceration (71.4% versus 37.5%, $p = 0.09$). Among the 13 cases with a history of TB, five had evidence of malabsorption (vomiting and/or diarrhea), versus none of the 11 controls with prior TB. These data support the hypothesis that RMR is seen primarily in individuals with a history of TB and who are HIV positive. Cases were frequently noncompliant with previous treatment for TB, had a history of incarceration, and had poor outcomes. **Sandman L, Schluger NW, Davidow AL, Bonk S. Risk factors for rifampin-mono-resistant tuberculosis: a case-control study.**



12. *HIV* in some settings

- **The 1999–2002 Global Surveillance *did not find HIV* to be a risk factor**
- **However, *numerous MDR-TB outbreaks* have been documented in HIV patients, and in some areas of the world HIV is a risk factor for MDR-TB**



The Impact of Human Immunodeficiency Virus Infection on Drug-resistant Tuberculosis

FRED M. GORDIN, EILEEN T. NELSON, JOHN P. MATTS, DAVID L. COHN, JEROME ERNST, DEBRA BENATOR, C. LYNN BESCH, LAWRENCE R. CRANE, JAMES H. SAMPSON, PATRICIA S. BRAGG, WAFAA EL-SADR, and the Terry Beirn Community Programs for Clinical Research on AIDS

Division of Infectious Diseases, Department of Veterans Affairs Medical Center, Washington, DC; Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis, Minnesota; Denver Community Programs for Clinical Research on AIDS, Denver Public Health, Denver, Colorado; Bronx Lebanon Hospital Center, New York; Louisiana Community AIDS Research Program, New Orleans, Louisiana; Wayne State University, Detroit, Michigan; The Research and Education Group, Portland, Oregon; Richmond AIDS Consortium, Richmond, Virginia; and Harlem Hospital Center, New York, New York

Infection with human immunodeficiency virus (HIV) has been associated with increased rates of single- and multidrug-resistant (MDR) tuberculosis in the New York City area. In order to examine the relationship of HIV infection to drug-resistant tuberculosis in other selected regions of the United States, we established a registry of cases of culture-proven tuberculosis. Data were collected from sites participating in an NIH-funded, community-based HIV clinical trials group. All cases of tuberculosis, regardless of HIV status, which occurred between January 1992 and June 1994 were recorded. Overall, 1,373 cases of tuberculosis were evaluated, including 425 from the New York City area, and 948 from seven other metropolitan areas. The overall prevalence of resistance to one or more drugs was 20.4%, and 5.6% of isolates were resistant to both isoniazid and rifampin (MDR). In the New York City area, HIV-infected patients were significantly more likely than persons not known to be HIV-infected, to have resistance to at least one drug (37% versus 19%) and MDR (19% versus 6%). In other geographic areas, overall drug resistance was 16%, and only 2.2% of isolates were MDR. In multiple logistic regression analyses, HIV infection was shown to be a risk factor for drug-resistant tuberculosis, independent of geographic location, history of prior therapy, age, and race. We concluded that HIV infection is associated with increased rates of resistance to antituberculosis drugs in both the New York City area and other geographic areas. MDR tuberculosis is occurring predominantly in the New York City area and is highly correlated with HIV infection. **Gordin FM, Nelson ET, Matts JP, Cohn DL, Ernst J, Benator D, Besch CL, Crane LR, Sampson JH, Bragg PS, El-Sadr W, and the Terry Beirn Community Programs for Clinical Research on AIDS. The impact of human immunodeficiency virus infection on drug-resistant tuberculosis.**



Characteristics of drug resistance and HIV among tuberculosis patients in Mozambique

A. Mac-Arthur, Jr,* S. Gloyd,[†] P. Perdigão,* A. Noya,[‡] J. Sacarlal,* J. Kreiss[†]

* National Tuberculosis and Leprosy Control Programme, Ministry of Health of Mozambique, Maputo, Mozambique;

[†] Department of Epidemiology and Medicine, School of Public Health, University of Washington, Seattle, Washington, USA;

[‡] Sexually Transmitted Diseases and AIDS Control Programme, Department of Epidemiology, Ministry of Health of Mozambique, Maputo, Mozambique

SUMMARY

SETTING: The rate of human immunodeficiency virus (HIV) seroprevalence among tuberculosis patients varies between 2% and 53% in Mozambique, depending on the region. Drug resistance surveillance has been performed in only a few cities in Mozambique.

OBJECTIVES: To establish the extent of drug resistance in areas of Mozambique with different levels of HIV prevalence, to estimate the prevalence of HIV among tuberculosis (TB) patients, and to examine the association between drug resistance and HIV infection.

DESIGN: All tuberculosis patients diagnosed at randomly selected health facilities over 9 months (September 1998 to June 1999) were enrolled in the study. Sputum was collected, smeared and cultured, and drug susceptibility tests were performed. Blood was tested for HIV in the respective provinces, and patients received pre-test and post-test counselling.

RESULTS: Of 709 culture-positive cases, 25.5% were HIV-positive. HIV-positive patients were significantly more likely to have a prior history of treatment (OR 2.2; 95%CI 1.9-3.6) and resistance to both isoniazid and streptomycin (OR 2.3; 95%CI 1.3, 4.5). In patients with no history of prior tuberculosis treatment, the multidrug resistance rate was 3.4% and resistance to isoniazid and streptomycin (HS) was 5.2%. Any drug resistance was significantly more common among those with a history of prior treatment (OR 3.1; 95%CI 2.1-4.7), particularly resistance to HS (OR 4.5; 95%CI 2.6-7.9).

CONCLUSIONS: This study demonstrates substantial levels of drug resistance in Mozambique. Differences in drug resistance between high and low HIV prevalence areas may be related to prior treatment.

KEY WORDS: tuberculosis patients; drug resistance; HIV; Mozambique



Multidrug-resistant tuberculosis: eight years of surveillance in France

J. Robert, D. Trystram, C. Truffot-Pernot, V. Jarlier

Multidrug-resistant tuberculosis: eight years of surveillance in France. J. Robert, D. Trystram, C. Truffot-Pernot, V. Jarlier. ©ERS Journals Ltd 2003.

ABSTRACT: The aim of this study was to evaluate the annual prevalence of multidrug-resistant tuberculosis (MDRTB) and to describe the characteristics of the patients with MDRTB in France.

Annual questionnaire surveys from 1992–1999 were mailed to all French microbiological laboratories performing mycobacterial cultures. A total of 264 distinct patients were reported to the National Reference Centre for Resistance of Mycobacteria to Antituberculosis Drugs during the 8-yr surveillance period resulting in a mean annual prevalence of MDRTB of 0.6%.

A mean of 16% of the MDRTB patients were reported over several subsequent years. The majority of patients were male (69.7%), foreign-born (55.7%), with a previous history of treatment (65.9%), and pulmonary involvement (92.8%) with smear-positive results (59.1%). Human immunodeficiency virus (HIV) coinfection was present in 20.8% of the patients. Strains were resistant only to isoniazid and rifampin in 37.9% of the cases, and additional resistance to both streptomycin and ethambutol was present in 25.8%. HIV coinfection and female status were statistically associated with primary resistance, whereas smear-positive results were associated with secondary resistance. Foreign-birth and smear-positive results were associated with a chronic status.

The prevalence of multidrug-resistant tuberculosis is low in France (<1%). However, a substantial proportion of patients remain positive for several years, suggesting nonoptimal management. Therefore, as recommended by the World Health Organization, a few reference teams, working in collaboration with national associations of physicians and microbiologists, should be established to improve the outcome of multidrug-resistant tuberculosis.

Eur Respir J 2003; 22: 833–837.

National Reference Centre for Antimicrobial Resistance of Mycobacteria, and Bacteriology-Hygiene Pitié-Salpêtrière Medical School, Paris, France.

Correspondence: J. Robert
Laboratoire de Bactériologie
Faculté de Médecine Pitié-Salpêtrière
91 Bd de l'hôpital
75634 Paris Cedex
France
Fax: 33 145827577
E-mail: jrobert@chups.jussieu.fr

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Impact of the growing HIV-1 epidemic on multidrug-resistant tuberculosis control in Latvia



I. Morozova,* V. Riekstina,* G. Sture,[†] C. Wells,[‡] V. Leimane*

* Latvian State Center for Tuberculosis and Lung Diseases, Latvian National Tuberculosis Program, Riga, [†] Latvian Ministry of Welfare, Latvian Center for Infectious Diseases, Riga, Latvia; [‡] US Centers for Disease Control and Prevention, Division of Tuberculosis Elimination, Atlanta, Georgia, USA

SUMMARY

Latvia, a country with levels of multidrug-resistant (MDR) TB among the highest in the world, experienced a 58-fold increase in HIV seroprevalence among all persons tested in the country from 1996 through 2001. In addition, HIV seroprevalence among TB cases increased from 0.4% to 1.4%, and among MDR-TB cases from 0% to 5.6% from 1998 through 2001, potentially compromising gains made to date in controlling the country's MDR-TB epidemic. The following will be critical to the future of MDR-TB control in Latvia: containing HIV transmission in the country, particularly among injection drug users who comprised 72% of all HIV

cases reported in the country by the end of 2001, as well as 81% of all MDR-TB cases co-infected with HIV; expanding capabilities to more rapidly detect and successfully treat patients with MDR-TB; developing mutual TB control strategies between the National TB and AIDS programs; and continuing to improve institutional infection control measures, particularly in hospitals and prisons where an increasing number of persons infected with HIV come into contact with persons with active MDR-TB.

KEY WORDS: tuberculosis; multidrug resistance; HIV; Latvia

Diagnosis of the MDR-TB. ***Case Finding and Confirmation***

The Diagnosis of the Patient with MDR-TB must start with the Identification of the Suspects of Resistances, and the Grade of Suspicion



To elaborate a **Hierarchy** regarding the Resources

Diagnosis of the MDR-TB

Hierarchy to Perform DST

- ***What factors help you decide the **optimal case-finding** strategies for a particular country***
 - ***Resources*** available (technical, financial, and human)
 - ***Practices of treatment*** in the past
 - ***Rates of MDR-TB*** in different groups

The strategies **range** from testing all patients with TB to only testing a select group of patients

Percentages of **MDR-TB** in the different re-treatment categories

Retreatment Group	Vietnam	Malawi	Benin	Nicaragua	Thailand	Brazil	Peru
	HE	HE	HT	HT	HR	HR	HR
Failures of Category I with HR					19/22 (86%)	29/91 (33%)	80/91 (88%)
Failures of Category I with HE	32/40 (80%)	0/11 (0%)					
Failures of Category I with HT			2/9 (22%)				
Relapse of Category I with HR					2/18 (11%)	2/37 (6%)	
Relapse of Category I with HE	3/39 (8%)						
Relapse of Category I with HT			1/23 (4%)				
Return after default of Category I with HR					1/19 (5%)		
Failures of retreatment with Category II				34/38 (89%)		49/78 (65%)	298/344 (87%)

Case Finding **Strategies**

1. Very **Low Income** Countries. Possible **No DST**

In some circumstances (very low resources, SLD not used in the past, low rate of Initial MDR-TB) patients can enter Category IV regimens **without DST** (although always DST to H+R is recommended):

- 1. Failures of Category II and **chronic** TB cases. Patients in whom Category II treatment failed in a well-run DOTS programs almost always have MDR-TB.***
- 2. TB patients who are **close contacts** of MDR-TB cases***
- 3. Category I **failures**. MDR-TB rates in this group can vary greatly, it is best to document the rate in the group.***

Case Finding Strategies

2. Low and Middle Income Countries (Minimal Requirements for DST)

1. Failures of Category II and Chronics

2. Exposure to a known MDR-TB case

3. Failure of Category I





Case Finding **Strategies**

3. **Best Settings. DST for all these Groups**

4. **Failure of anti-TB Treatment in the Private Sector**
5. **Patients who Remain Sm+ at 2-3 m. of the Cat. I**
6. **Relapses and Return after Defaults**
7. **Exposure in Institutions** that have MDR-TB out- breaks or a **high MDR-TB** prevalence
8. Residence in **Areas** with **high MDR-TB** prevalence
9. History of using antiTB drugs of **Poor or unknown Quality**
10. Treatment in **programmes** that operate **poorly** (especially recent and/or frequent **drug stock-outs**)
11. **Co-morbid** conditions associated with **malabsorption**
12. **HIV** in some settings

Case Finding **Strategies**

CONCLUSION (1)

1. **There is no one strategy** for choosing who will enter Category IV Regimens. The strategy must be adopted to the country situation and resources.
2. While there are some trends that may help us guess if MDR-TB rates will be high in a certain group, there are **many exceptions**.
 - For example, some failures of category I that used HE in the continuation phase had high rates of MDR-TB (80% in vietnam), while other groups had very low rates (0% in Malawi).
3. **Failures of category II** in a good DOTS program almost always have MDR-TB.
4. There are very high rates of MDR-TB in **Close Contacts**

Case Finding **Strategies**

CONCLUSION (1)

- 5. The only way to determine if **other groups** have a high enough rate of MDR-TB to enter category IV without DST is through **surveillance data**. DST patterns in populations are likely to change over time in response to drug exposure, so the exercise of obtaining local **representative DST patterns** in each population must be **periodically repeated**.**
- 6. **Groups with low to moderate rates of MDR-TB** will need to be screened for MDR-TB to determine who needs Category IV regimens and who will can safely enter standardized regimens with first line drugs.**

Diagnosis of the MDR-TB



Case-Findings Strategies

- 1. Suspects of MDR-TB***
- 2. Clasification of MDR-TB Cases***
- 3. Support of the Conventional TB Diagnostic Procedures to the MDR-TB Diagnostic***
- 4. How to Approach Diagnosis of MDR-TB***
- 5. Confirmation of MDR-TB. Reliability of DST***

Suspects of Resistances

CLASIFICACION

1. Initial MDR-TB Cases

- ***Never (<1 month) have received Anti-TB Drugs***

2. MDR-TB cases receiving only FLD

3. MDR-TB Cases receiving FLD and SLD

- ***Receiving only 1-2 SLD (injectable and/or Quinol.)***
- ***Receiving Many SLD***

It will Condition Different Therapeutic Strategies



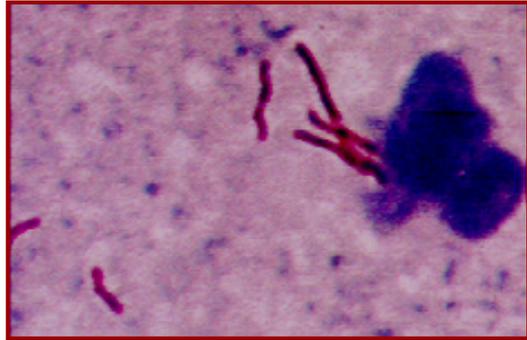
Diagnosis of the MDR-TB



Case-Findings Strategies

- 1. Suspects of MDR-TB***
- 2. Clasification of MDR-TB Cases***
- 3. Support of the **Conventional** TB Diagnostic Procedures to the **MDR-TB** Diagnostic***
- 4. How to Approach Diagnosis of MDR-TB***
- 5. Confirmation of MDR-TB. Reliability of DST***

Diagnosis



of



*TB with Drug
Resistance*

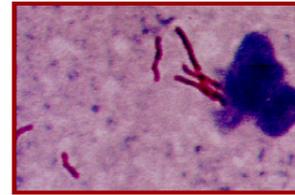


Diagnosis of TB disease

1. Clinical Evaluation



2. Microbiology



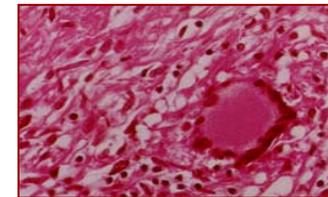
3. Radiology



4. Tuberculin Test



5. Anatomical pathology



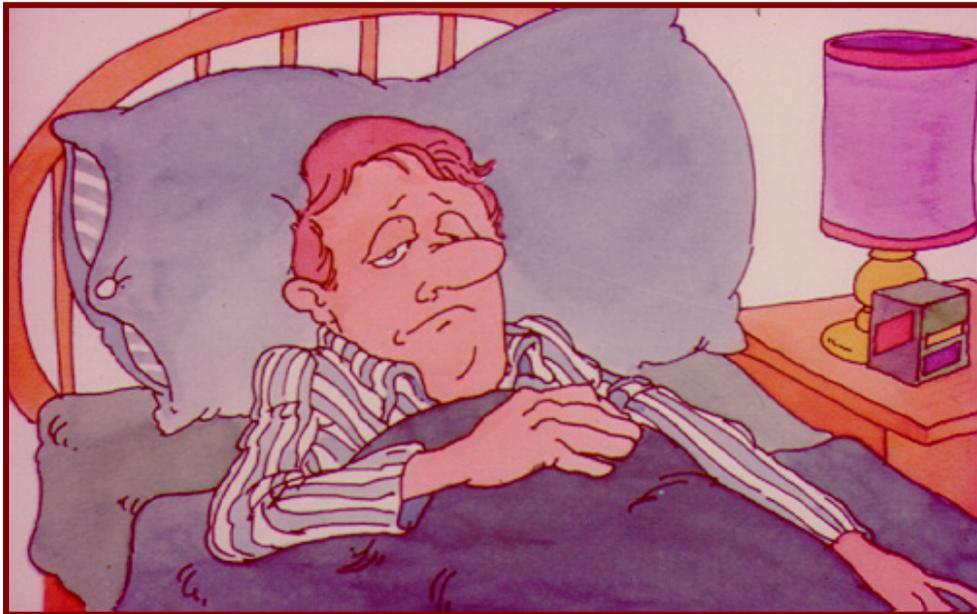
6. Non-Conventional and New Methods





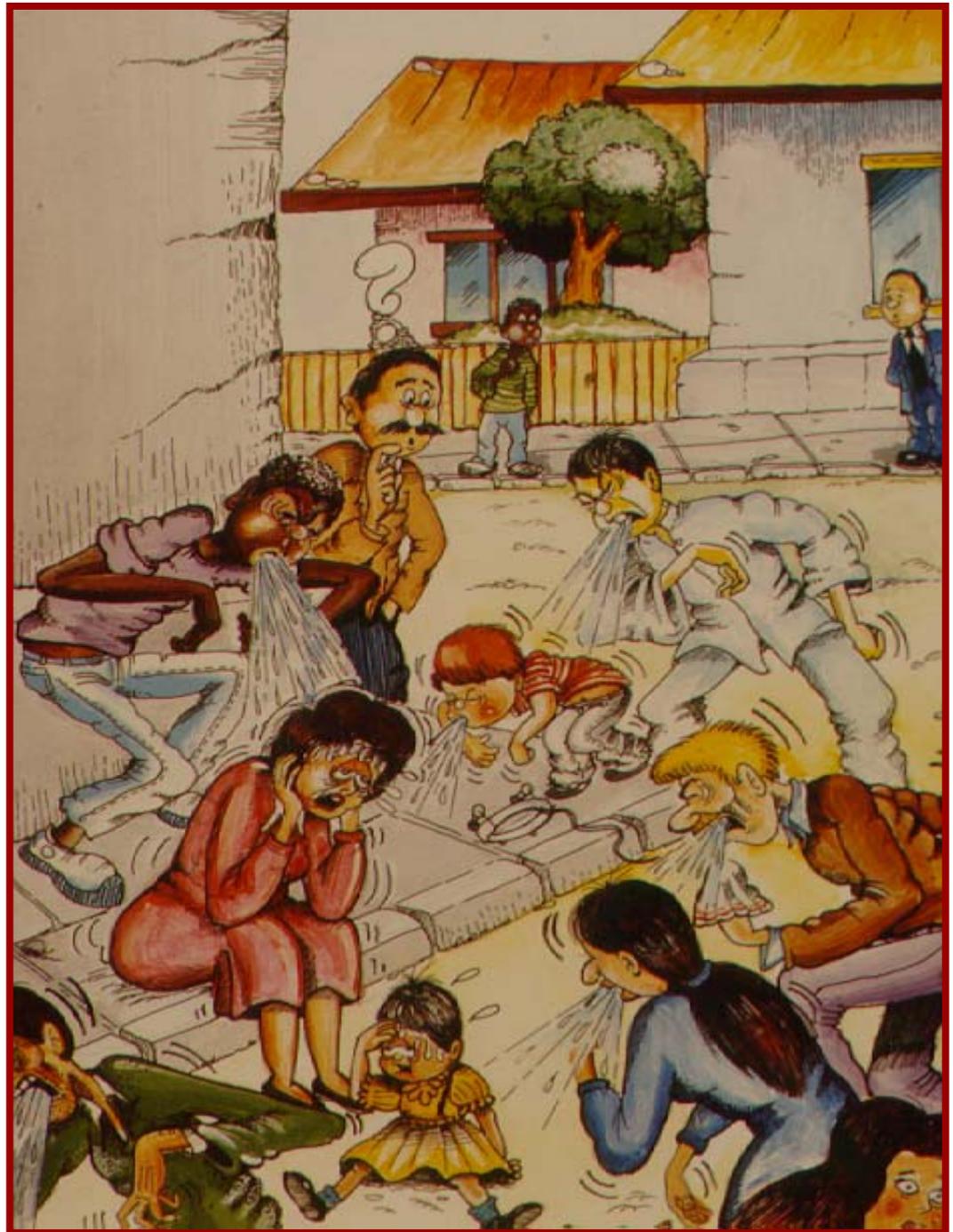
Clinical and X-ray film Manifestations of the TB

***The Importance in the Follow-up
and in the suspect of Failure***



***The cough and/or
expectoration
> 2 weeks
(Respiratory
Symptomatics)
are the most
important
Symptoms in the
MDR-TB***

***Not Differences
with MDR-TB***



Radiological Manifestations of TB

■ **In the diagnosis**

- Very easy and of great value in suspected diagnosis
- Unspecific: All X-ray patterns can be found in other diseases

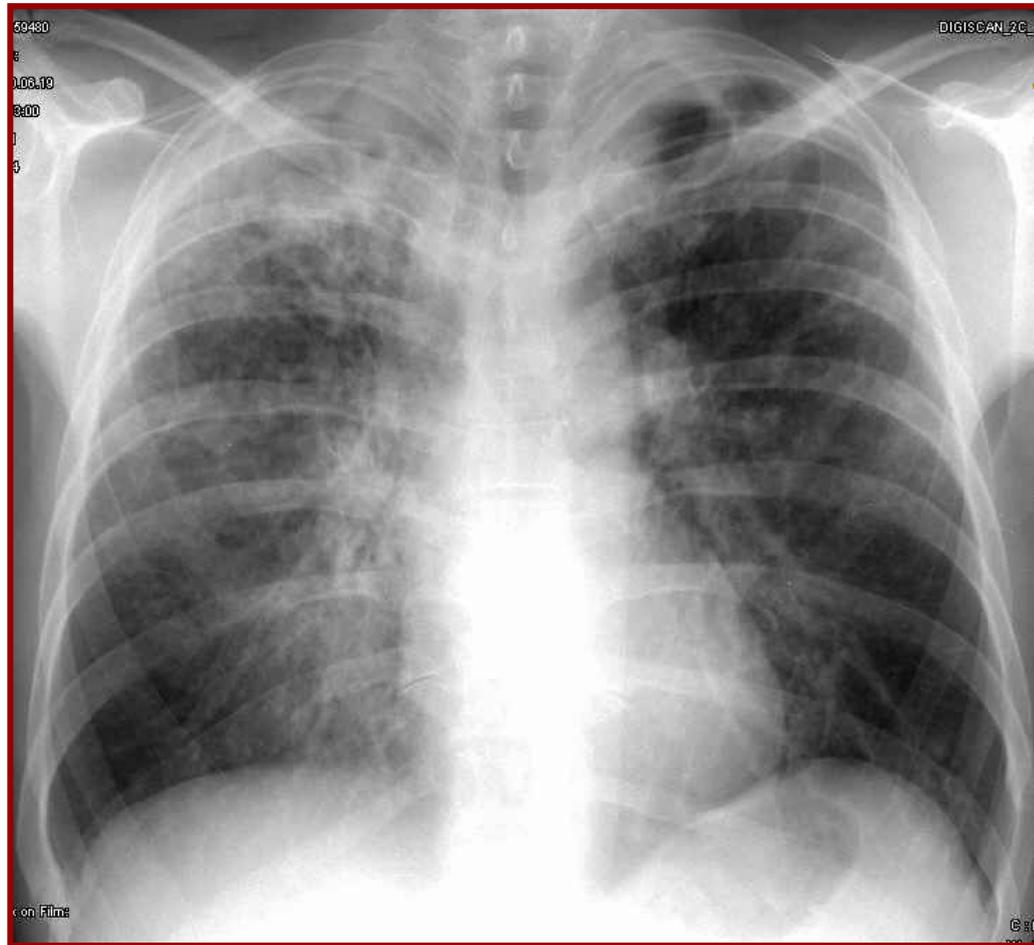
■ **In the prognosis** and in treatment response, it is not of decisive value either

- % deterioration in 1-2 months of treatment
- It is only indicated to take two chest X-rays for TB patients, at the start and end of treatment



Not Differences with MDR-TB

Radiological Manifestations of TB



TB Sensible



MDR-TB

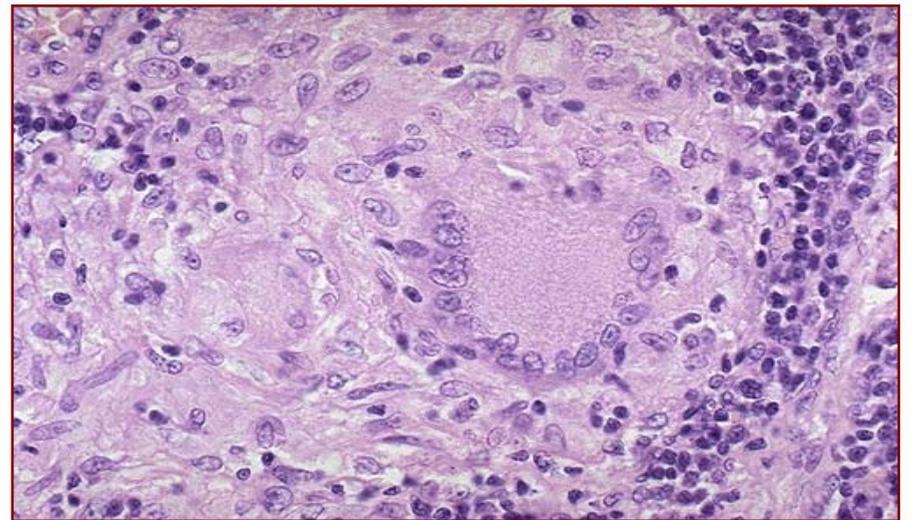
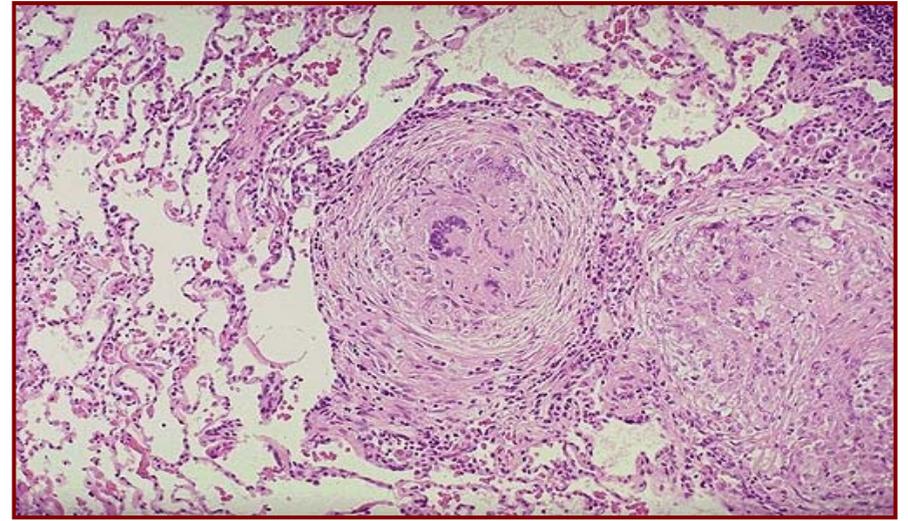
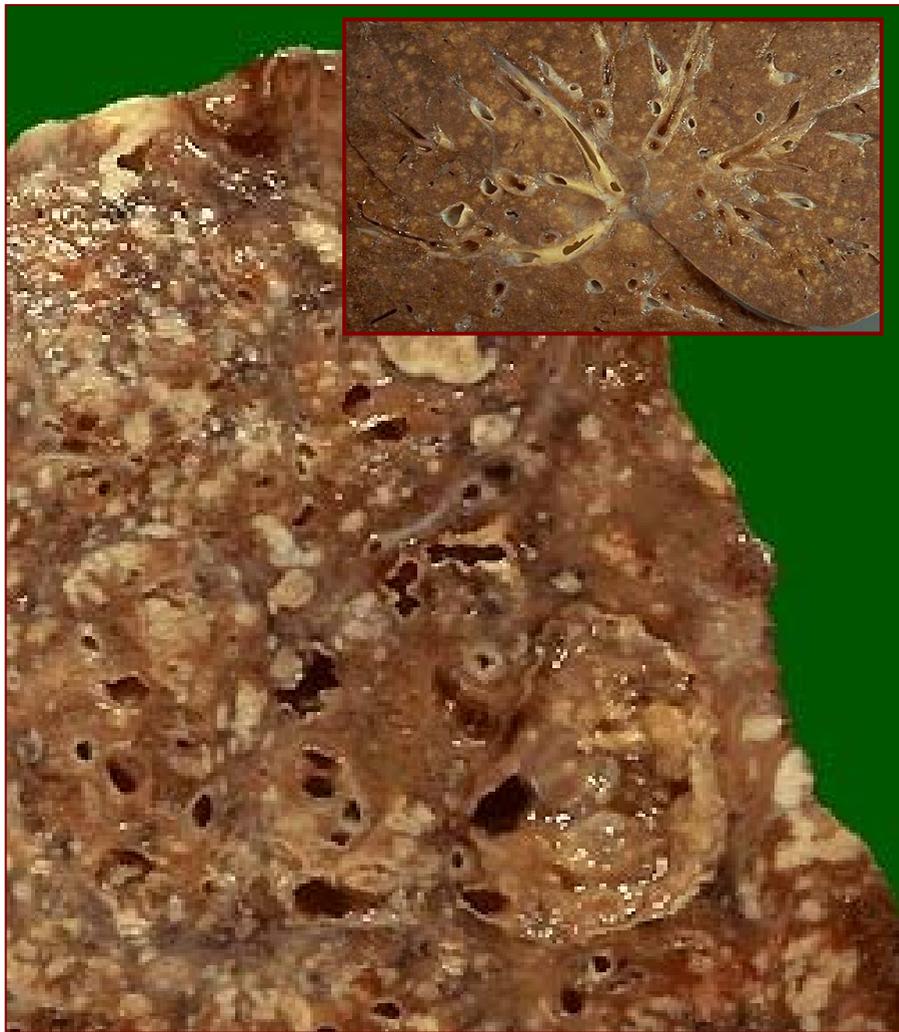


Limitations of the Clinical and X-ray film in the Dg of MDR-TB and in the suspect of Failure

- ***The **not Improvement** in the clinical and/or x-ray film manifestations during the treatment are very **not specific** data to diagnose **MDR-TB*****
- ***Other Disease, frequently associated with TBC (**Bronchiectasias**, Resp. Infections, etc), can justify this not improvement***
- ***These data must be evaluate only as a data more in the context of the patient***

Never accept **MDR-TB** only based in **Clinical** and/or **X-ray film** criteria





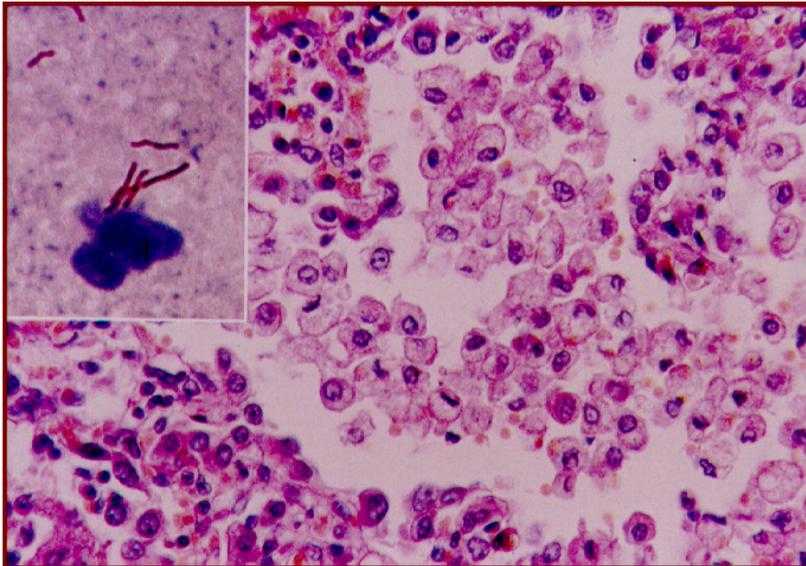
The *Histological* findings, as *Macroscopic* (Cavities, Infiltrates, Miliar), as *Microscopic* (Granulomas, Cellules of Langhans, etc), can be meet exactly equal in TB Sensible or Resistant

***The MDR-TB always
should be Confirmed by
Microbiological
Techniques***

***However, it is necessary to
Remark the Limitations of
these Techniques***



Contributions and **Limitations** † of the Conventional **Microbiologic** Techniques in the Management of the TB with Suspect of Drug **Resistance**



Conventional Microbiological Techniques in TB Diagnosis



1.- Bacilloscopy - Smear

2.- Culture

3.- Identification

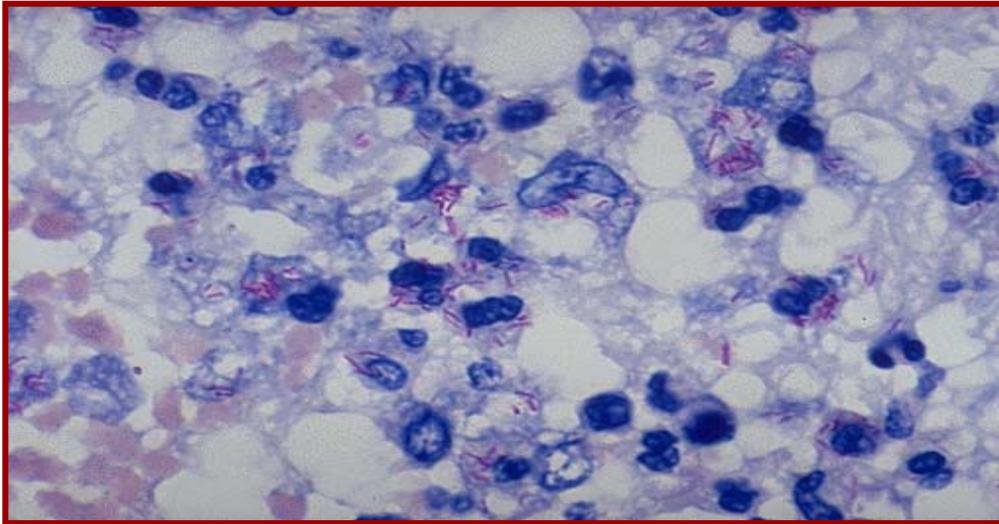
4.- Antibigram (DST)



Diagnosis of Tuberculosis



Bacilloscopy - Smear



- All mycobacteria look alike → Necessary to **Culture**.

A **Sm+** during the Treatment can be M.TB live, Dead, or other NMT

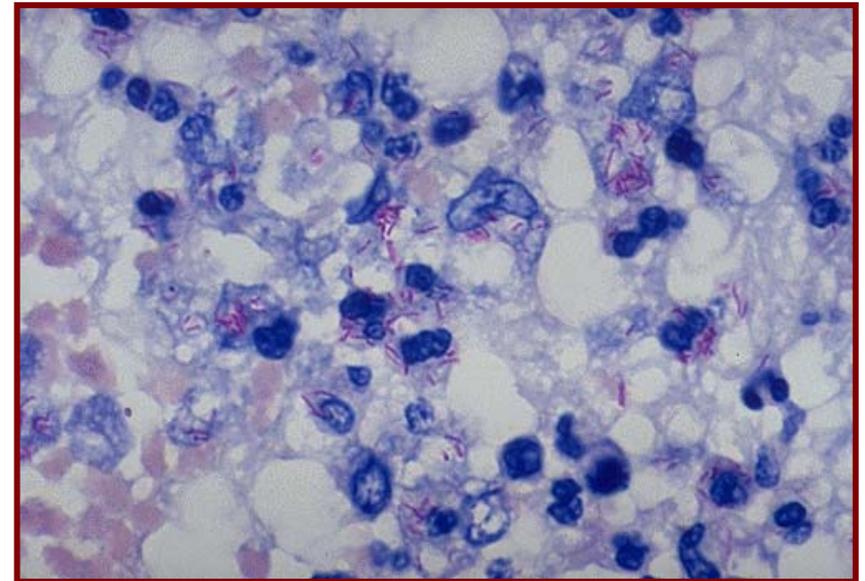


Direct Bacilloscopy

Sensitivity and Specificity

- ***10,000 bacillus / cc. sputum are required for KB +***

Sputum with 5,000 BAAR / cc. -->
spread 0.01 cc on the slide
(50 bacilli) --> 1 bacillus per
200 fields --> if the technician
examines 100 fields --> 50%
probability of seeing a bacillus



A patient can have Sm- at the end of 4^o months, but Culture +

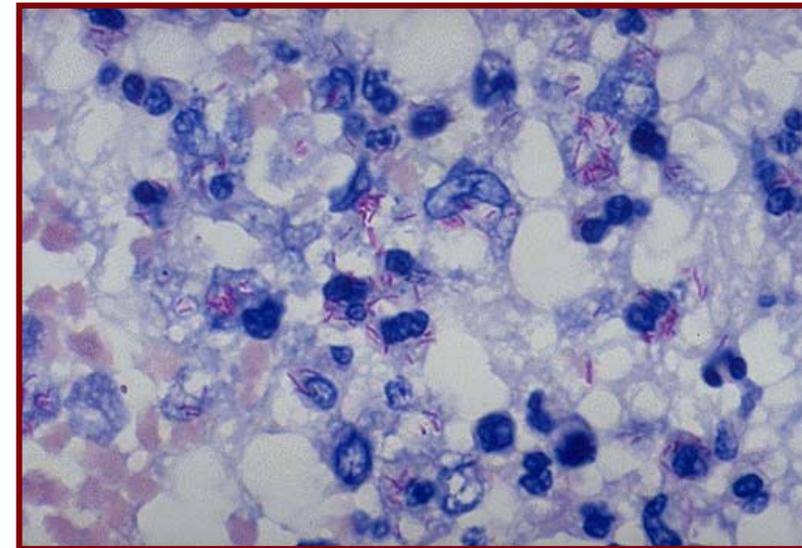
Direct Bacilloscopy

Sensitivity and Specificity

- **SPECIFICITY** -----> **96-99%**

- ***False Positives:***

- Mycobacteria
- Nocardiae
- Fungus
- Remains of food
- Dirt
- Scratches



- ***In a high-medium Endemic Country, over 99% of KB+ are TB***

This is why in practice, and under the **Programa** conditions, a **Certain TB Diagnosis** can be made from a KB+ result



Limitations of the Direct Smear in the Dg of MDR-TB and in the suspect of Failure

- **Relative Importance in the Follow-up (Died Bacillus)**
- **Limitation to Classify the Failure (Bk- 4° Mes)**
- **Contamin./Apparition other Mycobacteria**
- **Necessary CULTURE to Ident. and DST**

Anyway, Sm is very important in the Follow-up



The Management
of the TB with
Resistance
Always must be
by CULTURE



Conventional Microbiological Techniques in TB Diagnosis

2. Mycobacteria Culture



Mycobacteria Culture. Use

1. To establish a certain diagnosis

2. To identify the species

- *M. tuberculosis complex: M. tuberculosis or M. bovis*
- *NTM: MAC, M. kansasii,...*

3. Susceptibility study (DST). MDR



Culture. Mediums

■ **Solid mediums**

- ***Egg-based: Lowenstein Jensen, Coletsoo..***
 - ***Preferable for initial isolation***
- ***Non-egg-based: Middlebrook 7H10, 7H11***
 - ***Used more for sensitivity study***



■ **Liquid mediums**

- ***Monitorised and automatised systems***
- ***Radiometric (Bactec 466)***
- ***Non-radiometric (ESP, Bactec 9000, MB/Bact, MIGT)***
- ***Earlier growth detection than in solid mediums***
- ***Sensitivity study***

Not indicated in Low or Medium Income Countries



Mycobacteria Culture

ADVANTAGES

- *the only Diagnosis that confirms TB*
- *more sensitive KB (detects 10 KB / ml)*

DISADVANTAGES

- *Very Slow Growth (3-8 Weeks)*
- *Less accessible than KB*
- *More expensive than KB*

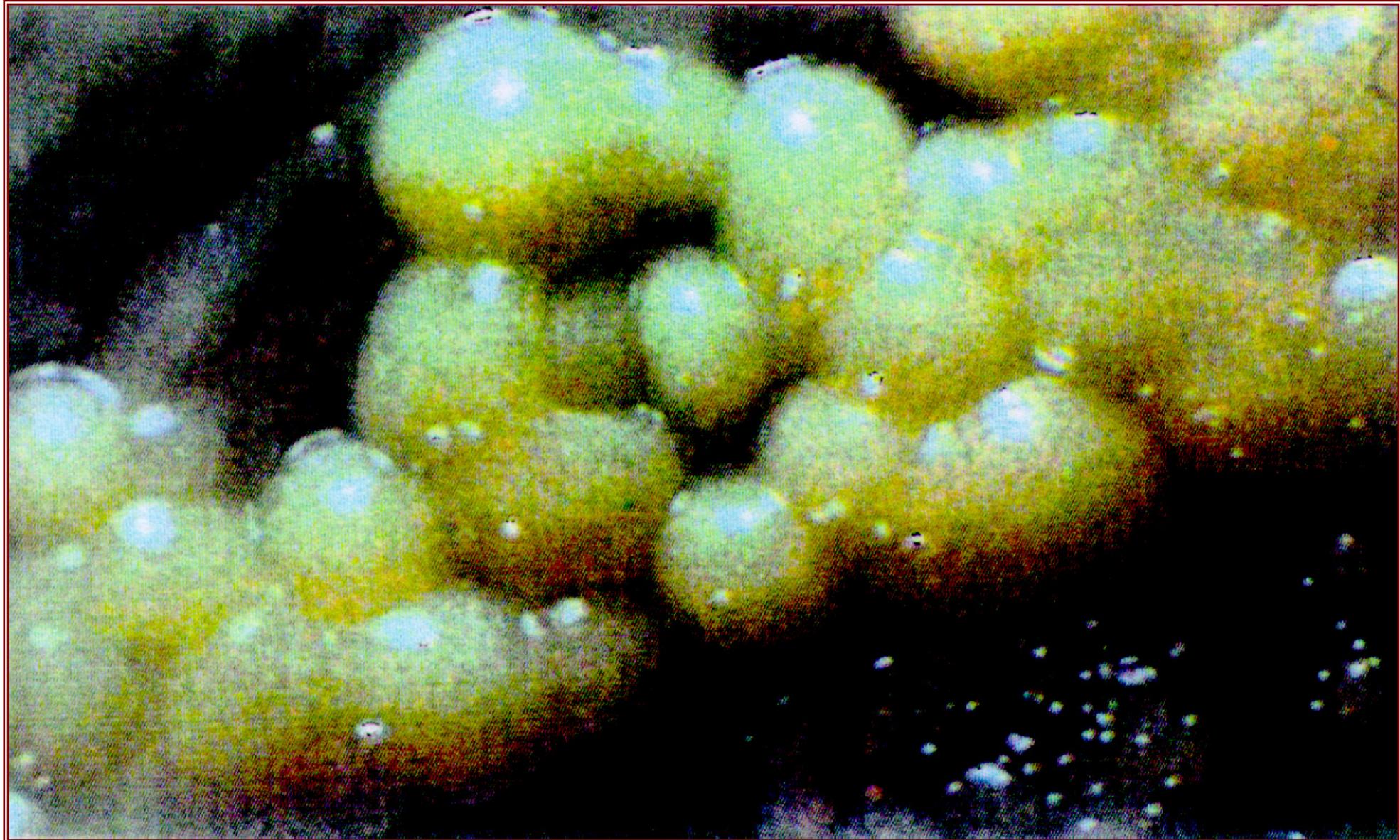
*Pivotal in the Diagnosis and Follow-up of **MDR-TB***



Mycobacterium tuberculosis (*Dissection microscope*)



Mycobacterium avium-intracelulare (Dissection microscope)



2 Concept that can Complicate the Follow-up of the patients with TB sensible and MDR

Died Bacillus

Bacillary Escapes



Conventional Microbiological Techniques in TB Diagnosis

3. Identification of Species



Identification of the species

■ **Phenotypic pattern**

• **Growth**

- *Growth medium. Growth time, morphology of colony, pigment production with/without light, ...*

• **Biochemical tests**

- *Niacin test, nitrate reduction, catalase, ...*

Pivotal in the MDR-TB Management

■ **Genotypical study**

• **ADN probes**

- *Fast technique*
- *Determines whether or not it belongs to tuberculosis complex*

Not indicated in Low or Medium Income Countries



Mycobacterium Fortuitum



Mycobacterium tuberculosis

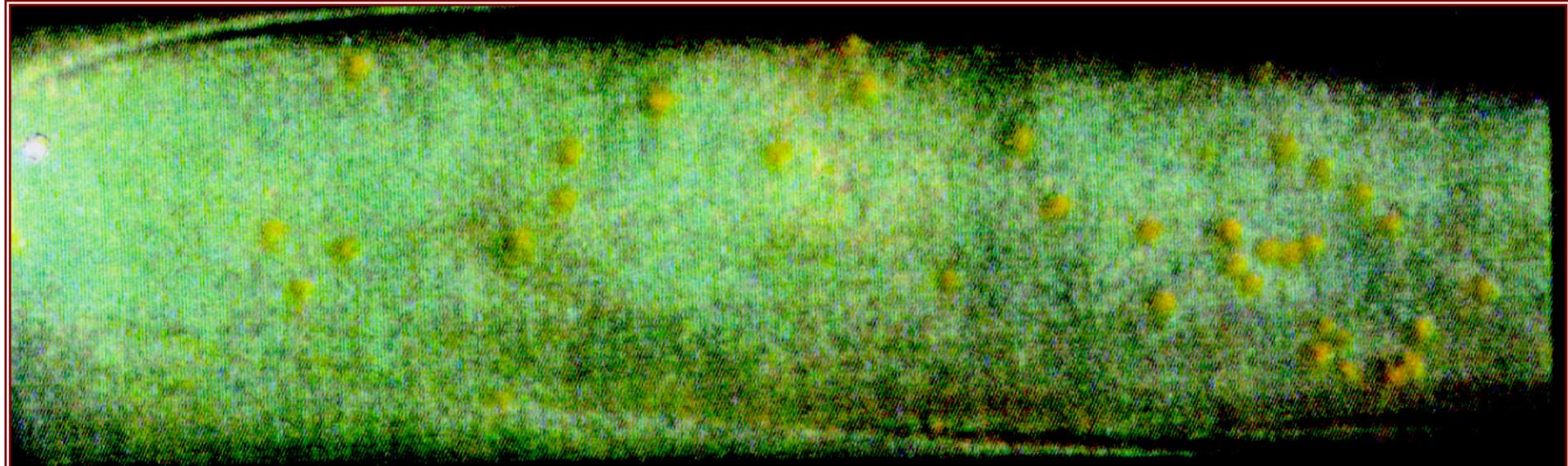


Mycobacterium kansasii



Mycobacterium kansasii

LW-J



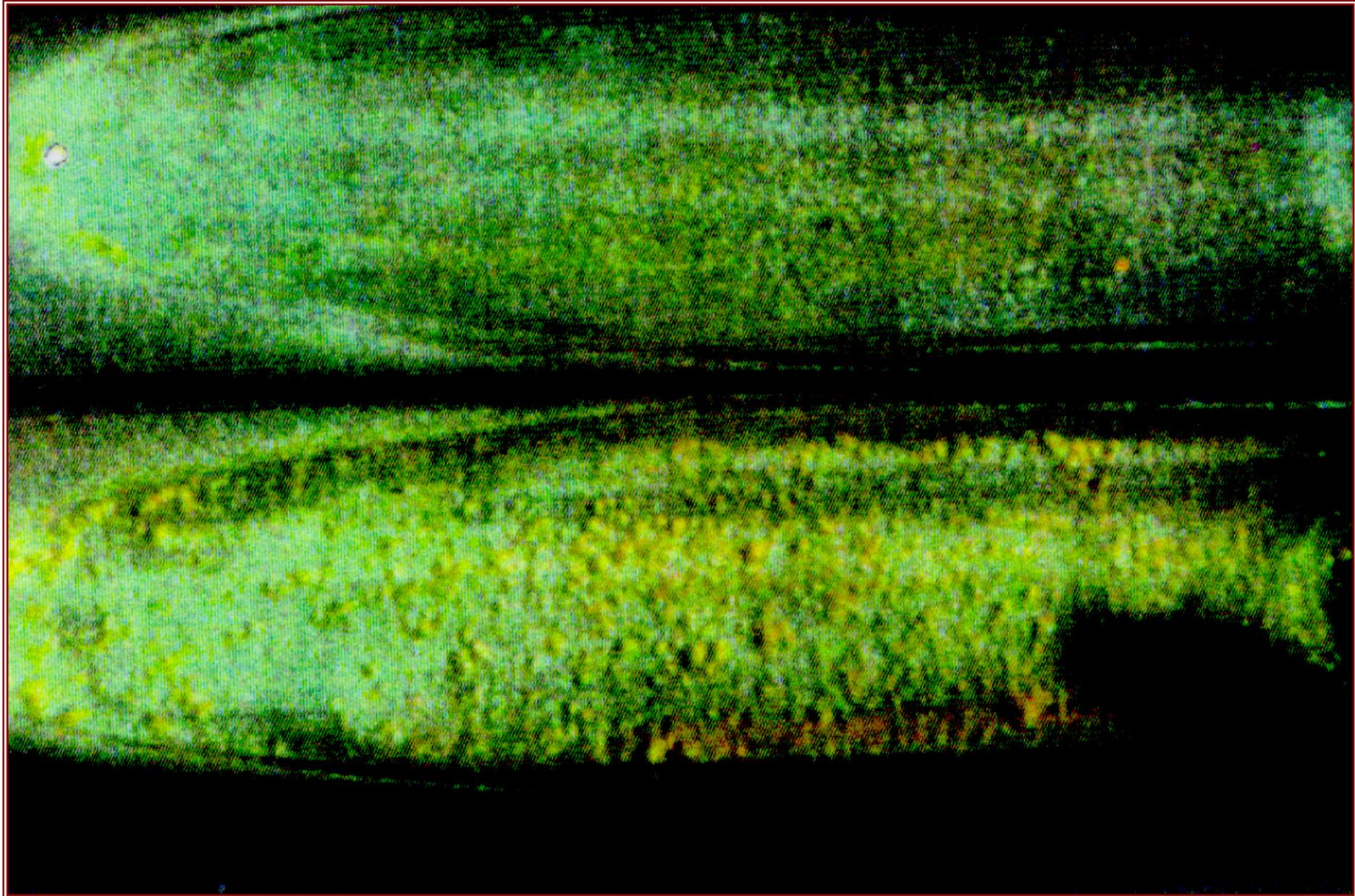
A.T.S.



Mycobacterium gordonae

LW-J

A.T.S.



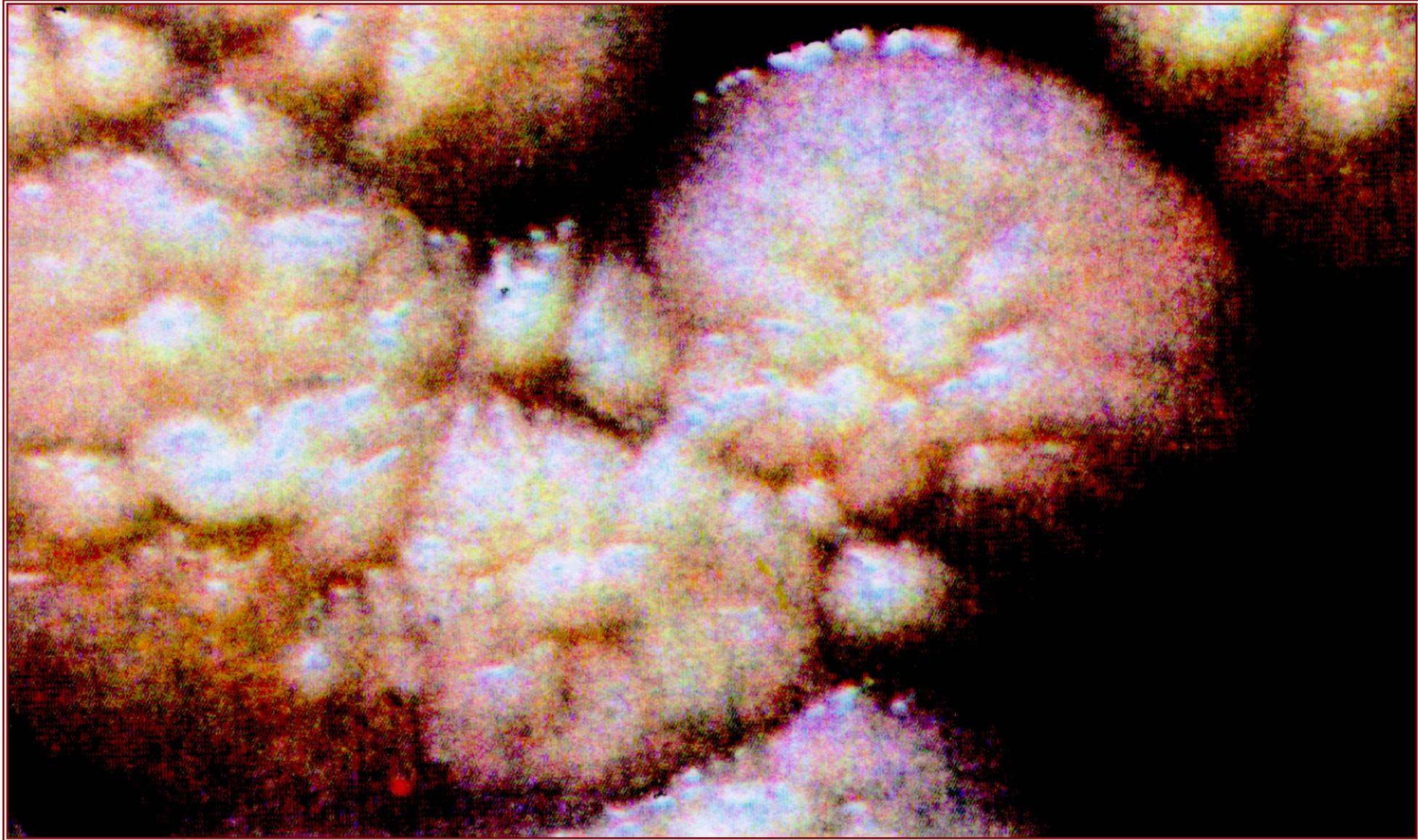
Mycobacterium tuberculosis (*Dissection microscope*)



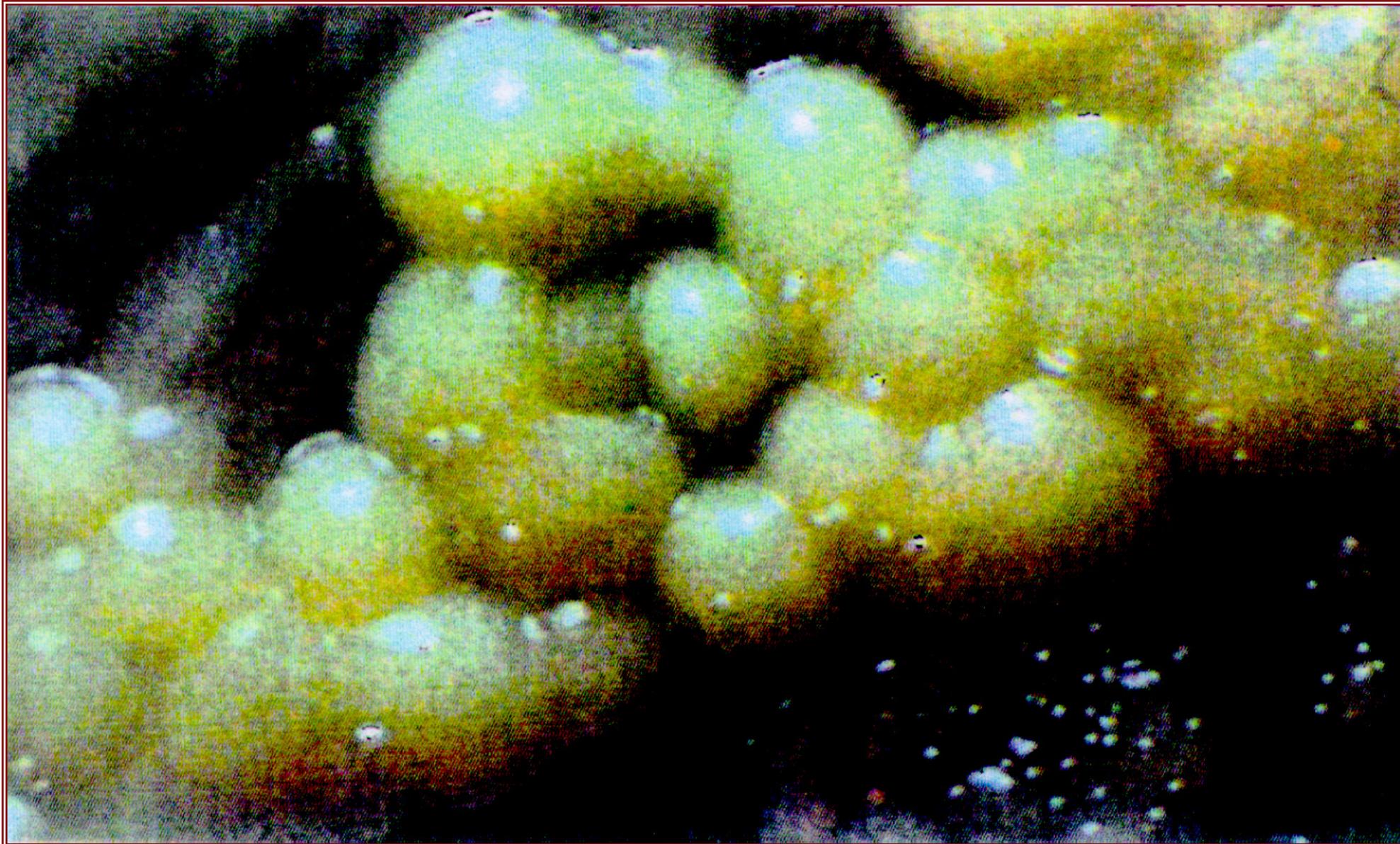
Mycobacterium bovis (*Dissection microscope*)



Mycobacterium kansasii (*Dissection microscope. Semi-rough, non-pigment. colonies*)



Mycobacterium avium-intracelulare (Dissection microscope)



Mycobacterium fortuitum (3 types of colonies –smooth and rough-)



Conventional Microbiological Techniques in TB Diagnosis

4. Drug Susceptibility Test (DST) **(Antibiogram)**



Although all the **MDR-TB** must be **confirmed** by DST, these tests have important **Limitations**. They must be known by the Personal managing these patients



How to approach *Diagnosis* of MDR-TB?

Droga	Paciente D.:												
	Enero	Febrero	Marzo	Año	Abril	Mayo	Junio	Julio	Agosto	Septiembre	Octubre	Noviembre	Diciembre
H													
R													
Z													
E													
S													
Kn													
AK													
Cp													
Of													
Cip													
Eth													
Pth													
Pas													
Cs													
Cfz													
*													
*													
*													
*													
Cultivo**													
Sensib***													

H: Isoniacida | R: Rifampicina | Z: Pirazinam. | E: Etambutol | S: Estreptom. | Kn: Kanamicina | Ak: Amikacina | Cp: Capreomic | Of: Ofloxacina | Cip: Ciproflo. | Eth: Etonam. | Pth: Protonam.
 Pas: PAS | Cs: Closerina | Cfz: Clofazim. | *: Otros

Cultivo: Reseñar el resultado del cultivo en la fecha realizada *Sensib.: Reseñar el resultado del antibiograma en la fecha realizada



Diagnosis of the MDR-TB



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