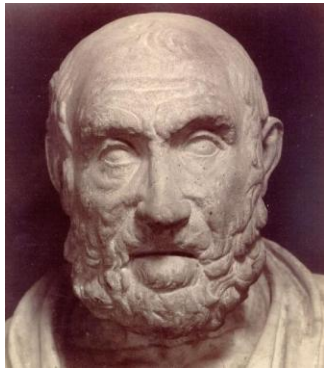


# **The changing face of tuberculosis**

Wim Sturm

University of KwaZulu-Natal

# Tuberculosis: as old as mankind



- **Spinal tuberculosis diagnosed in Egyptian mummies dated 2400 BC**
- **Hippocrates (460 BC – *ca.* 370 BC)**
  - **phtysis the most widespread disease of man**
  - **mostly fatal**

# ***Mycobacterium tuberculosis***



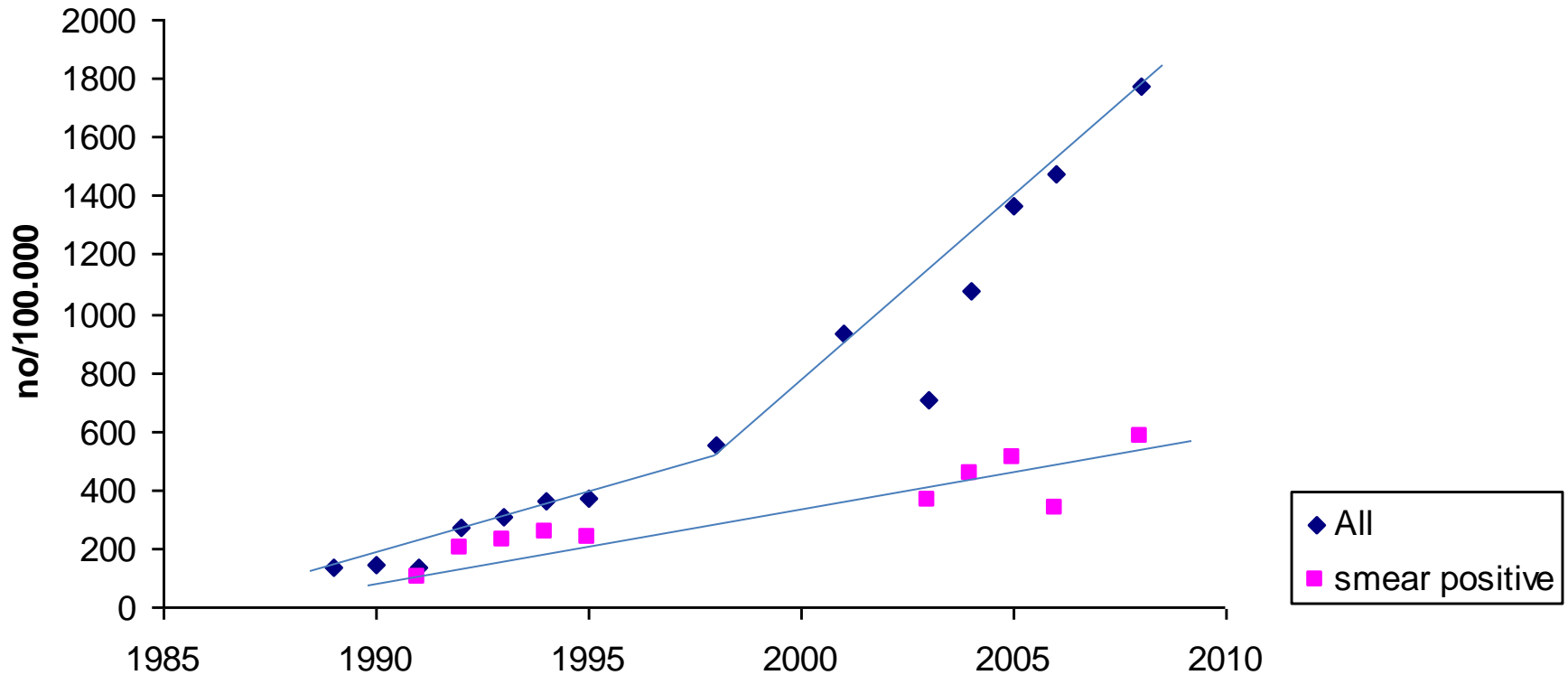
**Robert Koch**  
**1843 - 1910**

- **March 24, 1882**
  - **a new staining method**
  - **demonstrated it for the audience**
  - **stunned, silent audience**
- **Nobel Prize**
  - **physiology/medicine in 1905**

# **How is phtysiology currently (up till 2009) practiced in SA?**

- **Passive case finding**
- **Diagnosis by smear microscopy**
  - **smear negative patients do not pose a public health problem**
- **Culture with limited DST in problem cases only**
- **All patients starting on same drug regimen**
- **Counseling mainly re. adherence; little on prevention of transmission**
- **Drug resistant TB referred to centralised treatment initiation points**
- **Limited hospital infection prevention**

## Incidence of tuberculosis and of smear positive PTB in the Hlabisa sub-district of KZN



**The incidence of smear negative PTB increased 35 fold.**  
**The incidence of smear positive PTB increased 6 fold.**

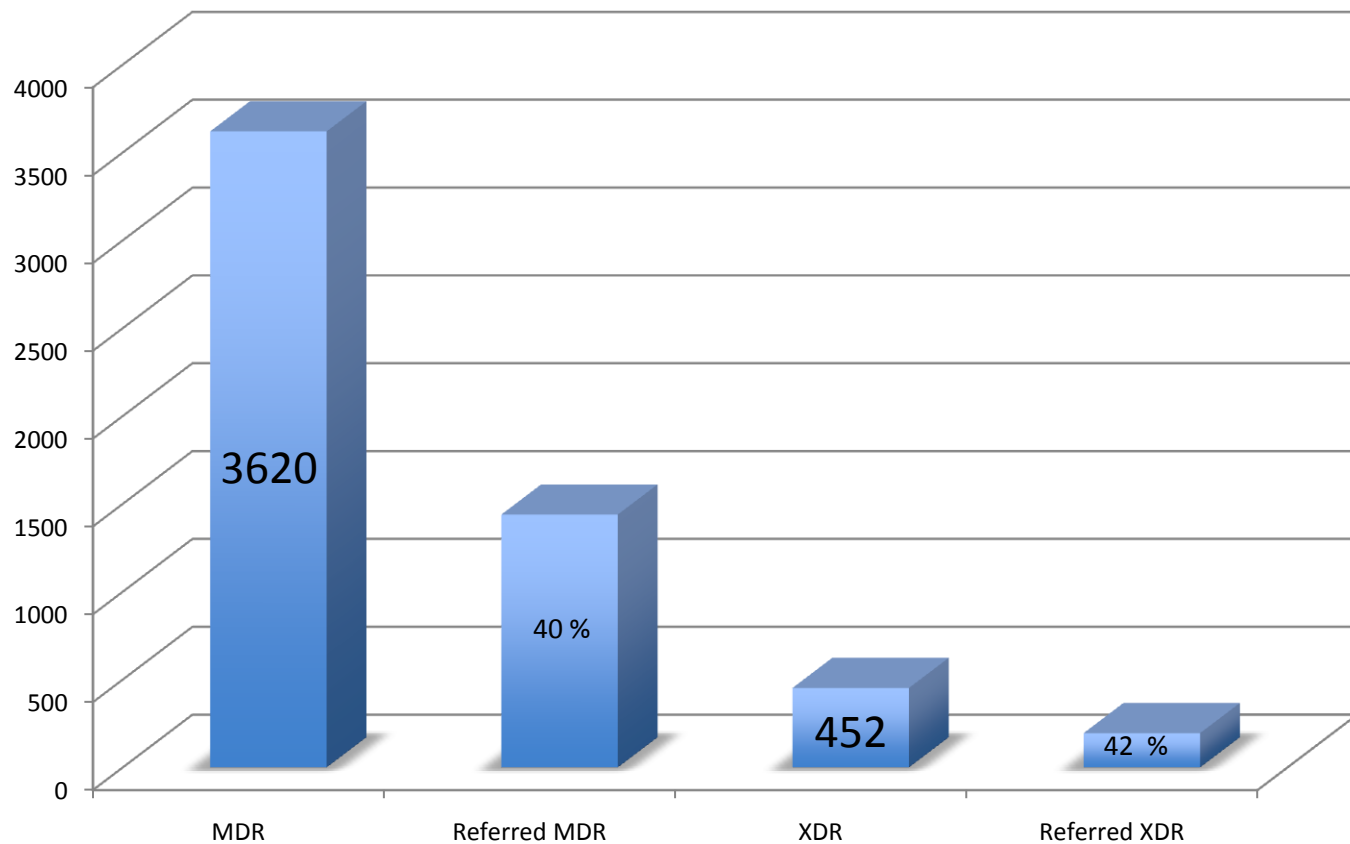
# MDR and XDR cases among patients with culture confirmed TB in KZN

District	Number of Culture Confirmed TB cases	Proportion of MDR (%) cases	Proportion of XDR (%) cases
Amajuba	146	29.5	1.4
eThekwini	11188	14.2	0.8
iLembe	891	18.4	1
Sisonke	474	19.8	1.9
uGu	783	32.7	1.3
uMgungundlovu	2993	15.3	1.9
uMkhanyakude	979	45.6	0.3
Umzinyati	1488	36.2	16
uThukela	398	17.1	2
uThungulu	1042	28.4	1.3
Zululand	476	44.7	0.8
<b>Total</b>	<b>20858</b>	<b>20</b>	<b>2.1</b>

# **Flaws in the TB control program**

- **A TB control program based on smears is obsolete**
  - **Low smear positivity rate**
    - **HIV infection**
  - **Smears do not provide drug susceptibility profiles**

# Patients with MDR-TB referred to the provincial MDR referral hospital



# **Flaws in the TB control program**

- **A TB control program based on smears is obsolete**
  - **low smear positivity rate**
    - **HIV infection**
  - **smears do not provide drug susceptibility profiles**
- **An MDR TB program that loses 60 % of patients in the referral process is dysfunctional**
  - **waiting time for admission at KGV: 2-3 months**

# What do we need ?

- **Patient management**
  - **Improved, active case finding**
  - **Initiation of appropriate treatment without delay for all**
    - **Laboratory diagnosis with full drug susceptibility profile on all patients**
- **Prevention of spread**
  - **Adherence to infection prevention strategies**
  - **Effective vaccine**
  - **Chemoprophylaxis**

# KwaZulu-Natal Health Districts



Compiled and Produced by

The GIS Unit



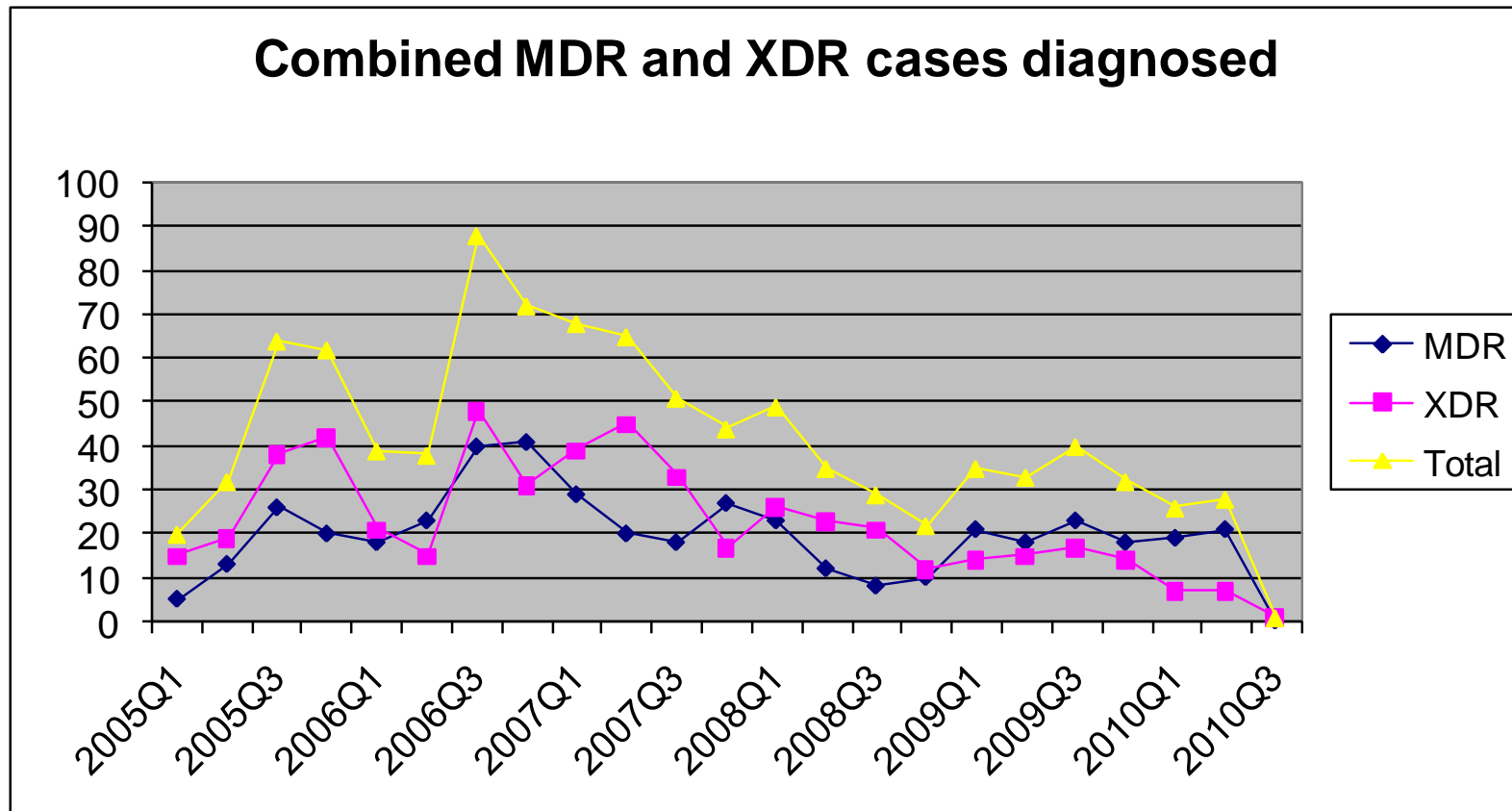
# Distribution of XDR-TB in KZN in 2006/07

District	Number of Culture Confirmed TB cases	Number of XDR cases	Proportion of XDR (%) cases
Msinga sub-district	1096	215	19.6
Umzinyati – without Msinga sub-district	392	23	5.9
Group 1- Sisonke, uMgungundlovu, uThukela	3865	74	1.9*
Group 2- uMkhanyakude, eThekwini, Zululand, iLembe, uGu, uThungulu, Amajuba	15505	131	0.8**

# **Interventions in the Msinga subdistrict**

- **Contact tracing**
- **Case finding in congregations**
  - **Including in the hospital and clinics**
- **Culture and DST on all suspected cases**
- **Treatment of MDR patients in the district**
- **Improvement of infection prevention**
  - **in hospital**
  - **attempt to infection prevention in households**
  - **patient and community education**

# Effect of combined interventions



# **If Tugela Ferry is the source .....**

- **Elimination of the source should lead to normalisation of the situation**

# Spread of XDR-TB in KZN



# MDR and XDR cases among patients with culture confirmed TB


District	Number of Culture Confirmed TB cases	Proportion of MDR (%) cases	Proportion of XDR (%) cases
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Zululand	476	44.7	0.8
Total	20858	20	2.1

# If Tugela Ferry is the source .....

- **Elimination of the source should lead to normalisation of the situation**
- **Too late**
- **Same interventions throughout ?**

└───> **Is that possible ?**

# Interventions

- **Contact tracing**
- **Case finding in congregations**
  - Including in hospitals and clinics
- **Culture and DST on all suspected cases**  
 **decentralization**
- **Decentralization of treatment of MDR patients**

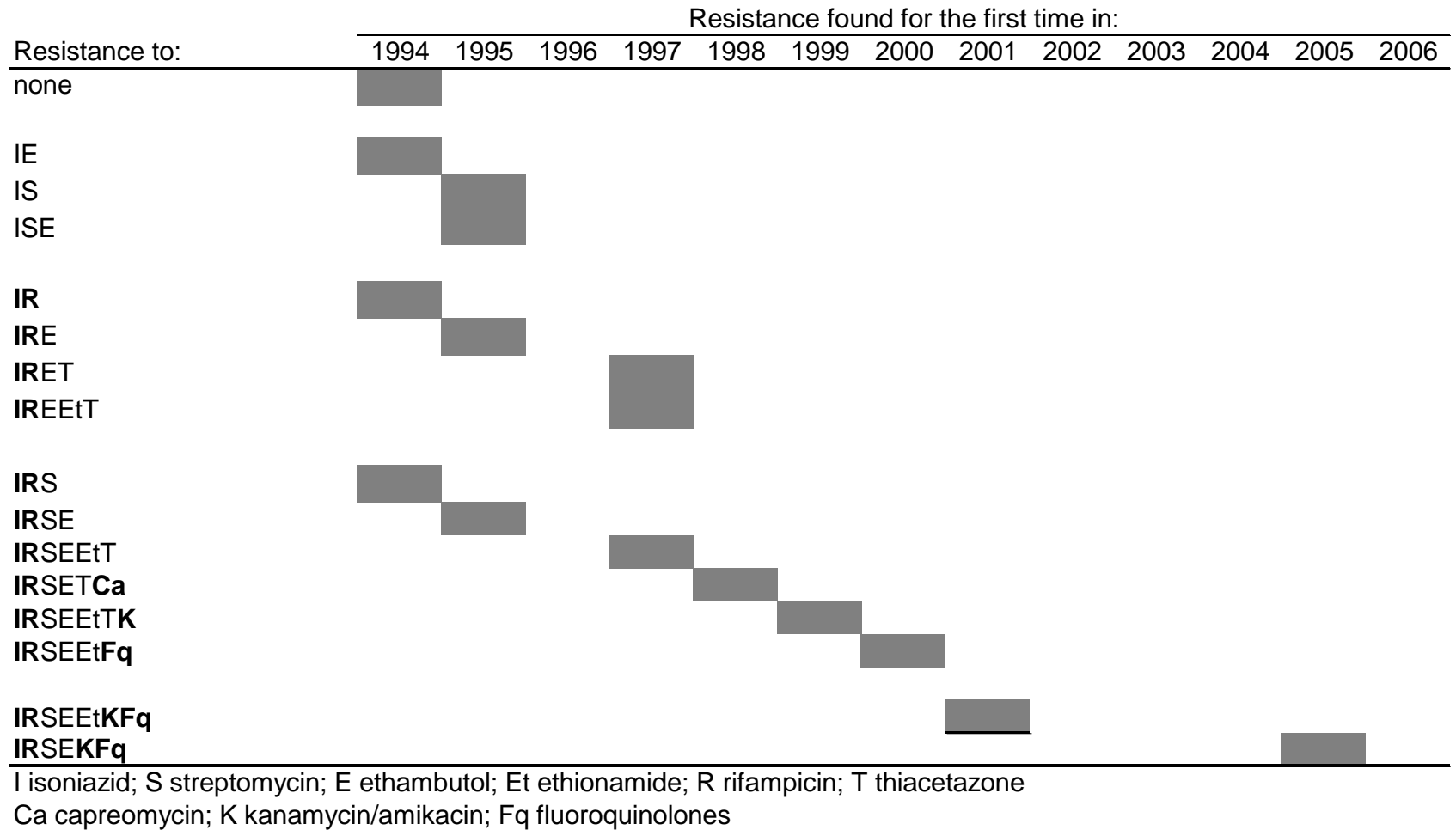
**MDR includes XDR**

**How far away are we from TDR ?**

# Treatment options for XDR

- **Capreomycin**
- **Linezolid**
- **PAS**
  
- **$\beta$ -lactam –  $\beta$ -lactamase inhibitor combinations**

**Fig 1. Resistance development in the KZN family of strains of *Mycobacterium tuberculosis* from 1994 till 2006**



(Pillay and Sturm, CID, 2007)

# Susceptibility pattern of isolates from Tugela Ferry (n=53)

	<b>Lancet (2006)</b>
<b>isoniazid</b>	<b>R</b>
<b>rifampicine</b>	<b>R</b>
<b>ethambutol</b>	<b>R</b>
<b>pyrazinamide</b>	
<b>streptomycin</b>	<b>R</b>
<b>ethionamide</b>	
<b>ofloxacin</b>	<b>R</b>
<b>moxifloxacin</b>	
<b>capreomycin</b>	
<b>kanamycin</b>	<b>R</b>
<b>amikacin</b>	
<b>PAS</b>	
<b>linezolid</b>	

(Gandhi et al, Lancet 2006)

# MICs of 54 isolates for the 3 injectables

No of clinical isolates with MIC Profile	Polymorphism in the <i>rrs</i> gene	MIC Profiles ( $\mu\text{g/ml}$ )		
		KAN	AMI	CAP
22	A1401G	>128	>128	>16
7	A1401G	>128	>128	16
1	None	4	2	8
5	None	4	2	4
10	None	2	2	4
9	None	2	1	4

**(Dookie et al, FIDDSA 2011, poster no. 17)**

# Association of mutations in *ssr* and resistance classification

<i>rrs</i> gene	Polymorphism	No. of Isolates			
		XDR	Pre-XDR	MDR	Susceptible
Region One	No	21	8	15	10
	polymorphism				
Region Two	A1401G	21	8	0	0
	No	0	0	15	10
	polymorphism				

(Dookie et al, FIDDSA 2011, poster no. 17)

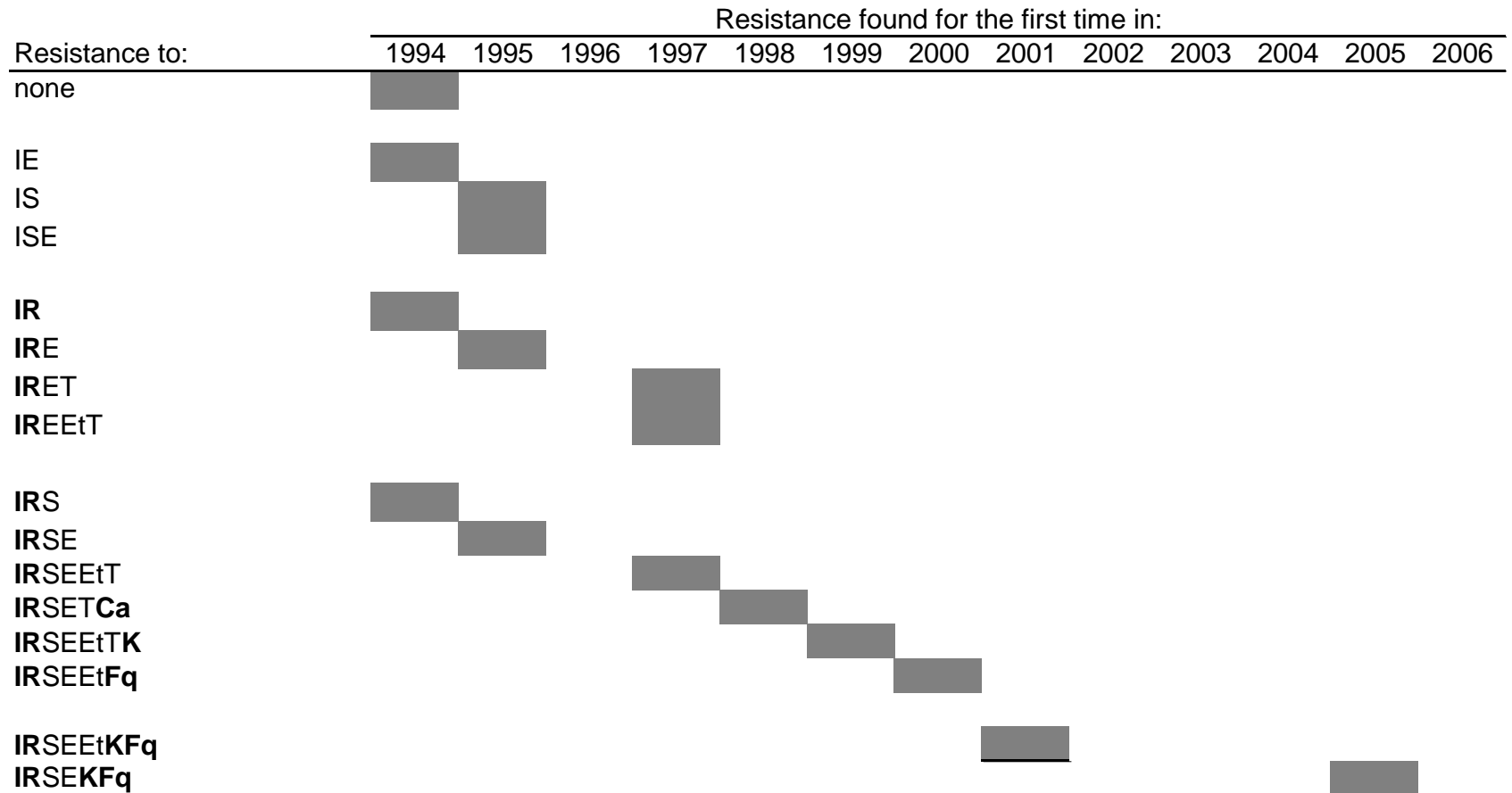
# Treatment options for XDR

- **Capreomycin**
- **Linezolid**
- **PAS**
  
- **$\beta$ -lactam –  $\beta$ -lactamase inhibitor combinations**

# **Is centralization the answer ?**

- **Do the doctors in XDR treatment hospitals so much different than what well trained doctors in elsewhere could do ?**
- **Should we treat while we do not have at least 3 (preferably more) drugs with proven efficacy ?**

**Fig 1. Resistance development in the KZN family of strains of *Mycobacterium tuberculosis* from 1994 till 2006**



I isoniazid; S streptomycin; E ethambutol; Et ethionamide; R rifampicin; T thiacetazone  
 Ca capreomycin; K kanamycin/amikacin; Fq fluoroquinolones

(Pillay and Sturm, CID, 2007)

# Era of the Sanatoria



**(1848 – 1915)**

- 1. Fresh air**
- 2. Nutrition**
- 3. Rest**



# What do we need ?

- **Patient management**
  - Improved, active case finding
  - Initiation of appropriate treatment without delay for all
    - Laboratory diagnosis with full drug susceptibility profile on all patients
- **Prevention of spread**
  - Adherence to infection prevention strategies
  - Effective vaccine
  - **Chemoprophylaxis**

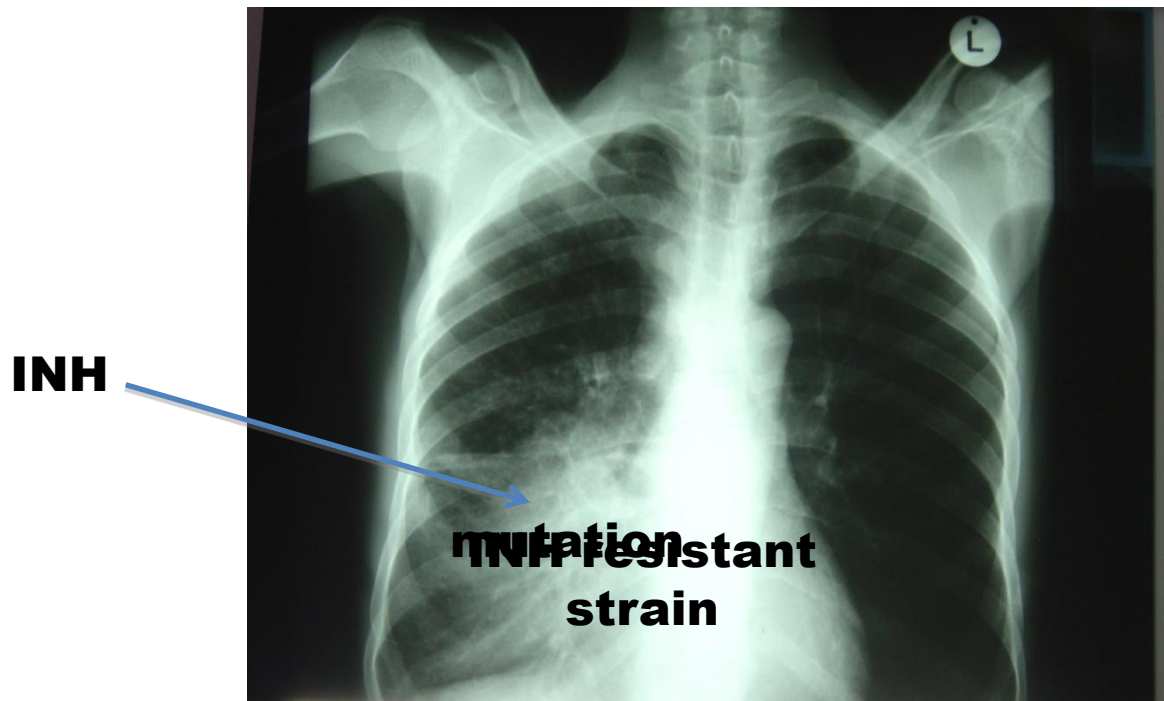
# INH resistance in culture confirmed cases in KZN

1 Jan 2006 – 30 June 2007

n=25537

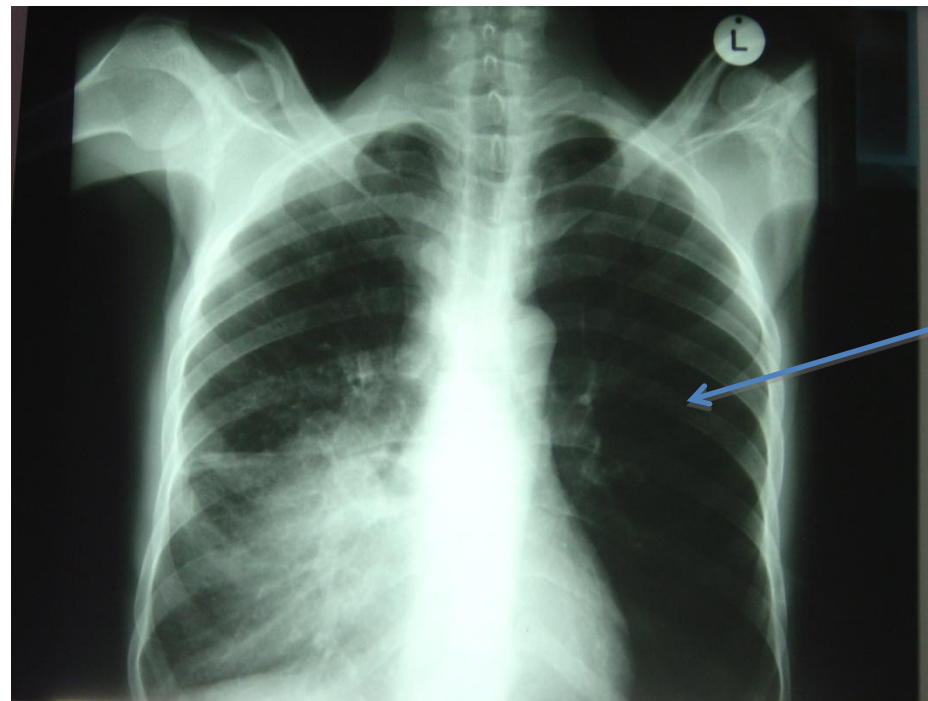
	No. of patients	%
All	6543	25.6
Single INH resistant	807	3.2
MDR	5377	21
pre-XDR	9	
XDR	610	2.4
others	1785	7

# “Development” of resistance



**actively multiplying organisms**

# “Development” of resistance



**If INH susceptible: no TB**

**If INH resistant: INH-R-TB**

**→ MDR/XDR ?**



# Effect of INH prophylaxis per 10000 patients

Months of therapy	1	2	3	4	5	6
Number "cured" (estimate, range)	0	0	36 (0-2969)	2284 (258-2975)	2972 (2459-3105)	2976 (2969-7417)
Disease prevented (estimate, range)	0	0 (0-114)	16 (0-1306)	1005 (114-1309)	1307 (1082-1366)	1309 (1306-3263)
New isoniazid resistance (estimate; range)	2065	2065 (1993-2065)	2900 (1752-2915)	2019 (1749-2814)	2006 (2005-2336)	2004 (10-2007)

**(Moodley et al; unpublished)**

# Conclusion

- **Our approach to TB control has to change**
- **Whether we can do so is dependent on resources**
- **We should try to prevent doing things that make the situation worse**
  - **treating XDR with incomplete regimens**
  - **? INH prophylaxis**