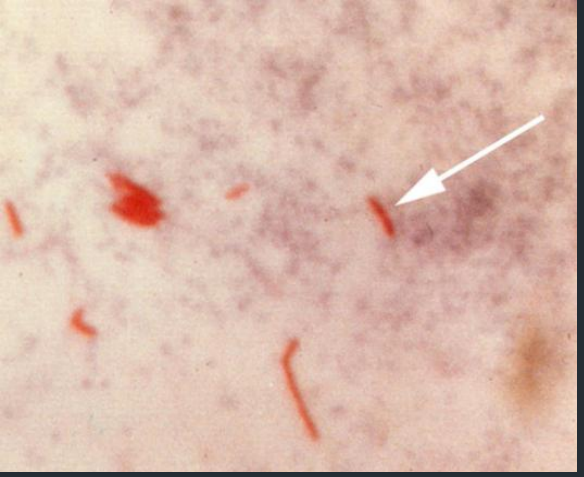
Multidrug resistant tuberculosis: Epidemiology and Treatment

Eiman Mokaddas MD, FRCPath
Professor of Clinical Microbiolgy
Faculty of Medicine
Kuwait University

Outline

- Introduction
- Definition of MDR/XDR/TDR TB
- Epidemiology of TB
- Epidemiology of MDR/XDR TB
- Management of MDR/XDR TB
- Experience from Kuwait

Introduction

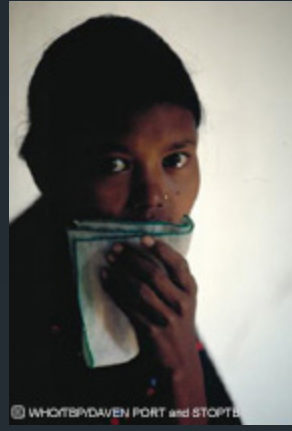


M.tuberculosis

Old Fashion Bug

VS

Celebrity Bug



- From 24th April- 6th May, 2009:
  - **31** people died from Swine flue
  - **253,442** reports written about H1N1 virus
  - **63,066** people died of TB
  - Only **6,501** new reports mentioning the disease
- The news (reports) to death ratio based on these findings is:
  - **8176:1** for H1N1
  - **0.1:1** for TB

Alarming Figures

TB Kills

- 1.7 million people

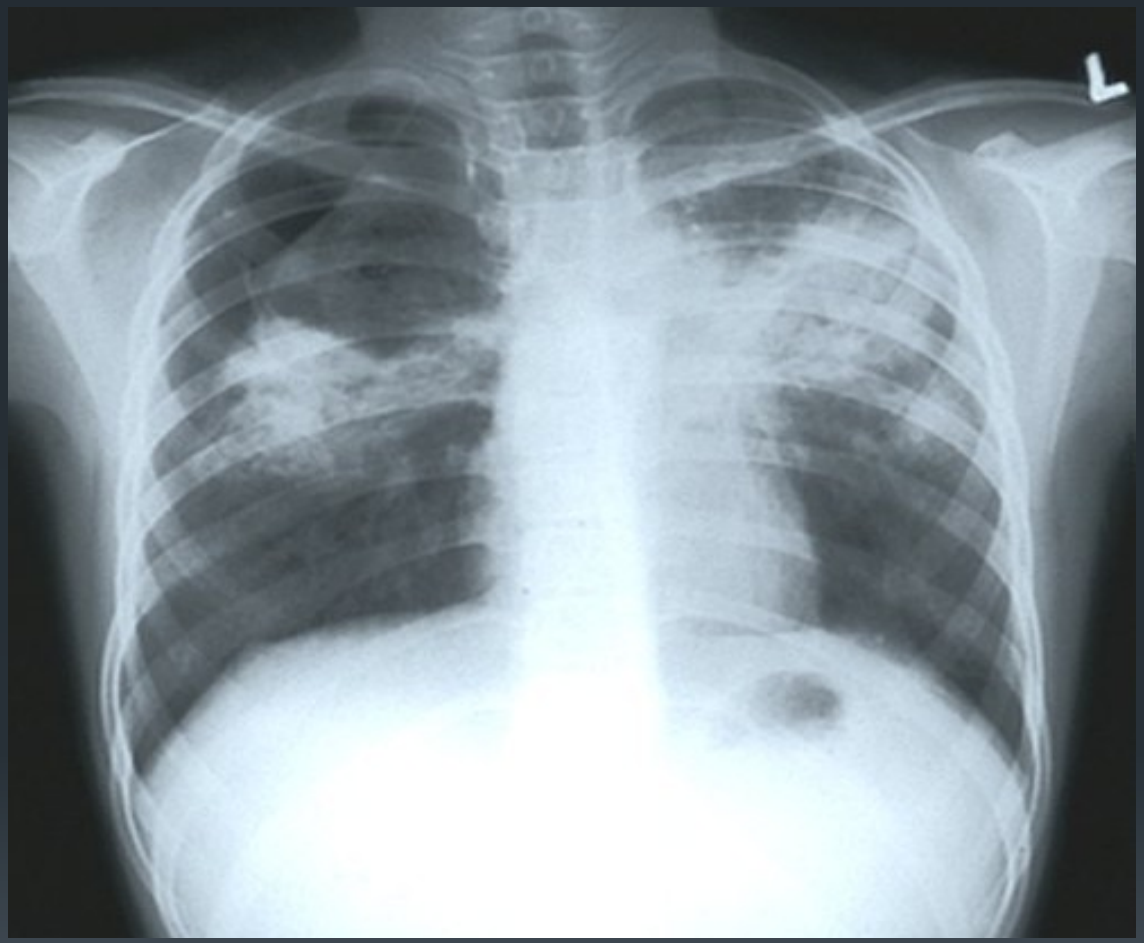
  Every year

- Nearly 5,000 people

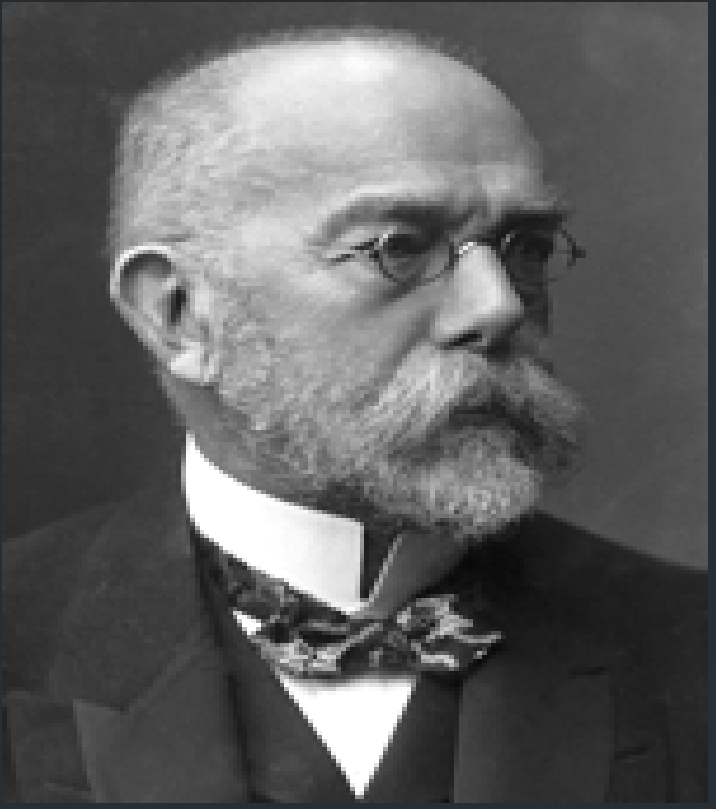
  Every day

- One person

  Every 20 seconds


L

History of TB Epidemiology and drug resistance



Robert Koch (1843–1910), who discovered *Mycobacterium tuberculosis* in 1882. Nobel Laureate Physiology or Medicine, 1905.

M.Tubeculosis **has been present in the human population since antiquity**

- Sanatorium: the first step against TB
- Measures available to doctors were still modest:
  - Improve social or sanitary conditions
  - Reduction of lung volume (thoracoplasty)
  - Radiation
- 1943-Streptomycin
- 1963- Rifampicin

- Resistance to streptomycin emerged in 85% cases

  *BMJ 1948;2: 10*09-1015
- Mid 1990-most countries registered MDR0-TB

  N Engl J Med 1993;328: 521-6
- 2006-XDR-TB term was coined

  Morb Mortal Wkly Rep. 2006;301-05

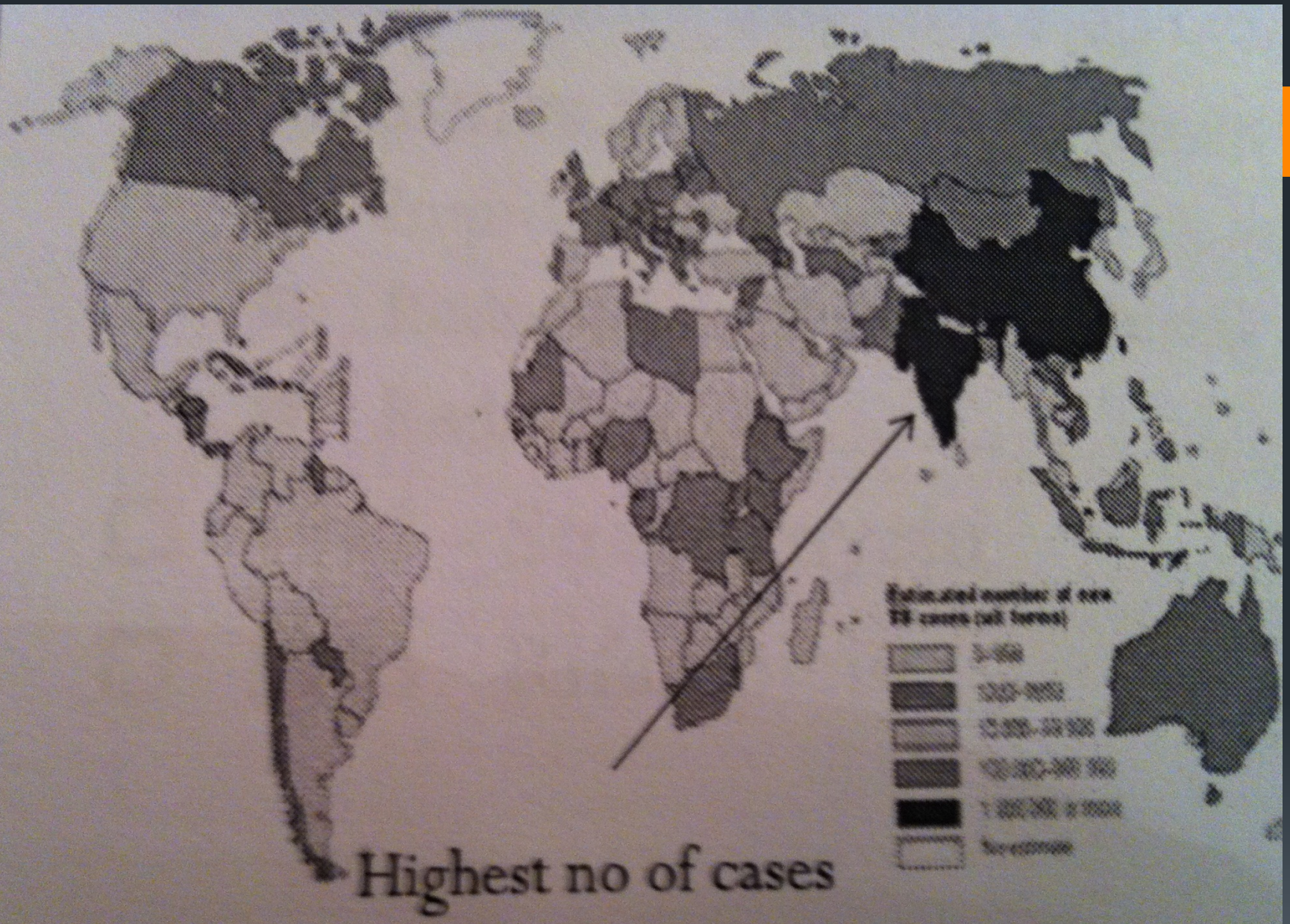
Epidemiology of TB

- An estimated 9.2 million new cases of TB in 2006 (139 per 100 000 population)
  - 4.1 million new smear-positive cases (44% of the total)
  - 0.7 million HIV-positive cases (8% of the total)
- An estimated 14.4 million prevalent cases
- Estimated 1.5 million deaths from TB in HIV-negative people
- Estimated 0.2 million death among people infected with HIV

Semin Respir Crit Care Med 2008;29: 481-491

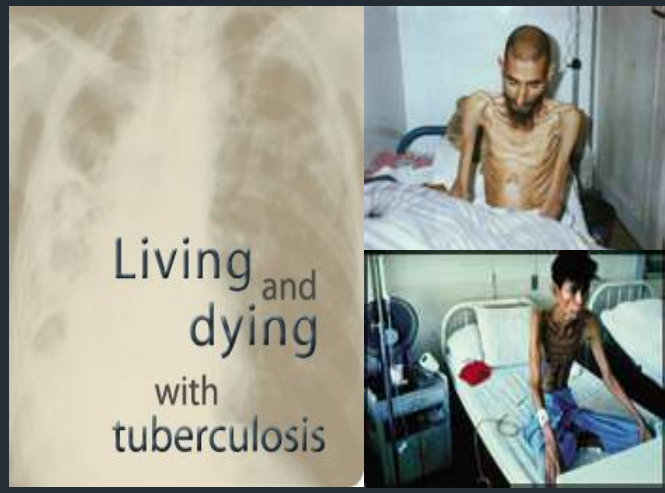
- Asia (China and India) accounts for 50% of global cases and Africa accounts for 31%
- India ranks 1st:
  - Incidence-168/1kh pop/yr
  - Prevalance-299/1kh pop/yr

- *WHO REPORT 2008/GLOBAL TUBERCULOSIS CONTROL*


Highest no of cases

The call to Stop TB

- Is a campaign that calls on world leaders, governments, organization, civil society, corporations, and individuals to endorse, fully fund and implementation the Global Plan to **Stop TB 2006-2015.**



Mortality & Morbidity

Global Impact

- WHO declared TB a global public health emergency in 1993
- Since then, the incidence of TB and its associated mortality have stabilized

Despite these relative successes, the prevention and control of TB is hampered by:

1. Emergence of drug resistance
2. Expanding HIV infection

Drug resistance in TB

Resistance to single agent:
Mono resistance

- Known since long
- Present in 74 of 77(96%) countries
- Resistance to at least one drug vary between 0% in some rich industrialized countries to 30% in several developing countries

Resistance to multiple agents

1. Poly resistant: Resistance to more than 1 drug
2. Multi-drug resistant

Multi-drug-resistant TB
MDR-TB

MDR-TB threatens WHO's target of tuberculosis elimination by 2050

MDR-TB:

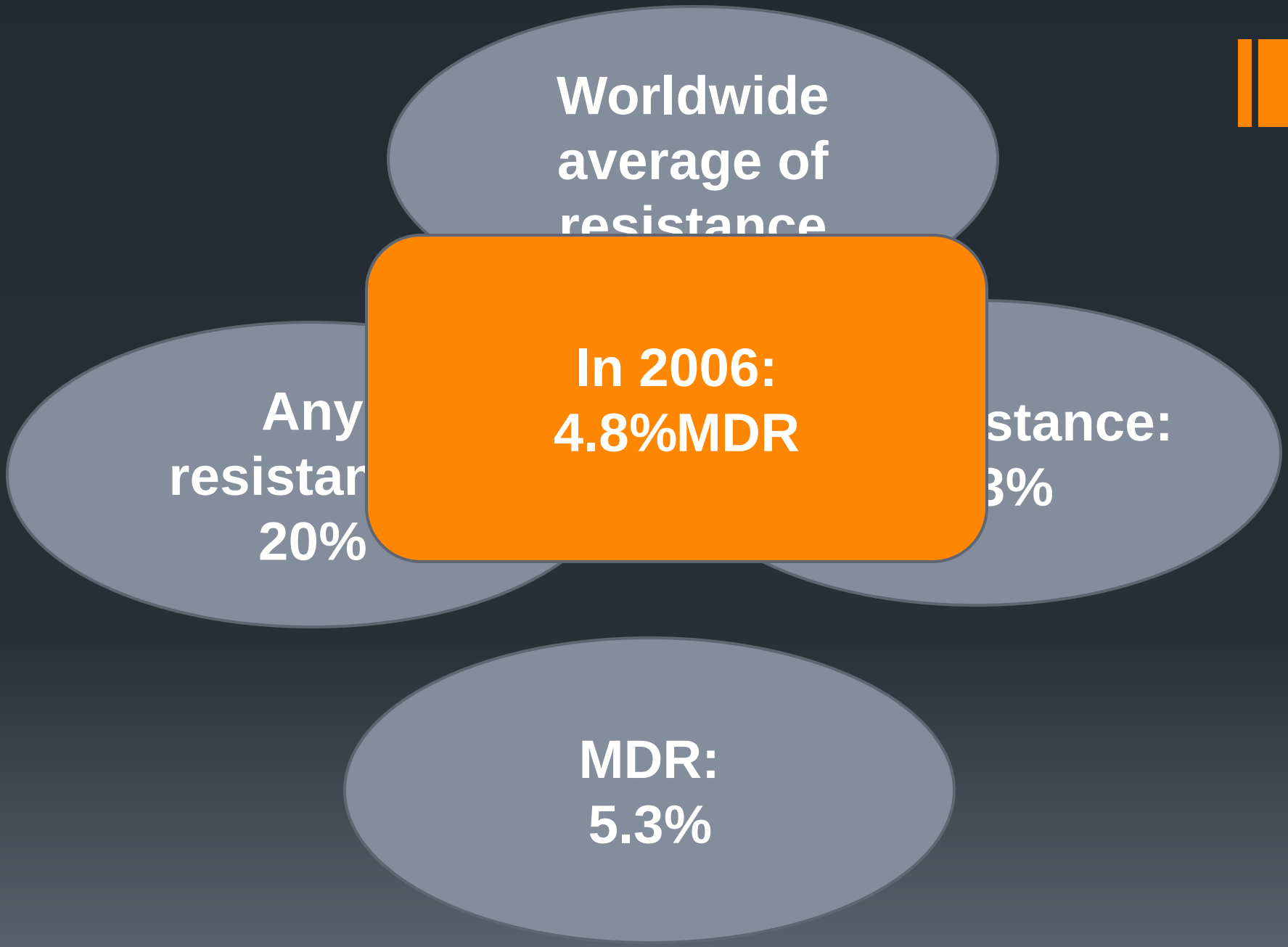
Resistance to both isoniazid (INH) and rifampicin (RIF) with or without resistance to other 1st -line agents

MMWR 2006;55:1167 WHO

Global epidemiology of MDR-TB

MDR-TB is a major threat to global public health??

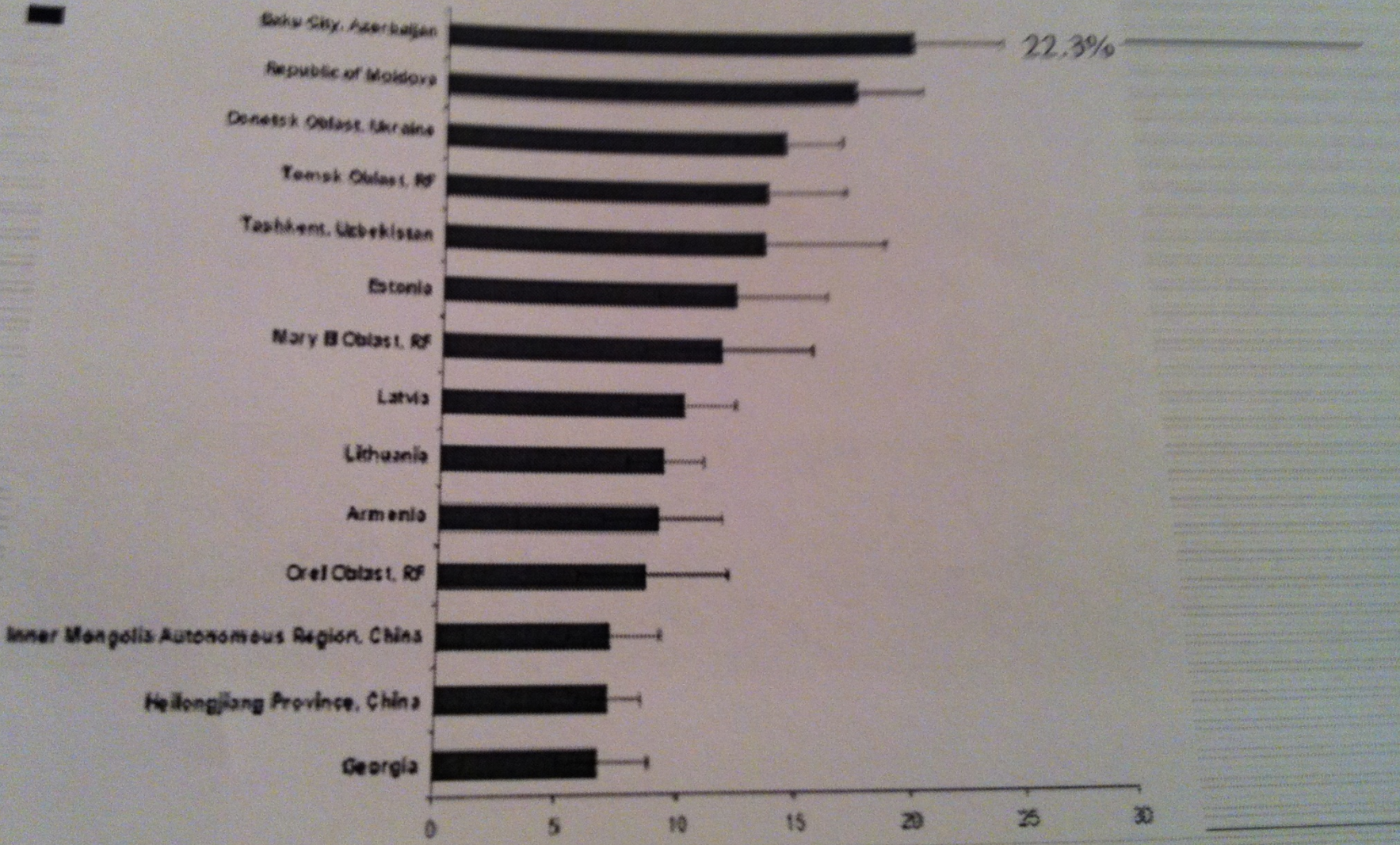
- Difficult to treat
- Often results in relapse or treatment failure
- A major risk factor for the emergence of XDR-TB:


Worldwide average of resistance
Any resistar 20%
stance: 3%
In 2006: 4.8%MDR
MDR: 5.3%

- An estimated 489,139 cases of MDR-TB in 2006
- Accounts for 4.8% of all TB cases
- Increase of 12% since 2004 and 56% since 2000
- China and India carry approximately 50% of the global burden of MDR-TB

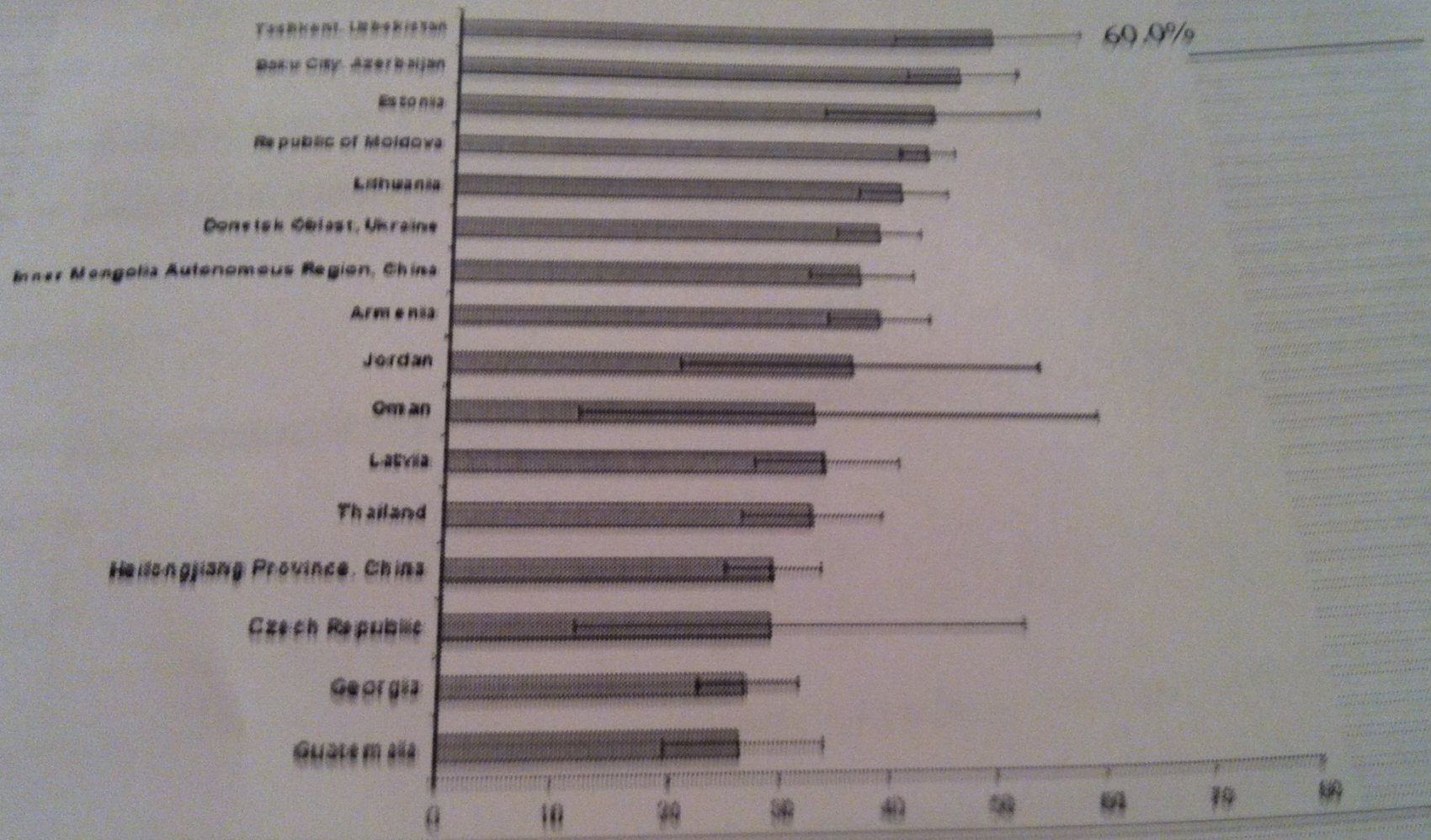
Semin Respir Crit Care Med 2008;29: 481-491

MDR PREVALENCE HIGHER THAN 5.0% AMONG NEW CASES 2002-2007



WHO/IUATLD Drug Resistance Surveil

MDR PREVALANCE HIGHER THAN 30% AMONG PREVIOUSLY TREATED CASES, 2002-2007



WHO/IUATLD Drug Resistance Sur

XDR-TB

WHO and CDC have jointly released definition of **XDR-TB** *(MMWR2006;55:1176)*

MDR

and

Resistance to any new generation flouroquinolone

and

At least one of the injectable 2nd line drugs (i.e. amikacin, kanamycin, or capreomycin)

OR

MDR

and

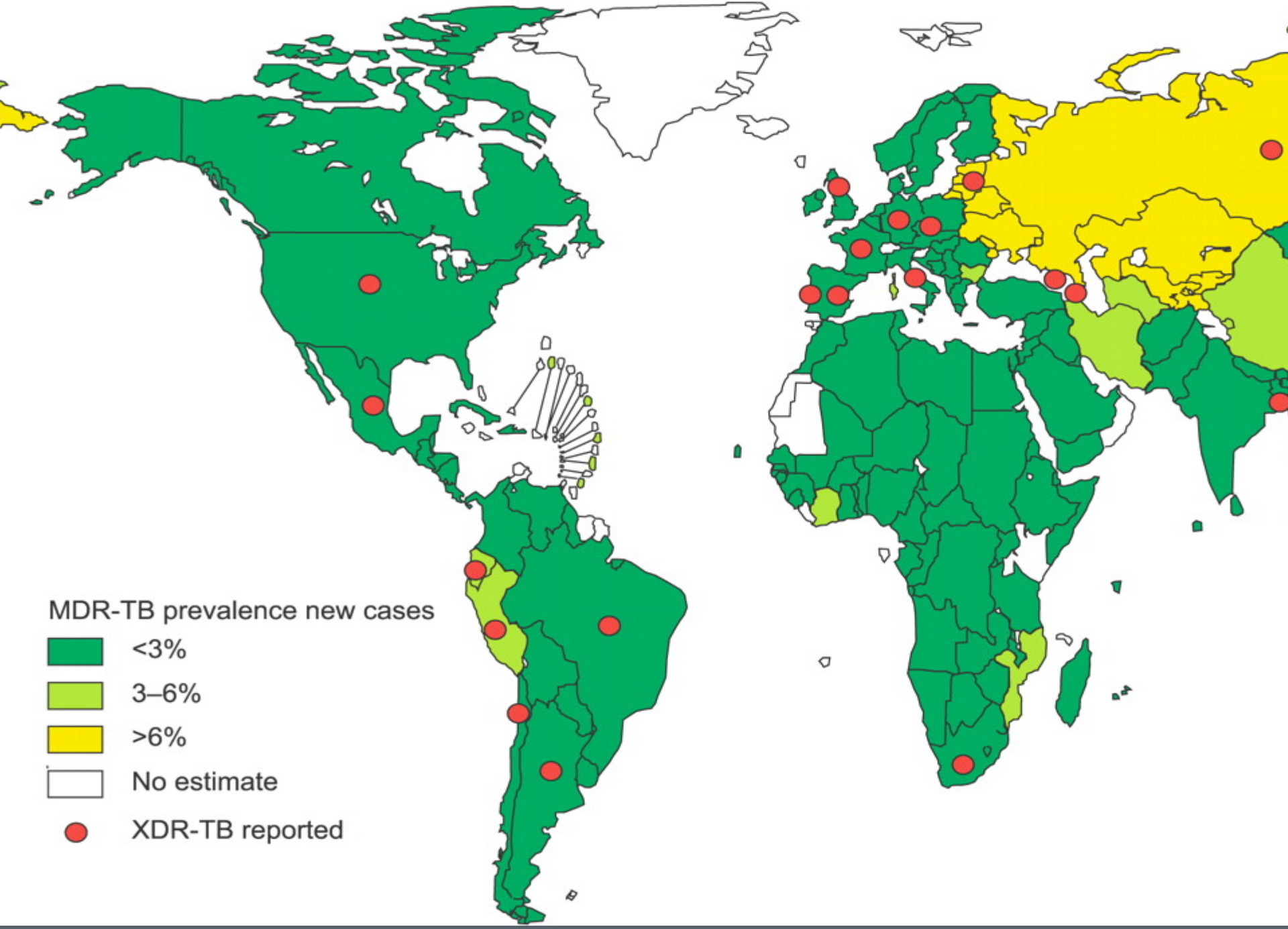
3 of the 6 main classes of second-line drugs

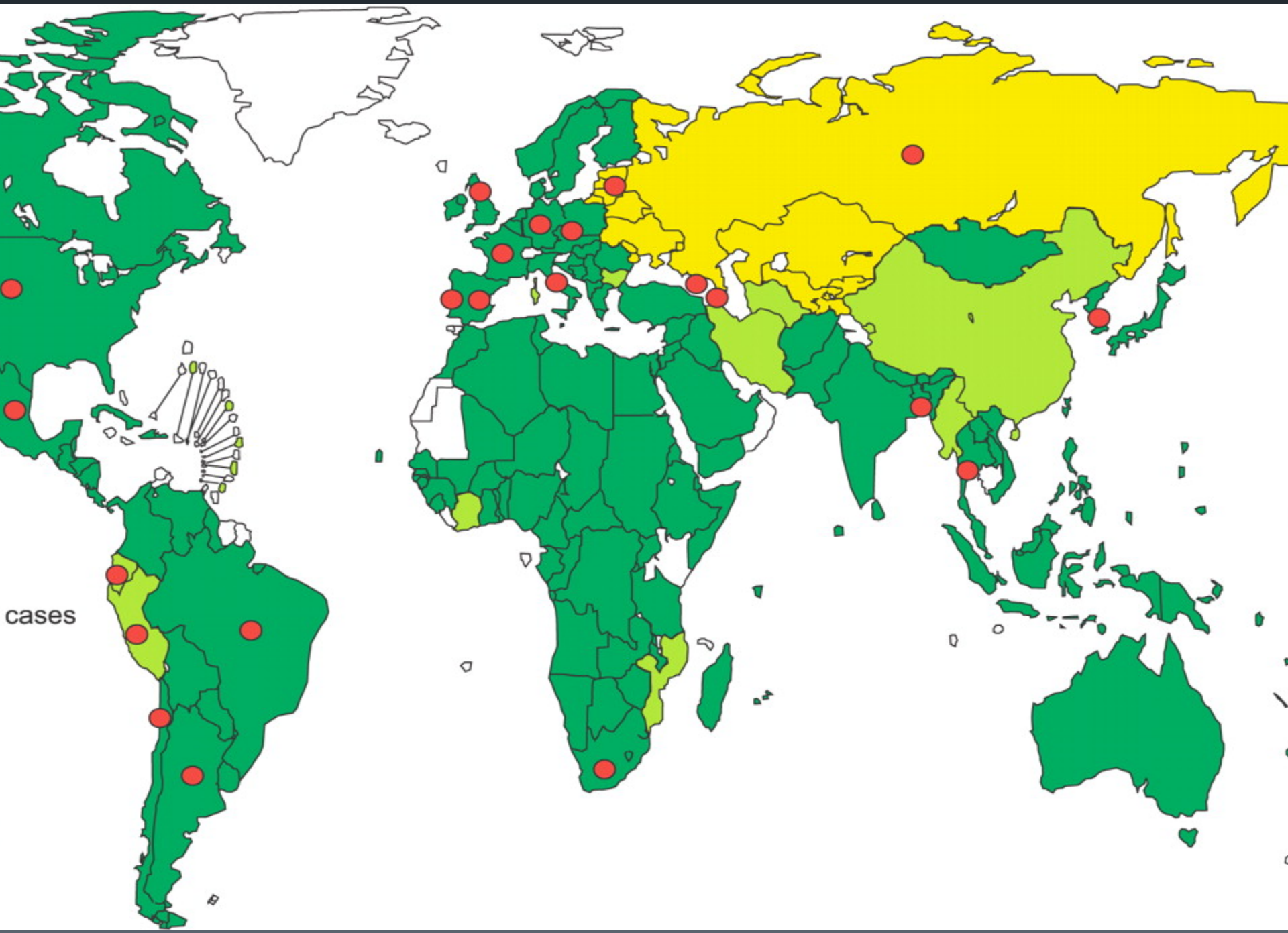
Epidemiology of XDR-TB

- The overall prevalence of XDR-TB is 2%
- 7% of total MDR-TB are XDR-TB
- Countries conducting routine surveillance-XDR represent between 7% and 34% of MDR isolates

The WHO/IUATLD Global Project on anti-tuberculosis Drug Resistance Surveillance 2002-2007

The global MDR-TB &XDR-TB Response Plan 2007-2008


MDR-TB prevalence new cases
<3%
3–6%
>6%
No estimate
XDR-TB reported


cases

In India

- An estimated 110,132 cases of MDR-TB in 2006
- Accounts for 48% of all TB cases
- Prevalence among new cases 2.8%
- Prevalence among treated cases 17.2%
- For XDR 7.4 & 9.3% among MDR-TB

Who Report 2008/ Global tuberculosis control

TDR-TB

Case Presentation

- 32 year old Bangladishi porter working in the main ICU of Ibn Sina Hospital
- Pregnant in her 2nd trimester
- Presented to the polyclinic with persistent cough for the last one month
- No history of fever
- No history of loss of weight or night sweat
- She was treated symptomatically and continued to work moving between Ward 6 and Main ICU

- After about a month, she was so tired and unable to work
- Seen by casualty doctor from Al Sabah Hospital
- CXR was done which showed an apical suspicious lesion
- Sputum examination for both smear and culture was requested

- Sputum ZN stain showed **+++ AFB**
- Patient was admitted to TB wards in Chest disease Hospital
- Notification of case was done **TO** Sabah Hospital
- **Culture grew MTB** within a week of incubation in MGIT
- AST to ATT was done
- **MTB resistant to INH, RIF, ETH, STP**

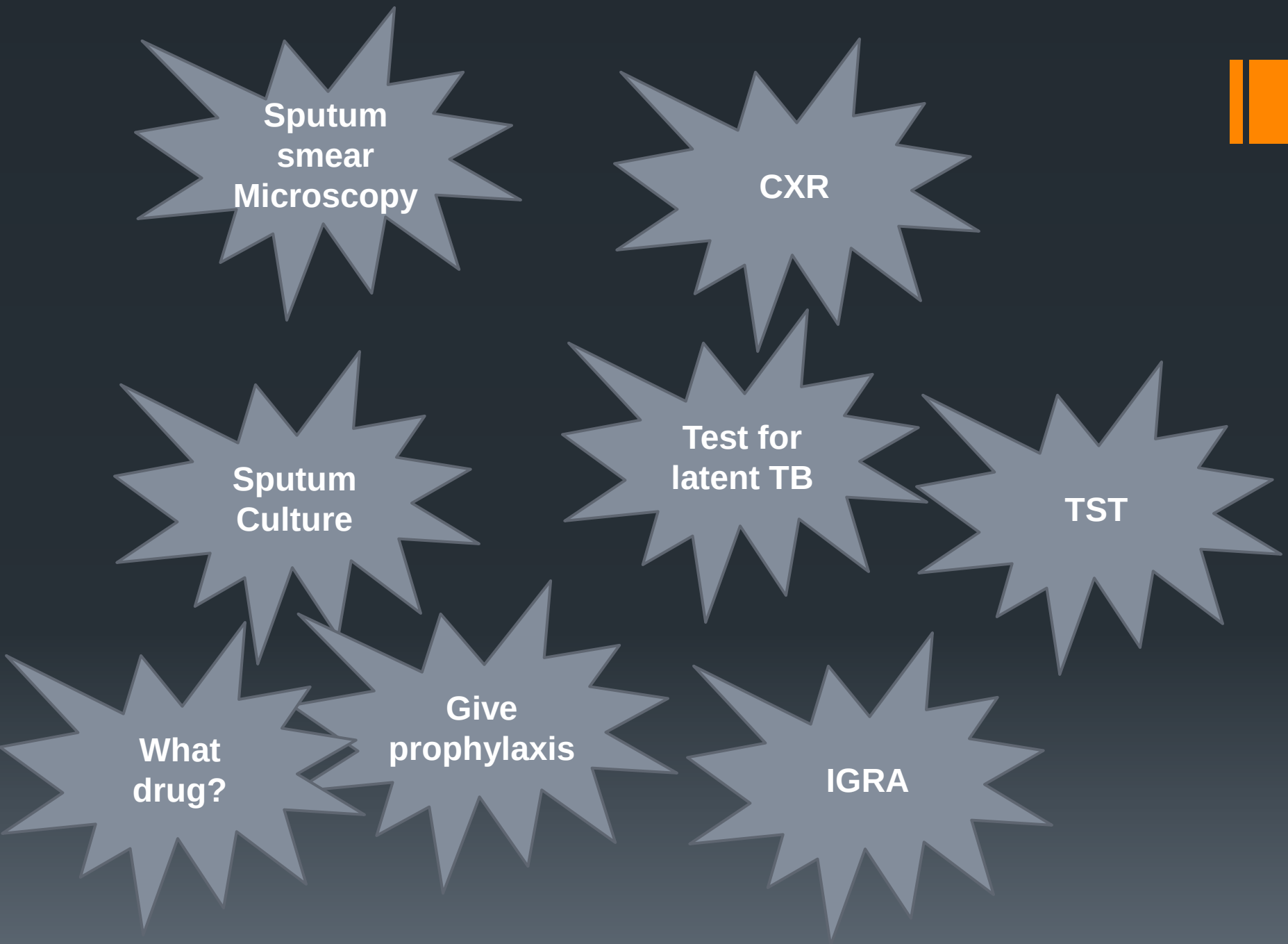
Till this time
Ibn Sina Hospital was not informed

- Second-line treatment was started
- Contact tracing was carried out by the ICD in Ibn Sina Hospital who knew about the case **by chance**
- **An emergency IC meeting was called for**
- The nurse member of the ICC was asked to provide a list of all nurses that worked in both Main ICU and Ward 6 during this period
- IC nurse was asked to provide a list of all doctors, physiothertapist, porters, cleaners who fulfilled the criteria of a close contact

- A total of:
  - Husband
  - 34 nurses
  - 5 doctors
  - 7 porters
  - 15 house hold contacts
  - 5 cleaners

A Total of 72 close contacts of an MDR-TB case

What to do next??


Sputum smear Microscopy
CXR
Sputum Culture
Test for latent TB
TST
What drug?
Give prophylaxis
IGRA

Data from Kuwait

Epidemiology of MDR TB in Kuwait

INT J TUBERC LUNG DIS 12(3):1–7

Secular trend … bacterium *tuberculosis* iso…

E. Mokaddas,* S. Ahmad,* …

* Department of Microbio… National Central Laboratory, Chest Diseases Hospital, …

Q: "Safat" OK as set?

SUMMARY

OBJECTIVE: To determine the inci… and multidrug resistance (MDR), 0.9%. drug resistance among all *Mycobacterium tuberculosis* The resistance rates over the 10-year period remained strains isolated during a 10-year perio… significant differences were noted DESIGN: Drug susceptibili… MDR among pulmolates recovered from … any drug, INH tuberculosis (TB… expatriate to December … were divide… ug resisPrior treatm… re found RESULTS: Fro… light the culture-positive … mit the de44% from extra-pu… *M. tuberculosis* Kuwaiti nationals and 4482 … tified throughout Kuwait. Overall … as follows: any drug 12.5%, isoniazid (INH) 9.1%; rifampicin (RMP) 1.1%, ethambutol (EMB) 2.0%, strep-

… *Mycobacterium tuberculosis*; drug resistance; incidence; Kuwait

Jan,1996-Dec,2005

5399 culture-positive TB cases

Overall resistance rates:
INH: 9.1
Rif: 1.1
Ethambutol: 2%
Streptomycin: 4.3%
MDR: 0.9%

	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Total isolate	530	472	561	552	576	648	614	574	547	754	763	1207	902	950
% R														
Any	13.2	11.6	12.5	13.0	12.1	14.7	11.6	10.5	14.1	9.9	11.9	13	11.9	17.1
INH	10.4	9.7	9.8	8.5	10.1	9.1	6.7	8.2	11.7	6.7	8.4	10.2	8.9	11.5
RF	0.6	0.8	2.3	1.1	0.9	0.9	1.3	1.4	1.1	1.5	2	2.7	1.1	1.7
EB	1.5	1.7	0.9	2.3	1.7	3.4	2.4	1.6	1.8	0.9	1.8	2.1	1	1.5
SM	4.7	1.9	4.3	4.3	4.2	6.3	3.7	4.3	4.5	4.4	5.2	5	4.5	6.9
MDR	0.6	0.8	2.1	0.5	0.5	0.8	0.8	1.2	1.1	1.1	1.7	**2.7**	1.1	1.4

MDR TB
Molecular basis

- Drug resistance can be achieved by:
  - Barrier methods
  - Degrading or inactivating enzymes
  - Drug target modification

} **Natural resistance**

Resistance to ATT

- MDR-TB reflects step wise accumulation of individual mutation
- Spontaneous mutation leading to resistance accur at random

Tubercle 1987; 68: 5-18
Lancet 1994; 344: 293-8

Mechanism of Drug action

- Cell wall synthesis:
  - Isoniazid: mycolic acid sysnthesis
  - Cycloserine
- Inhibit RNA sysnthesis:
  - Rifampicin: inhibition of transcription
- Inhibit protien synthesis:
  - Aminoglycosides
- Inhibit DNA Gyrase:
  - Flouroquinolones
- Inhibition of arabinogalactan and riboarabinomannan:
  - Ethambutol

Mechanism of drug resistance

- Isoniazid:
  - Mutation in *katG*
  - Overexpression of *inhA*
  - *ahpC* mutation
- Rifampicin:
  - Mutation in *rpoB* gene
- Ethambutol:
  - Over expression of EmbB gene
- Fluroquinolone:
  - *gyrA* mutation

Data from Kuwait

ELSEVIER

International Journal of Antimicrobial Agents 23 (2004) 473–479

INTERNATIONAL JOURNAL OF
Antimicrobial
Agents

www.ischemo.org

Contribution of AGC to ACC and other mutations at codon 315 of the *katG* gene in isoniazid-resistant *Mycobacterium tuberculosis* isolates from the Middle East

Suhail Ahmad*, Eiman Mokaddas

Department of Microbiology, Faculty of Medicine, Kuwait University, P.O. Box 24923, Safat 13110, Kuwait

Received 2 September 2003; accepted 6 October 2003

Original Paper

Medical Principles and Practice

Med Principles Pract 2001;10:129–134

Received: January 31, 2001
Revised: May 14, 2001

Genetic Polymorphism at Codon 463 in the *katG* Gene in Isoniazid-Sensitive and -Resistant Isolates of *Mycobacterium tuberculosis* from the Middle East

S. Ahmad[a] E. Mokaddas[a] A.T. Abal[b] G.F. Araj[c] E. Fares[d] A.S. Mustafa[a]

Departments of [a]Microbiology and [b]Medicine, Faculty of Medicine, Kuwait University, Kuwait;
[c]Department of Pathology and Laboratory Medicine, American University of Beirut, Lebanon;
[d]Department of Health and Laboratory Services, Rashid Hospital, Dubai, UAE

Microbiol. Immunol., **46**(11), 767–771, 2002

Molecular Fingerprinting of Isoniazid-Resistant *Mycobacterium tuberculosis* Isolates from Chest Diseases Hospital in Kuwait

Eiman Mokaddas[1], Suhail Ahmad*[,1], and Adnan T. Abal[2]

[1]Department of Microbiology, and [2]Medicine, Faculty of Medicine, Kuwait University, Kuwait

Received April 12, 2002; in revised form, August 12, 2002. Accepted August 23, 2002

Host factors

- Certain HLA types:
- DRB1*14 occured in 30.9% of MDR cases and 6.8% in the drug sensetive cases
- Patients with HLA-DRB1*14 have a eight-fold risk of developing MDR-TB
- Odd ratio= 8.2

Sharma S K etal. Infection, Genetics and Evolution 3 (2003) 183-188

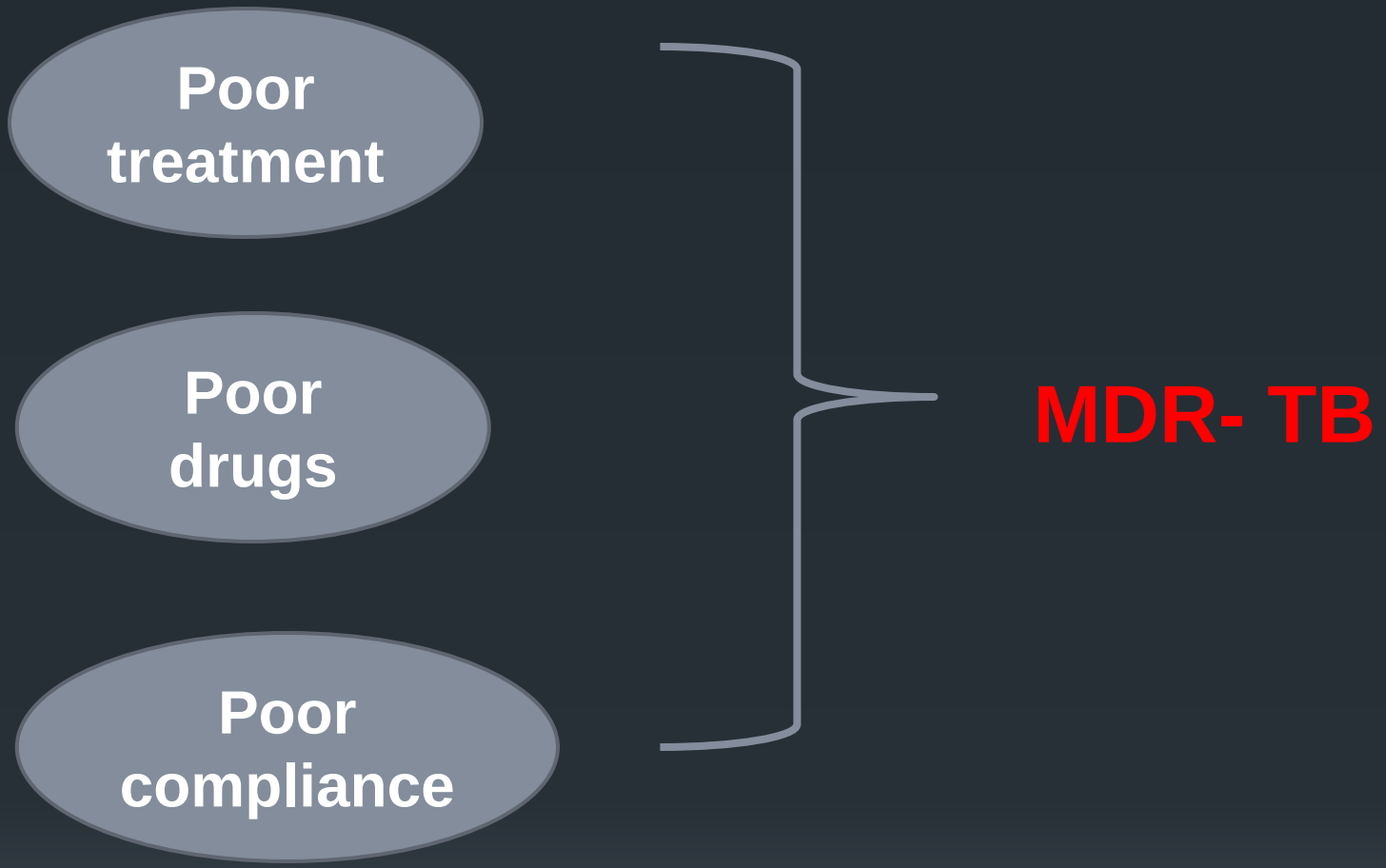
Agent factor

- The most wide spread *M.tuberculosis* strains are Beijing family
- W-Beijing genotype strong association with MDR
- World wide prevalent

Int J Tuberc Lung Dis 2005;9: 646-653

Factors related to previous treatment

MDR-TB is a man-made phenomenon



Indian J Med Res 2004; 120: 354-376

The most common error is to add single drug to failing regimen

A history of previous treatment

Indian J Med Res 2004; 120: 354-376

Causes of inadequate treatment

Provider/program: Inadequate regimens

Drugs: Inadequate supply/quality

Patients: Inadequate drug iontake

Lambregts et al Tubercle and Lung Disease 1995: 76;455-548

Difficulty in testing susceptibility of 2nd line drugs

- Invitro drug instability
- Drug loss due to protien binding
- Heat inactivation
- Incomplete dissolution
- Filter steralization
- Varying drug potency
- Critical concentration very close to the minimal inhibitory concentration (MIC)

Guidelines for mangt of DR-TB Update 2008 WHO

Classes of anti-tubercular drugs

Group 1
1st line oral agents

Isoniazid
Rifampicin
Ethambutol
Pyrazinamide

Guidelines of the programmatic mngmt of DR tuberculosis, WHO, 2008

Group 2
Injectable agents

Kanamycin
Amikacin
Capreomycin
Streptomycin

Guidelines of the programmatic mngmt of DR tuberculosis, WHO, 2008

Group 3
Flouroquinolones

Guidelines of the programmatic mngmt of DR tuberculosis, WHO, 2008

Moxifloxacin
Levofloxacin
Ofloxacin

Group 4
2nd line agents
Oral
bacteriostatic

Ethionamide
Protionamide
Cycloserine
Terizidone
PAS

Guidelines of the programmatic mngmt of DR tuberculosis, WHO, 2008

Group 5
Agents with unclear efficacy
Not recommended by WHO for routine use in MDR-TB patients

Clofazimine
Linezolid
Amoxi/Clavulanate
Imipenem

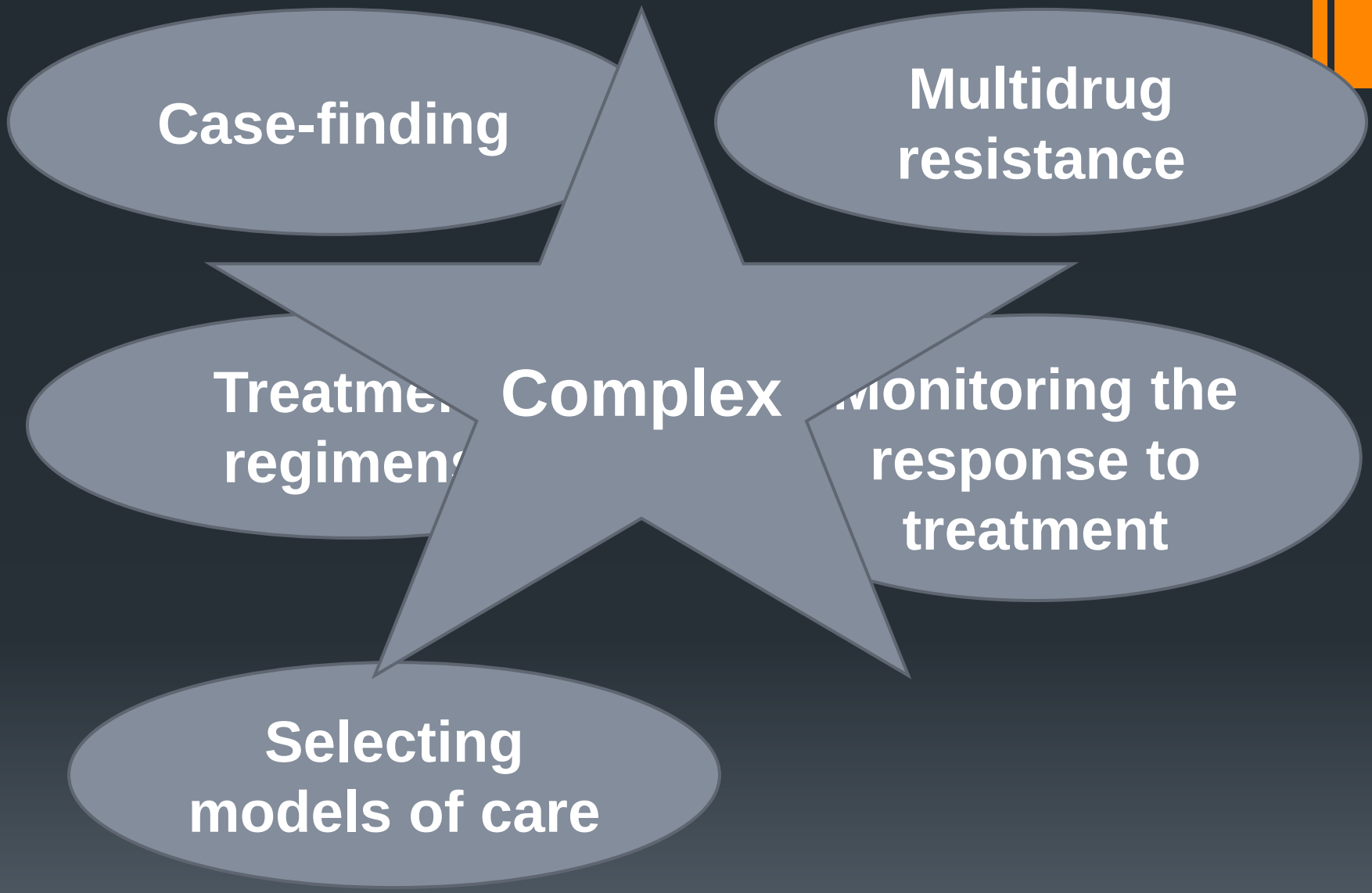
Guidelines of the programmatic mngmt of DR tuberculosis, WHO, 2008

Basic Principles of the treatment of MDR-TB

WHO Guidelines for the programatic management of drug-resistant tuberculosis

2011 Update

Objectives of the guidelines and target audience


Case-finding
Multidrug resistance
Treatme regimen
Complex
Monitoring the response to treatment
Selecting models of care

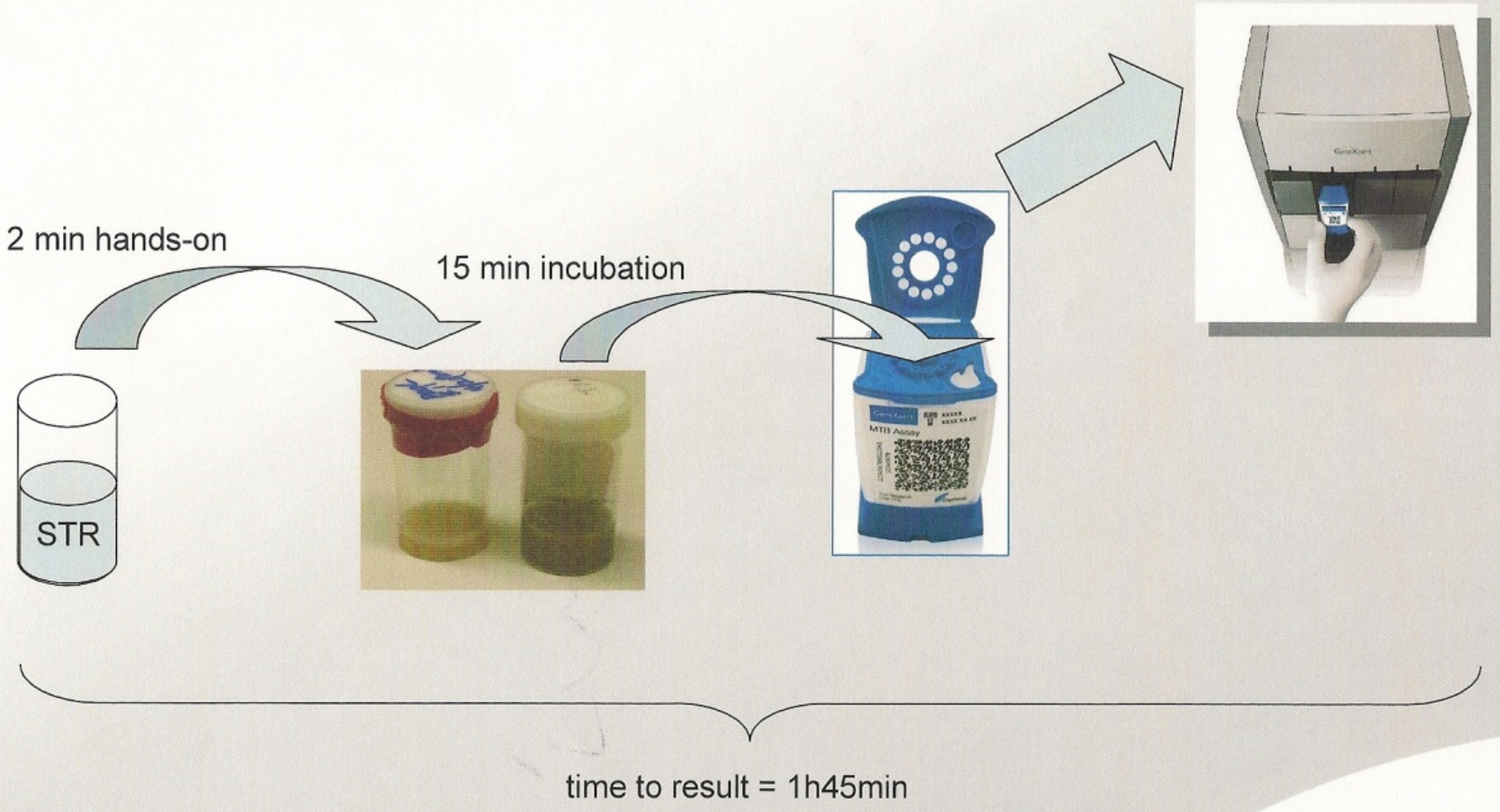
1. Rapid drug susceptibility testing for start of appropriate treatment

Wider use of rapid drug-susceptibility testing with molecular techniquies

To detect TB with rifampicin and isoniazid resistance

Provide adequate treatment

Xpert MTB Protocol



of IPT in low-income settings, based on screening for symptoms among HIV-infected patients,[2] has major limitations: the symptom screen alone misses a considerable proportion of patients with culture-proven TB, particularly in regions with high TB prevalence. Further research on screening approaches is urgently needed, including on the automated molecular testing system GeneXpert MTB/RIF, which Lawn presents as a safe tool for reliably excluding TB in HIV-infected patients before IPT initiation. Such an assay may prove to be a major step forward. We would, however, like to sound a note of caution: both a high sensitivity and reasonably high specificity are required for a test to reliably rule out a condition.[3] Taking the sensitivity of 73% given by Lawn, and assuming a specificity of 99%, results in a likelihood ratio of a negative test of 0.27. A negative GeneXpert MTB/RIF test would thus reduce the pre-test probability of 15% quoted by Lawn to 4.6%.

Finally, we stress that the survey of practices reported in our article was from 2008 and may not reflect the current situation. Since then, numerous clinical trials on IPT and the new WHO guidelines on IPT implementation in ART programmes have been published. We plan to repeat our survey in the near future within the framework of the International epidemiological Databases to Evaluate AIDS (IeDEA) in sub-Saharan Africa.[4]

Lukas Fenner*
Andrew Boulle†
Matthias Egger*†
*Institute of Social and Preventive Medicine
University of Bern
Bern, Switzerland
†Centre for Infectious Disease
Epidemiology and Research
School of Public Health and Family Medicine
University of Cape Town
Cape Town, South Africa
e-mail: lfenner@ispm.unibe.ch
http://dx.doi.org/10.5588/ijtld.11.0407-2

References

1 Fenner L, Forster M, Egger M, and others, for the ART-LINC collaboration of IeDEA. Tuberculosis in HIV programmes in lower-income countries: practices and risk factors. Int J Tuberc Lung Dis 2011; 15: 620–627.
2 World Health Organization. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva, Switzerland: WHO, 2011.
3 Pewsner D, Battaglia M, Minder C, Marx A, Bucher H C, Egger M. Ruling a diagnosis in or out with 'SpPIn' and 'SnNOut': a note of caution. BMJ 2004; 329: 209–213.
4 Egger M, Ekouevi D K, Williams C, et al. Cohort profile: the international epidemiological databases to evaluate AIDS (IeDEA) in sub-Saharan Africa. Int J Epidemiol 2011. http://dx.doi.org/10.1093/ije/dyr080 (epub ahead of print).

GeneXpert® MTB/RIF for rapid detection of *Mycobacterium tuberculosis* in pulmonary and extra-pulmonary samples

Tuberculosis (TB) is a leading public health problem worldwide causing ~9 million active disease cases and ~2 million deaths annually. Delayed diagnosis and incomplete/improper treatment of TB patients leads to the evolution of drug-resistant strains of *Mycobacterium tuberculosis*, including multidrug-resistant (MDR) and extensively drug-resistant TB (XDR-TB).[1] In developing countries, effective treatment of MDR-TB is difficult, while XDR-TB is virtually untreatable.[1] Pulmonary TB accounts for ~85% of active disease cases, ~60% of which are smear microscopy positive, representing infectious disease status. Furthermore, ~15% of smear-negative pulmonary cases have also been linked with transmission of infection to close contacts.[2] Early detection of active disease is therefore essential to reduce mortality and to minimise further transmission of infection.

A single cartridge-based automated, real-time PCR assay (GeneXpert® MTB/RIF System, Cepheid, Sunnyvale, CA, USA; GX) has recently been developed for rapid detection of *M. tuberculosis* and resistance to rifampicin (RMP).[3,4] Efficacy of GX for detection of *M. tuberculosis* was tested in clinical samples at the National Tuberculosis Reference Laboratory in Kuwait, a country with low to intermediate incidence of TB.[5]

Clinical specimens included 206 pulmonary (196 sputum, 6 bronchoalveolar lavage, 4 endotracheal aspirate) and 29 extra-pulmonary (11 pleural fluid, 9 fine needle aspirate/pus, 5 cerebrospinal fluid, 2 gastric aspirate, 2 urine) samples collected from June to December 2009. All samples were tested using smear microscopy, solid and liquid culture and drug susceptibility testing (DST) of *M. tuberculosis* isolates against RMP using MGIT 960 and BACTEC 460TB systems.[5] GX was performed and results were interpreted according to the manufacturer's instructions.[3,4] Positive and negative controls were tested each day.

Seventy-two (60 pulmonary and 12 extra-pulmonary) samples yielded *M. tuberculosis* by culture, while 56 (78%) culture-positive samples (46 pulmonary and 10 extra-pulmonary) were also smear-positive. GX exhibited 98% agreement for smear-positive, culture-positive samples and 69% agreement for smear-negative, culture-positive samples for detection of *M. tuberculosis*. Similar to another study,[4] overall concordance with culture was 92%. Another study using a larger number of smear-negative, culture-positive specimens reported lower sensitivity (~80%).[3] There was 98% and 64% agreement for smear-positive and smear-negative pulmonary specimens, respectively. Sensitivity in smear-negative, culture-positive pulmonary specimens is similar to other studies.[3,4] The lower sensitivity in smear-negative, culture-positive pulmonary specimens could possibly be due to lower bacillary load in sputum specimens. GX exhibited 100% agreement with culture for both smear-positive,

culture-positive and smear-negative, culture-positive extra-pulmonary specimens. The higher GX sensitivity in our extra-pulmonary specimens is likely due to higher smear positivity (10/12, 83%), as fewer smear-positive, culture-positive extra-pulmonary samples were analysed in another study that reported lower sensitivity.[6] Consistent with previous data,[5] only one of 72 (1.4%) *M. tuberculosis* isolates was resistant to RMP by both phenotypic DST and GX. Other studies have reported a higher frequency of RMP resistance detection by GX; however, these studies analysed samples from countries with a higher incidence of RMP resistance.[4,5]

The rapidity and simplicity of the closed cartridge GX test make it a good TB diagnostic test for routine use in reference laboratories of countries with low to intermediate incidence of TB, and may also help in reducing further transmission of infection in such settings.

Shumaila N. M. Hanif*
Hana S. Eldeen*
Suhail Ahmad†
Eiman Mokaddas*†
*National Tuberculosis Reference Laboratory
Shuwaikh
†Department of Microbiology
Faculty of Medicine
Kuwait University
Safat, Kuwait
email: suhail_ab@hsc.edu.kw
suhail_ab2000@yahoo.com
http://dx.doi.org/10.5588/ijtld.11.0394

References

1 Ahmad S, Mokaddas E. Recent advances in the diagnosis and treatment of multidrug-resistant tuberculosis. Respir Med 2009; 103: 1777–1790.
2 Behr M A, Warren S A, Salamon H, et al. Transmission of *Mycobacterium tuberculosis* from patients smear-negative for acid-fast bacilli. Lancet 1999; 353: 444–449.
3 Helb D, Jones M, Story E, et al. Rapid detection of *Mycobacterium tuberculosis* and rifampin resistance by use of on-demand, near-patient technology. J Clin Microbiol 2010; 48: 229–237.
4 Boehme CC, Nabeta P, Hillemann D, et al. Rapid molecular detection of tuberculosis and rifampin resistance. N Engl J Med 2010; 363: 1005–1015.
5 Mokaddas E, Ahmad S, Samir I. Secular trends in susceptibility patterns of *Mycobacterium tuberculosis* isolates in Kuwait, 1996–2005. Int J Tuberc Lung Dis 2008; 12: 319–325.
6 Hillemann D, Rüsch-Gerdes S, Boehme C C, Richter E. Rapid molecular detection of extrapulmonary tuberculosis by the automated GeneXpert MTB/RIF system. J Clin Microbiol 2011; 49: 1202–1205.

Hepatotoxicity in the treatment of tuberculosis using moxifloxacin-containing regimens

Fluoroquinolones may be used as alternative anti-tuberculosis agents in subjects at high risk of, or experiencing, hepatotoxicity.[1] A 2008 UK drug alert documented an idiosyncratic fulminant hepatitis as a result of moxifloxacin (MXF).[2] Recent data from MXF-substitution tuberculosis (TB) treatment trials showed no association with hepatotoxicity.[3,4] However, none focused specifically on hepatotoxicity, and human immunodeficiency virus (HIV) status was the only risk factor recorded. As we manage a number of TB patients with risk factors for drug-induced hepatotoxicity, this prompted us to review our single-centre data.

We compared active TB cases treated with standard quadruple therapy (rifampicin [RMP], isoniazid [INH], pyrazinamide [PZA] and ethambutol) with those given MXF-containing regimens between January 2005 and March 2008. Hepatotoxicity events were assessed as the highest recorded transaminases (AST/ALT), upper limit of normal (ULN) 40 IU/L, and subsequent treatment cessation. Hepatotoxicity was categorised as 1.25–2.5, 2.5–5.0, 5.0–10 and >10 fold increase over the ULN.[5] In those who had raised transaminases at baseline, toxicity was defined as deteriorating transaminases by one or more hepatotoxicity grades.

We identified 159 patients who received standard quadruple therapy and 35 patients who received an MXF-containing regimen for more than 3 days (range 4–730 days). The MXF group were more likely to be older ($P \leq 0.0001$), have active viral hepatitis (active hepatitis B $P = 0.0007$; hepatitis C $P = 0.06$) and underlying liver disease (liver disease of any cause, $P = 0.0001$; cirrhosis $P = 0.02$; liver transplant $P = 0.001$). In the MXF group, 27/35 were initially treated with MXF and 8/35 patients were switched from standard therapy. Indications for MXF were cerebral disease 9/35, abnormal liver function tests at baseline/hepatic cirrhosis 7/35, renal failure 5/35, hepatotoxicity on first-line therapy 4/35, drug-resistant TB 4/35, concern over HIV-related non-tuberculous mycobacterial disease 4/35, intolerance to first-line drugs 1/35, and disseminated TB 1/35. Drugs co-administered with MXF were varied: 20% RMP+INH; 20% RMP+INH with PZA. Median baseline transaminase values were normal in both groups.

The proportion experiencing hepatotoxicity was comparable (43% of the MXF group, 37% of controls, $P = 0.63$; Fisher's Exact test). After adjusting for age and prior hepatic disease using multivariate logistic regression, there was no association observed between ALT/AST >5 ULN and MXF use (odds ratio [OR] = 0.96; 95%confidence interval [CI] 0.23–4.03; $P = 0.95$).

Treatment interruption due to hepatotoxicity was similar (11.4% MXF vs. 6.9% comparator, $P = 0.48$). On multivariable analysis, no association was observed between treatment interruption for hepatotoxicity and MXF use (OR = 1.46; 95%CI

INT J TUBERC LUNG DIS 15(1):110–115

Performance comparison of four methods for detecting multidrug-resistant *Mycobacterium tuberculosis* strains

N. M. Al-Mutairi, S. Ahmad, E. Mokaddas

Department of Microbiology, Faculty of Medicine, Kuwait University, Kuwait

SETTING: National Tuberculosis Reference Laboratory, Kuwait.

OBJECTIVE: To compare Genotype MTBDR*plus* (gMTBDR+), INNO-LiPA Rif.TB (INNO-LiPA), polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) and DNA sequencing for detecting rifampicin (RMP) and/or isoniazid (INH) resistance-associated mutations in the *rpo*B hot-spot region (HSR-*rpo*B), the *kat*G codon 315 (*kat*G315) and the *inh*A regulatory region (*inh*A-RR) among multidrug-resistant *Mycobacterium tuberculosis* (MDR-TB) isolates.

DESIGN: A total of 82 MDR-TB and 43 pansusceptible *M. tuberculosis* BACTEC 460-characterised isolates were processed using molecular techniques and the Mycobacterial Growth Indicator Tube (MGIT) 960 system.

INNO-LiPA and HSR-*rpo*B sequencing. Tw
Ins514TTC mutation were detected as
by gMTBDR+ but as RMP-susceptible by
One isolate with L533P mutation, detec
susceptible by gMTBDR+, was detected as
by INNO-LiPA. Two of three isolates dete
susceptible by gMTBDR+, INNO-LiPA,
quencing and the MGIT 960 system cont
mutation that is outside HSR-*rpo*B. INH
detected in respectively 76, 60, 60 and
strains by gMTBDR+, *kat*G315 PCR-R
sequencing and *inh*A-RR sequencing.

CONCLUSIONS: Although gMTBDR+
tected ~88% of MDR-TB strains, some *r*
were either missed or were outside the reg

ELSEVIER

International Journal of Antimicrobial Agents 26 (2005) 205–212

INTERNATIONAL JOURNAL OF
Antimicrobial
Agents

www.ischemo.org

The occurrence of rare *rpoB* mutations in rifampicin-resistant clinical *Mycobacterium tuberculosis* isolates from Kuwait

Suhail Ahmad*, Eiman Mokaddas

Department of Microbiology, Faculty of Medicine, Kuwait University, P.O. Box 24923, Safat 13110, Kuwait

Received 14 April 2005; accepted 15 June 2005

BRIEF REPORT

Molecular fingerprinting reveals familial transmission of rifampin-resistant tuberculosis in Kuwait

Eiman Mokaddas;* Suhail Ahmad;* Adnan T. Abal;† Abdul S. Al-Shami‡

*Department of Microbiology and
†Department of Medicine, Faculty
of Medicine, Kuwait University,
‡Chest Diseases Hospital, Kuwait

Correspondence to:
Dr. Suhail Ahmad
Department of Microbiology
Faculty of Medicine,
Kuwait University
P.O. Box 24923
Safat 13110, Kuwait
Tel: 965-531-2300 Ext.6503
Fax: 965-533-2719
suhail_ah@hsc.edu.kw
suhail_ah2000@yahoo.com

Accepted for publication:
January 2005

Ann Saudi Med 2005;25(2):150-153

ELSEVIER

Diagnostic Microbiology and Infectious Disease
44 (2002) 245–252

DIAGNOSTIC MICROBIOLOGY AND INFECTIOUS DISEASE

www.elsevier.com/locate/diagmicrobio

Mycobacteriology

Characterization of *rpoB* mutations in rifampin-resistant clinical *Mycobacterium tuberculosis* isolates from Kuwait and Dubai

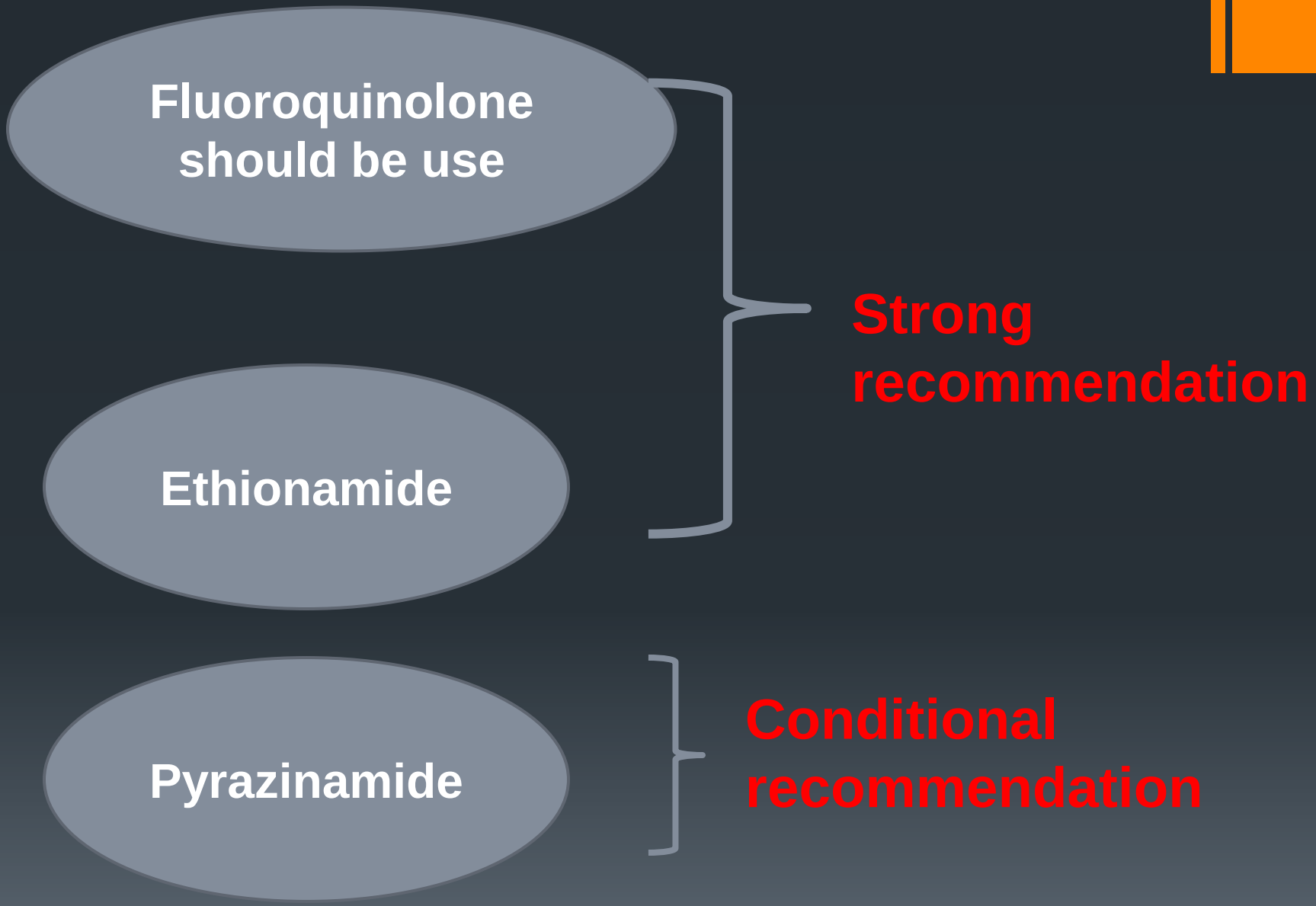
Suhail Ahmad[a,*], Eiman Mokaddas[a], Esther Fares[b]

[a]*Department of Microbiology, Faculty of Medicine, Kuwait University, P.O. Box 24923, Safat 13110, Kuwait*
[b]*Department of Health and Medical Services, Rashid Hospital, Dubai, U.A.E.*

2. Monitoring the response to MDR-TB treatment

Using sputum smear microscopy and culture rather than sputum smear microscopy alone is recommended for the monitoring of patients with MDR-TB during treatment

3. Composition of second-line anti-tuberculosis regimens


Fluoroquinolone should be use
Ethionamide
Strong recommendation
Pyrazinamide
Conditional recommendation

4. Duration of second-line anti-tuberculosis regimens

Intensive phase of at least 8 months

Conditional recommendation

A total treatment duration of at least 20 months

Conditional recommendation

5. Models of care for managing MDR-TB

Patients with MDR-TB should be treated using mainly ambulatory care rather than models of care based principally on hospitalization

Patients with MDR-TB

Dilute them in the community

Data from Kuwait

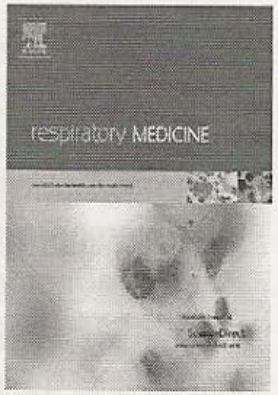
Respiratory Medicine (2009) 103, 1777–1790

ELSEVIER

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/rmed



REVIEW

Recent advances in the diagnosis and treatment of multidrug-resistant tuberculosis

Suhail Ahmad*, Eiman Mokaddas

Department of Microbiology, Faculty of Medicine, Kuwait University, Kuwait

Received 30 March 2009; accepted 19 July 2009
Available online 5 August 2009

INTERNATIONAL JOURNAL OF MEDICAL AND BIOLOGICAL FRONTIERS

Volume 16, Issue 7/8

TABLE OF CONTENTS

NO. 80

New approaches in the diagnosis and treatment of susceptible, multidrug-resistant and extensively drug resistant tuberculosis

Suhail Ahmad*, and Eiman Mokaddas

Department of Microbiology, Faculty of Medicine, Kuwait University, Kuwait

Running title: Diagnosis and treatment of TB, MDR-TB and XDR-TB

*Correspondence to:

Prof. Suhail Ahmad,

Department of Microbiology, Faculty of Medicine,

Chapter

TUBERCULOSIS: RISK FACTORS, DRUG RESISTANCE, RAPID DETECTION AND TREATMENT

Suhail Ahmad and ***Eiman Mokaddas***
Department of Microbiology, Faculty of Medicine,
Kuwait University, Kuwait

ABSTRACT

The global burden of tuberculosis (TB) is still enormous despite increases in both public and private investment and joint efforts of the World Health Organization and health care systems of various countries to control this dreadful disease. With nearly 9 million active disease cases and 2 million deaths occurring worldwide every year, TB is a major public health problem and a leading cause of death from an infectious agent.

Active TB disease is caused primarily by the obligate human

Resistance to second line drugs

Quinolones

Al-Mutairi et al. BMC Research Notes 2011, 4:123
http://www.biomedcentral.com/1756-0500/4/123

BMC Research Notes

SHORT REPORT Open Access

First report of molecular detection of fluoroquinolone resistance-associated *gyrA* mutations in multidrug-resistant clinical *Mycobacterium tuberculosis* isolates in Kuwait

Noura M Al-Mutairi, Suhail Ahmad* and Eiman Mokaddas

Abstract

Background: Nearly 5% of all *Mycobacterium tuberculosis* strains worldwide are resistant at least to rifampicin and isoniazid (multidrug-resistant tuberculosis, MDR-TB). Inclusion of a fluoroquinolone and an injectable agent (kanamycin, amikacin or capreomycin) in multidrug therapy is crucial for proper treatment of MDR-TB. The incidence of MDR-TB in Kuwait is ~1%. MDR-TB strains additionally resistant to fluoroquinolones and injectable agents are defined as extensively drug-resistant (XDR-TB) strains and have been detected in >55 countries. Infections with XDR-TB strains have very poor prognosis. This study detected the occurrence of *gyrA* mutations associated with fluoroquinolone resistance among MDR-TB strains in Kuwait.

Findings: Direct DNA sequencing of quinolone resistance-determining region of *gyrA* gene was performed to detect fluoroquinolone resistance-associated mutations in 85 MDR-TB strains isolated from 55 TB patients and 25 pansusceptible *M. tuberculosis* strains. For isolates exhibiting *gyrA* mutations, 3'-end of *rrs* (16S rRNA) was sequenced for the detection of XDR-TB. Fingerprinting of fluoroquinolone resistant MDR-TB strains was performed by detecting mutations in three (81 bp hot-spot, N-terminal and cluster II) regions of *rpoB*, *katG* codon 315 and *inhA*-regulatory region, polymorphisms at *gyrA* codon 95 and *katG* codon 463 by DNA sequencing and by double-repetitive-element PCR for determining strain relatedness. None of the pansusceptible but six of 85 MDR-TB strains contained *gyrA* mutations. Only *gyrA* codon 94 was mutated in all six (D94A in one and D94G in five) strains. Three of six mutant strains were recovered from the same patient while three other strains represented individual patient isolates. Fingerprinting studies identified all individual patient isolates as epidemiologically distinct strains. All six strains with a *gyrA* mutation contained wild-type *rrs* sequence.

Conclusions: Although fluoroquinolones are generally not used for chemotherapy of TB and drug susceptibility testing for second-line drugs is not carried out in Kuwait, four of 55 (7%) individual patient MDR-TB strains contained mutations in *gyrA* gene. The data advocate routine drug susceptibility testing for this important second-line drug for proper management of MDR-TB in Kuwait. Lack of mutations in 3'-end of *rrs* gene that confer resistance to injectable agents reduce the likelihood of occurrence of XDR-TB, at present, in Kuwait.

Keywords: *M. tuberculosis* Fluoroquinolone resistance, *gyrA* mutations, Kuwait

* Correspondence: suhail_ah@hsc.edu.kw
Department of Microbiology, Faculty of Medicine, Kuwait University, Kuwait

- Tested 85 MDR-TB strains isolated from 55 TB patients and 25 pan-susceptible MTB strains
- Detection of mutation in QRDR of the *gyrA* gene by DNA sequencing was performed
- Then fingerprinting of MDR-TB strains carrying *gyrA* mutation was performed
- Out of the **85** MDR TB isolates, **6** of them carried the *gyrA* mutation
- Non of the pan-susceptible isolates carried the mutation

Role of fluoroquinolones in the treatment of tuberculosis

Suhail Ahmad [1], Eiman Mokaddas [1]

[1] *Department of Microbiology, Faculty of Medicine, Kuwait University, Kuwait*

Abstract

Introduction: The increasing incidence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains of *Mycobacterium tuberculosis* is hampering efforts to control the global tuberculosis (TB) epidemic. Although treatment of drug-susceptible TB is possible in ≥ 95% of disease cases, long (≥ 6 months) duration supervised combination therapy is challenging. Non-adherence to treatment often results in much lower cu rates. Treatment of MDR-TB and XDR-TB is far less effective. The aim of this review is to summarize the cu rent status of fluoroquinolones in shortening the duration of drug-susceptible pulmonary TB and in improv the outcome of MDR-TB/XDR-TB.

Methods: All the relevant articles were identified through a search of PubMed and Scopus databases by u

Acknowledgement

Dr. Hana Saad ElDeen
Dr. Shamaela Hanif
Mrs Najah Ayed
All technical staff

Kuwait National TB Reference Laboratory

Professor Suhail Ahmed

Molecular Mycobacteriology Reference Lab
Faculty of Medicine
Kuwait University

Conclusion

A basic Principle of Medical Practice

Diagnosis before Treatment

Editorial report by Small and Pai
rightly referred to rapid detection technology as

Game Changer

On the MOVE against tuberculosis
Transforming the fight towards elemination

World TB Day

2011 Campaign

Key Messages

It’s time

It’s time to break the barriers to a world free of TB

It’s time for an ambitious new research agends

It’s time for public health programmes to reach all TB patients

It’s time for ambitious new goals on MDR-TB treatment

It’s time to move rapidly towards zero deaths from TB/HIV

The war against TB: A fight to the finish

Finish of the *M.tuberculosis*


Large Scale Evaluation of Multiplex PCR and DNA Sequencing of 16S-23S I
Transcribed Spacer Region for Rapid Differentiation and Mycobacterium
Isolates in Kuwait
*Mokaddas E, Ahmad S
Department of Microbiology, Faculty of Medicine, Kuwait University, Kuwait
POSTER
WINNER
Thank You