Research priorities in DR-TB

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TB Research Methods course

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Overview

- Definitions:
- Importance of DR-TB globally.
  - How we got here - Case studies in 5 countries
- Research needs - how DR develops – from bacilli to populations
- Research needs in DR-TB Diagnosis – briefly
- Research needs in DR-TB Treatment –
  - What has been done?
  - What needs to be done

Definitions

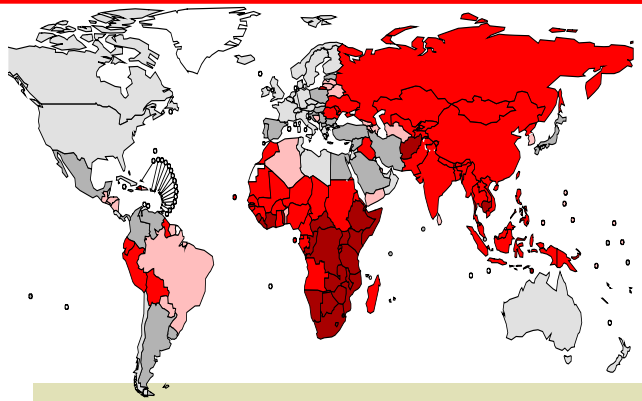
- Primary DR: Resistance in person treated <1 month or not at all
- Acquired DR: Resistance in person treated ≥ 1 month
- Mono-drug resistance: Resistance to 1 drug
- Poly-drug resistance: Resistance to >1 drug, but not MDR.
- MDR: resistant to isoniazid and rifampin
- XDR: MDR & resistance to Quinolones & Injectable

Epidemiology of DR-TB - summary

- Global total in new cases: 17%
  - 3% MDR and 0.5% XDR
  - 14% other forms (INH most common)
- Highest in Former Soviet Union
  - And certain Latin American countries
  - Increasing in China, India, S Africa
- Low in Canada, US and Western Europe – mostly seen in immigrants from these high risk regions

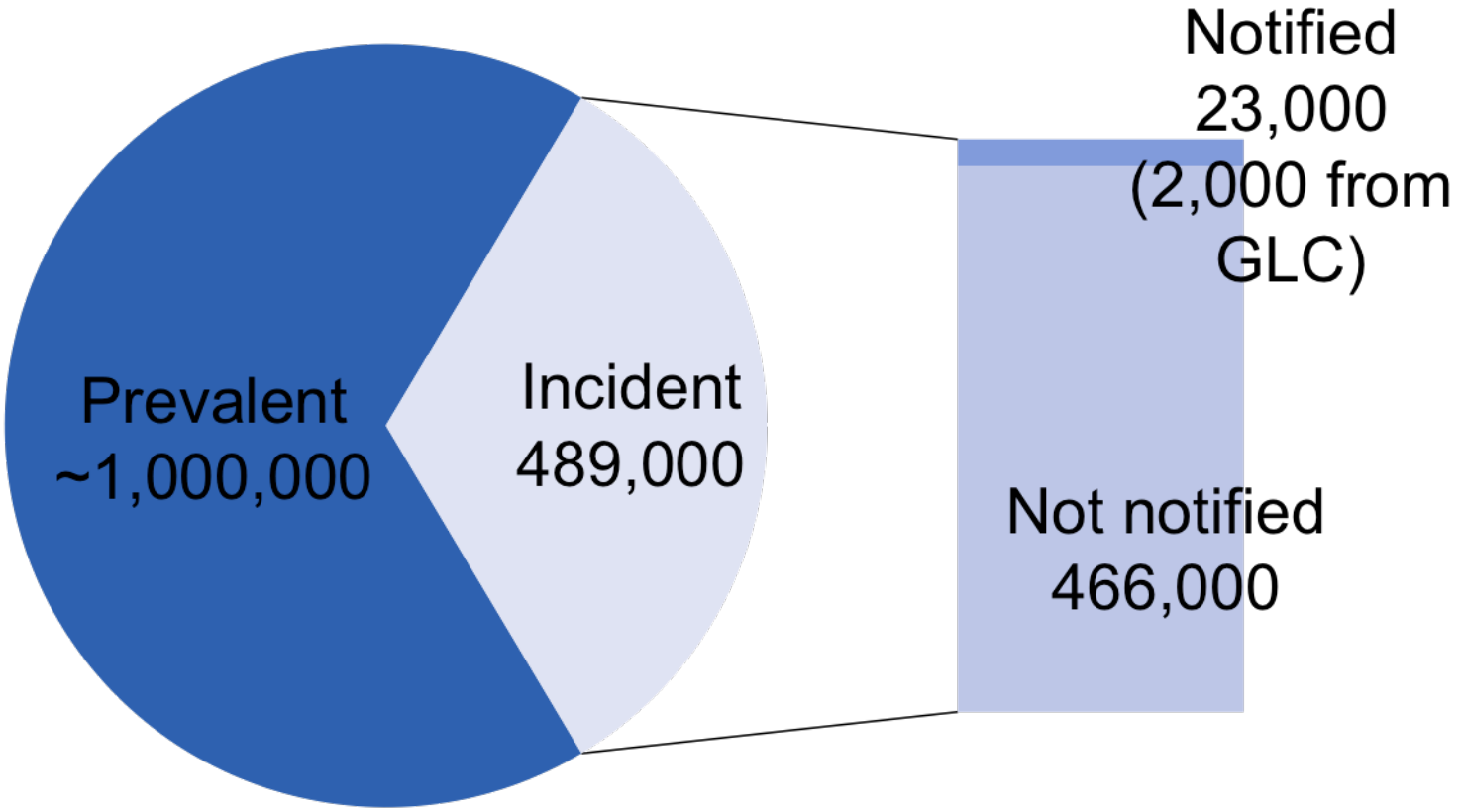
Global TB Estimates

WHO THE STOP TB DEPARTMENT



	Estimated number of cases	Estimated number of deaths
All forms of TB Greatest number of cases in Asia; greatest rates per capita in Africa	9.23 million	1.7 million
Multidrug-resistant TB (MDR-TB)	489,000 (5.3%)	120,000
Extensively drug-resistant TB (XDR-TB)	40,000 (0.5%)	20,000

Estimated global MDR-TB cases



Source: WHO. 4th Report Anti TB Drug Surveillance, 2008

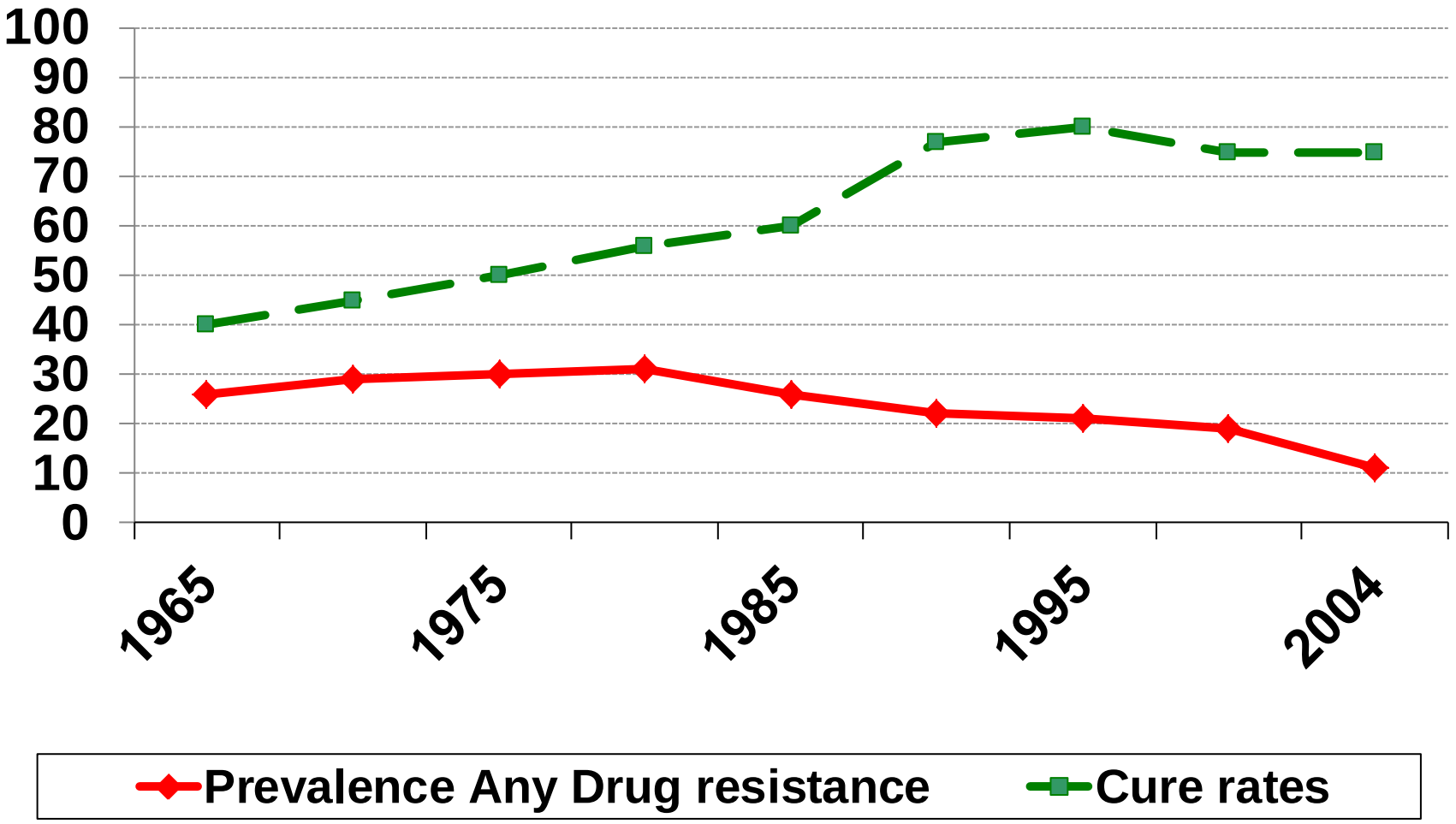
Research priority # 1
How did we get to this?

- Observational data from 5 countries

Emergence of DR – Korea

- Very poor economic situation up to 1960
  - Rapid improvement in economy since
- Weak NTP with high rates of default
- Drugs prescribed and sold in private sector
- NTP strengthened in 1984-85

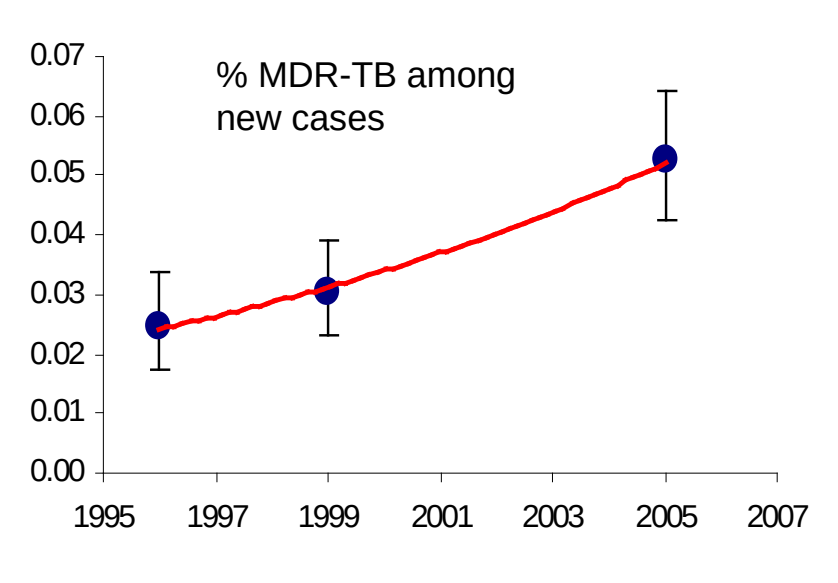
Association of cure rates with trends in drug resistance – Korea 1980-1995

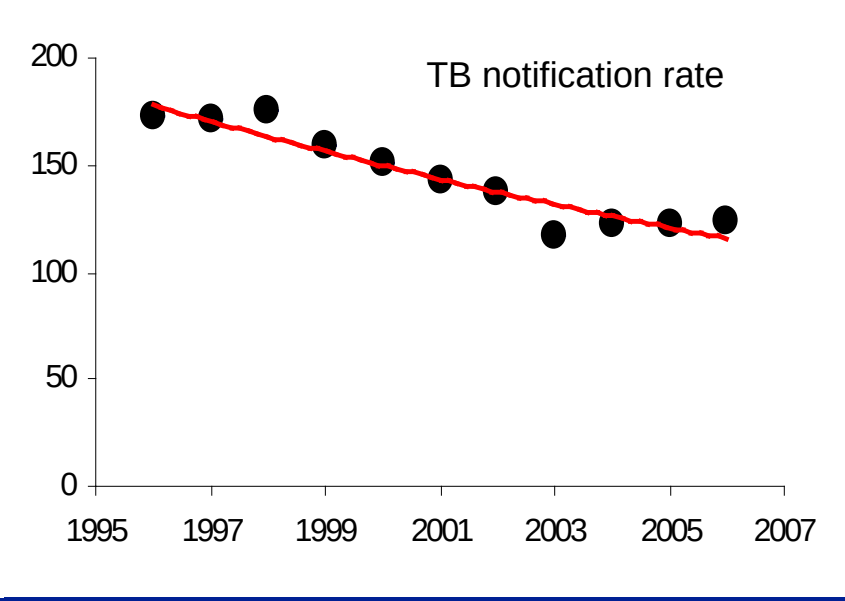


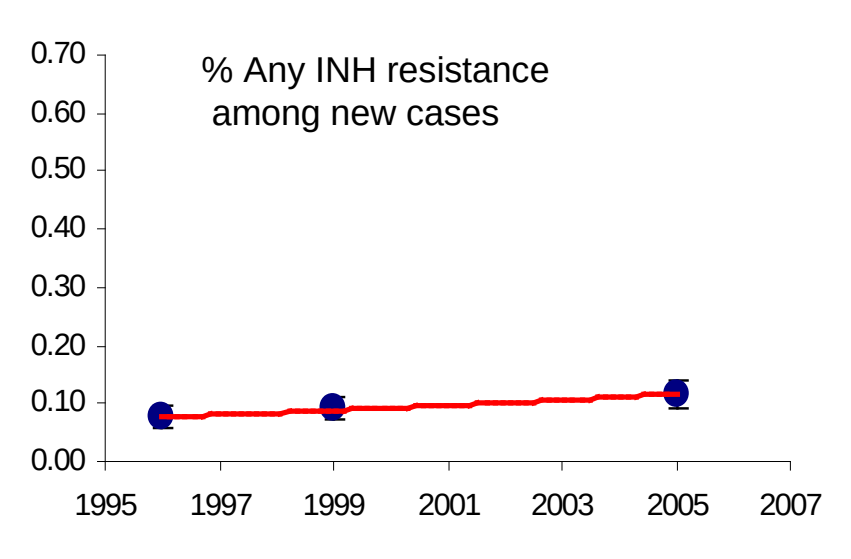
Emergence of DR – Peru

- Massive internal migration to Lima in 1970's
  - Severe deprivation, shantytowns in Lima
- Pre 1990 - Treatment success low in NTP
- TB drugs widely available and uncontrolled
  - Large private sector
- DOTS strengthened beginning 1990
  - Coincident with economic improvements
- No HIV

TB notification rate per 100,000 and % MDR-TB in new cases, Peru, 1996 – 2005



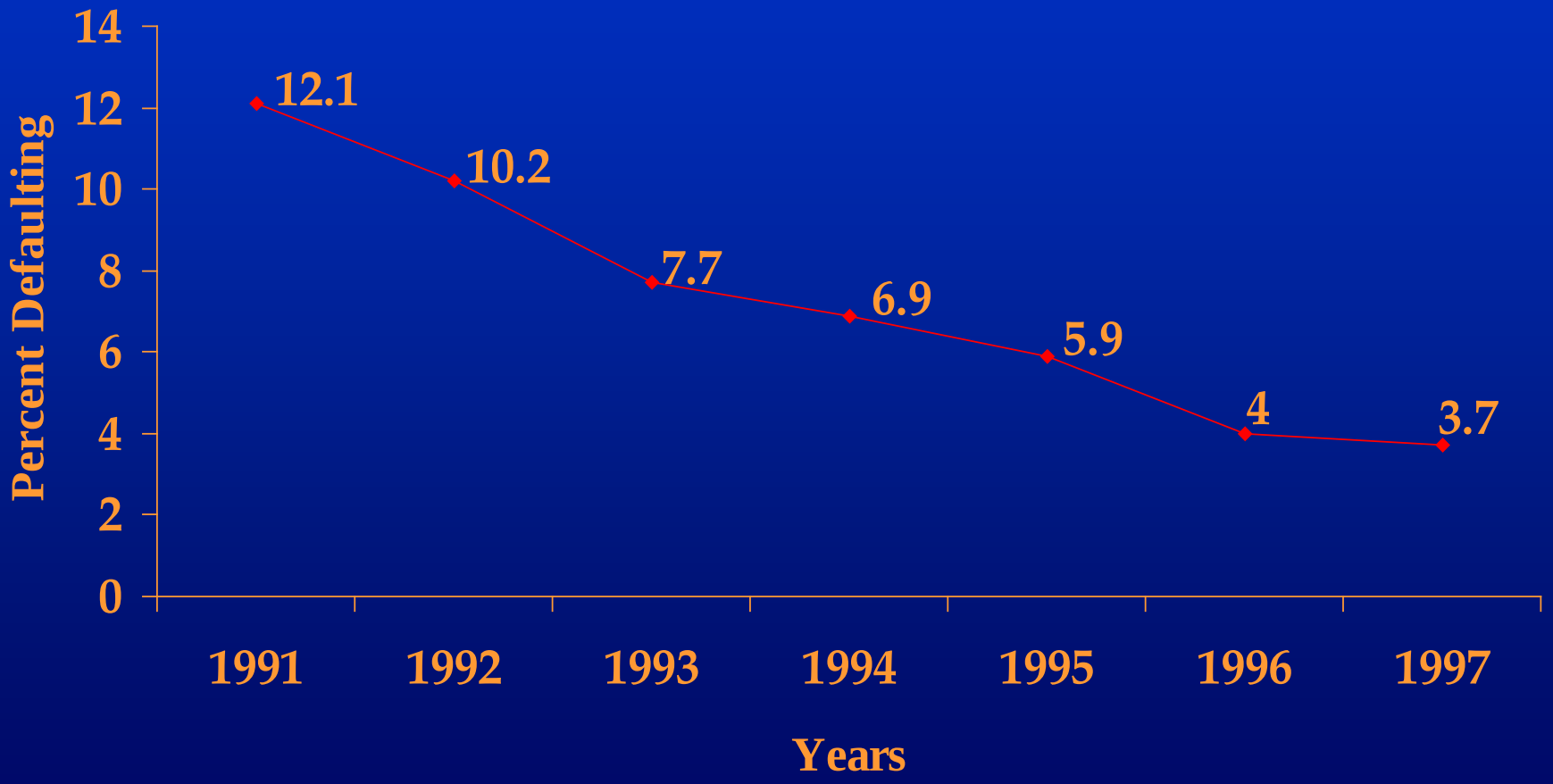




Peru 1996-2005

PERU - Trend in default rate following country wide implementation of DOTs in 1990-91

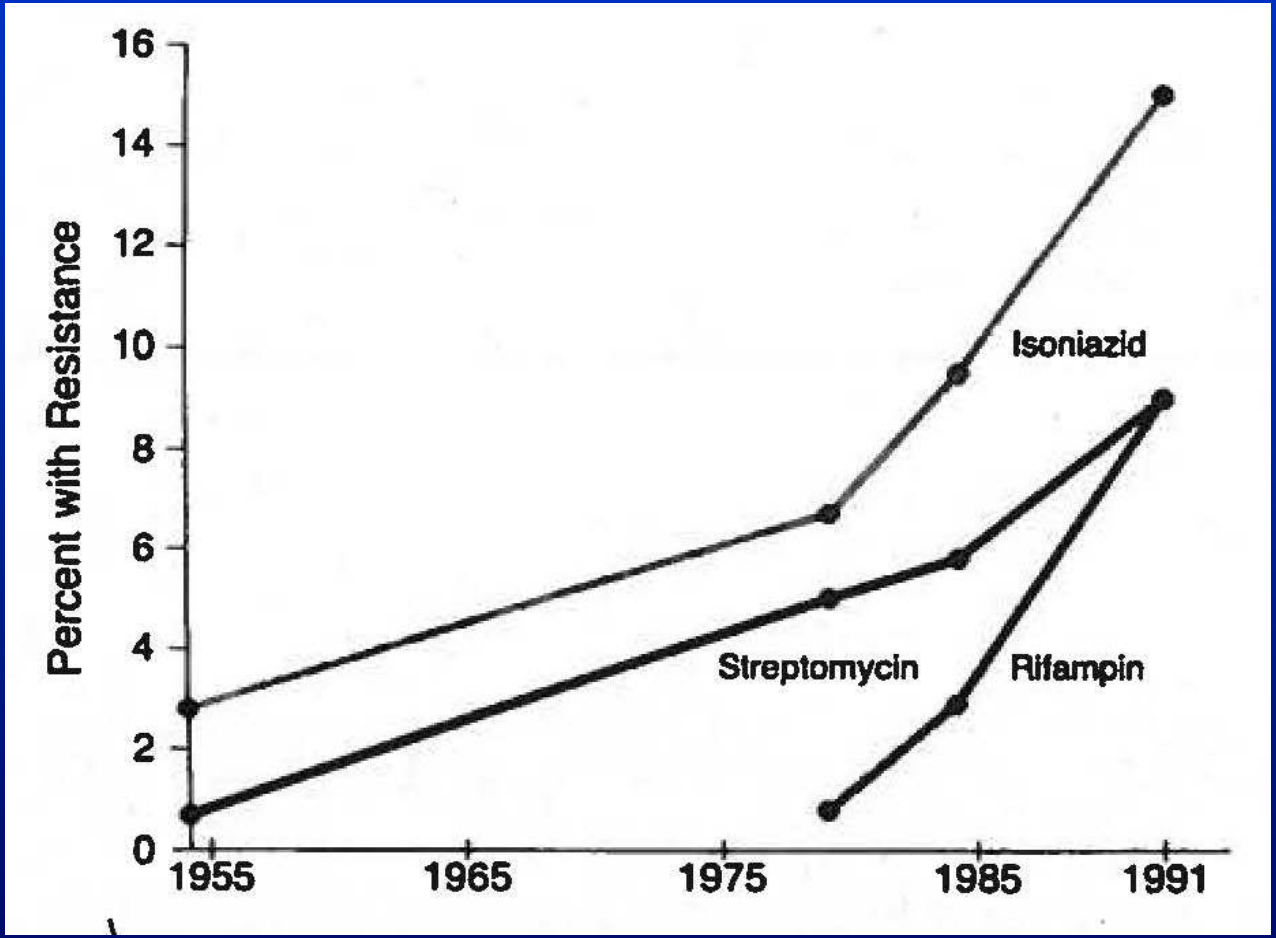
All patients treated with 2RHZE/4 R_2H_2



From: *JID 2001; 184*

Emergence of DR – New York City

Rapid increase in drug resistance – New York City: 1980 – 1991 *(Frieden et al, NEJM; 1993:328:521-6)*



New York City: Funding, Resources and TB

Year	Resources	Incidence of TB / 100,000	
		Harlem	All NYC
1968	$40 million total 1000 TB Beds 22 Chest Clinics	130	34
1978	$23-$25 million total $1.6 million – TB control No TB beds 9 Chest clinics	51	20
1988	$4 million TB control Total unknown (but less than 1978)	160	33

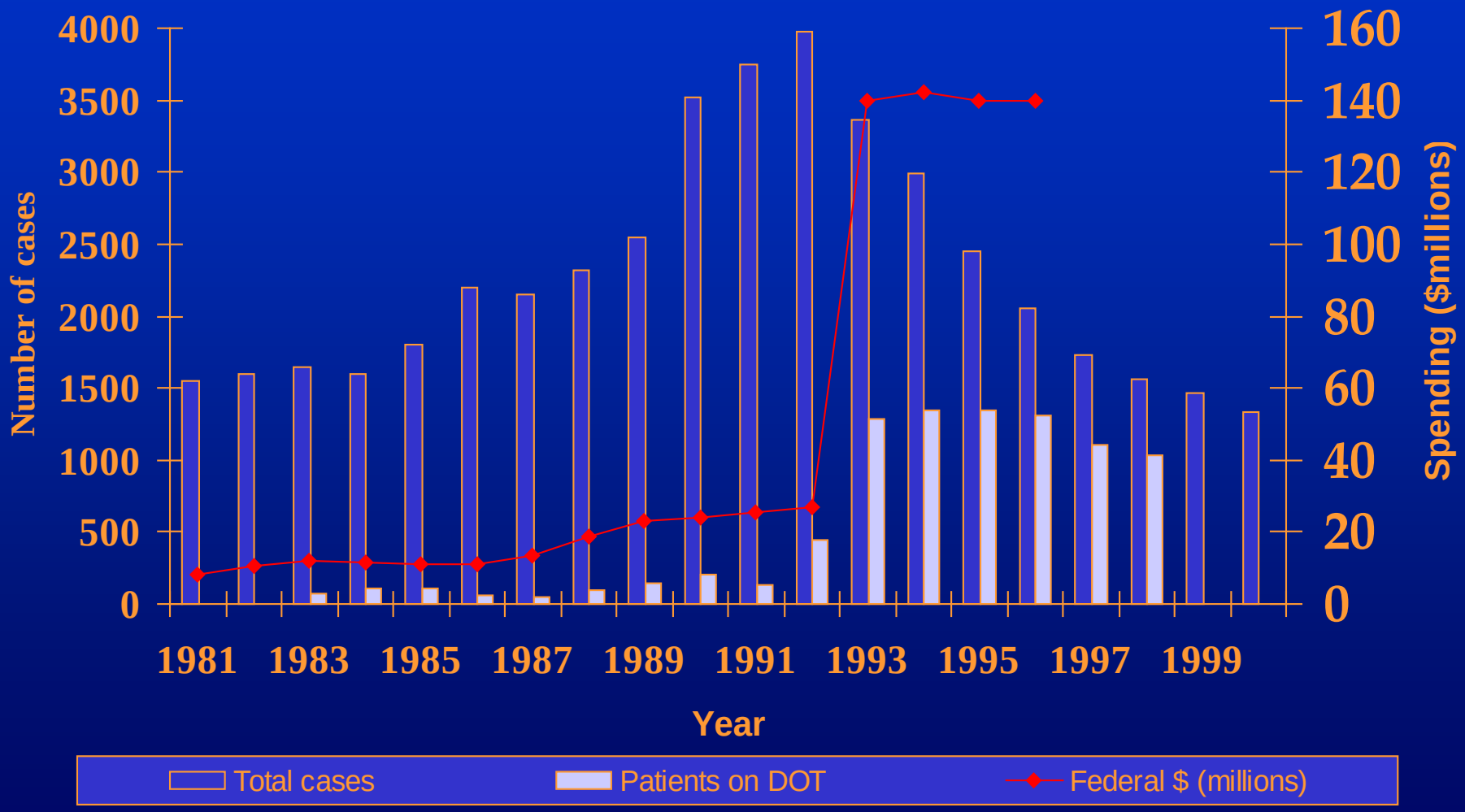
Resurgent TB in New York City: HIV, homelessness, and the decline of TB control programs

(Brudney and Dobkin. ARRD, 1991;144:745-49)

- 224 patients admitted to Harlem hospital with TB
  - 53% alcoholic
  - 68% homeless or unstable housing
- 46 died. 178 improved and discharged
  - 19 of 178 (11%): cured, or still on treatment,
  - 11 died other causes
  - **148** (83%): < 3 months treatment completed
- 48 of 148 readmitted within 12 months with active TB
  - 40 improved and discharged
  - **35** (88%) lost again
- 8 of 35 admitted a third time with active TB

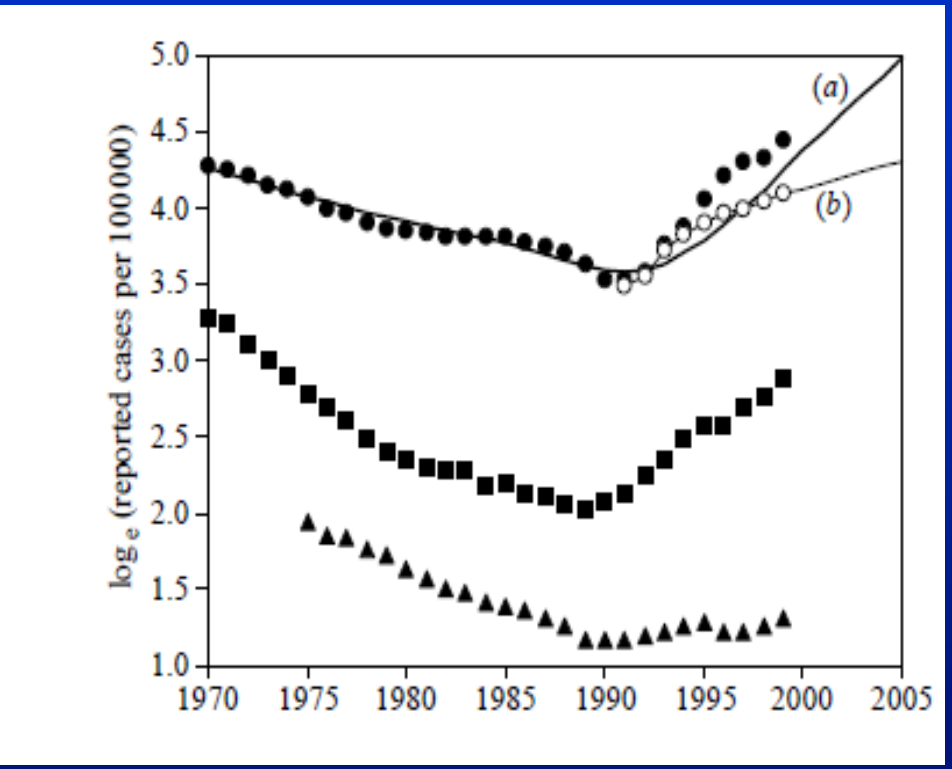
New York City – What really turned the tide

(From: Frieden et al., NEJM, 1995: 333; 229-233)

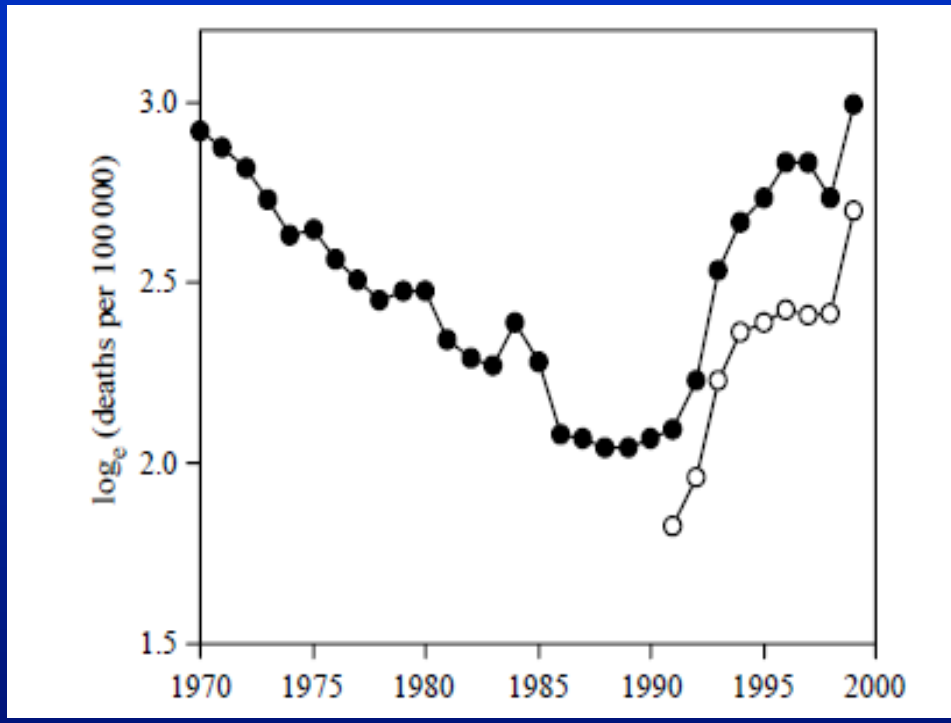


Emergence of DR – Russia

Trends in TB cases - Russia



Trends in case notification 1970-1990 and projections to 2005



Trends in the reported TB death rate

Trends in Global Drug Resistance in New Cases

(AZIZ, Lancet 2006)

Middle Income	1994 - 96	2001 – 02
Latvia		
Any Resistance	34%	32%
MDR	14%	12%
Russia (Tomsk)		
Any Resistance	29%	37%
MDR	**7%**	**14%**

Emergence of DR – South Africa

Tripling of MDR cases in S Africa – in 6 years

(Streicher et al, Infection, Genetics and Evolution, 2011)

Province	2004	2005	2006	2007	2008	2009	Total
Eastern Cape	379	545	836	1092	1501	1858	6211
Free state	116	151	198	179	381	253	1278
Gauteng	537	676	732	986	1028	1307	5266
Kwazulu-Natal	583	1024	2200	2208	1573	1773	9361
Western Cape	1085	1192	1179	1771	2220	2078	9525
All S. Africa	**3219**	4120	5774	7429	8198	**9070**	37810

7-fold increase in XDR cases in S Africa – in 6 years

(Streicher et al, Infection, Genetics and Evolution, 2011)

Province	2004	2005	2006	2007	2008	2009	Total
Eastern Cape	3	18	61	108	175	123	488
Free state	1	6	3	4	3	3	20
Gauteng	5	14	19	38	30	65	171
Kwazulu-Natal	59	227	336	241	181	254	1298
Western Cape	12	16	28	42	60	73	230
All S. Africa	**85**	298	464	458	488	**594**	2387

Emergence of DR – South Africa

- HIV epidemic fueling massive TB epidemic
- Health facilities - focal points of transmission *(Calver 2010, Gandhi 2006)*
  - ? Role of gold mines in transmission
- TB completion rates:
  - Nationally less than 50% *(NTP data)*
  - 18% in Kwazulu Natal recently *(Loveday 2008)*
- TB Drugs controlled by NTP.
  - But poor quality Rifampin documented *(McIlleron et al)*

Summary - What we know about how drug resistance develops

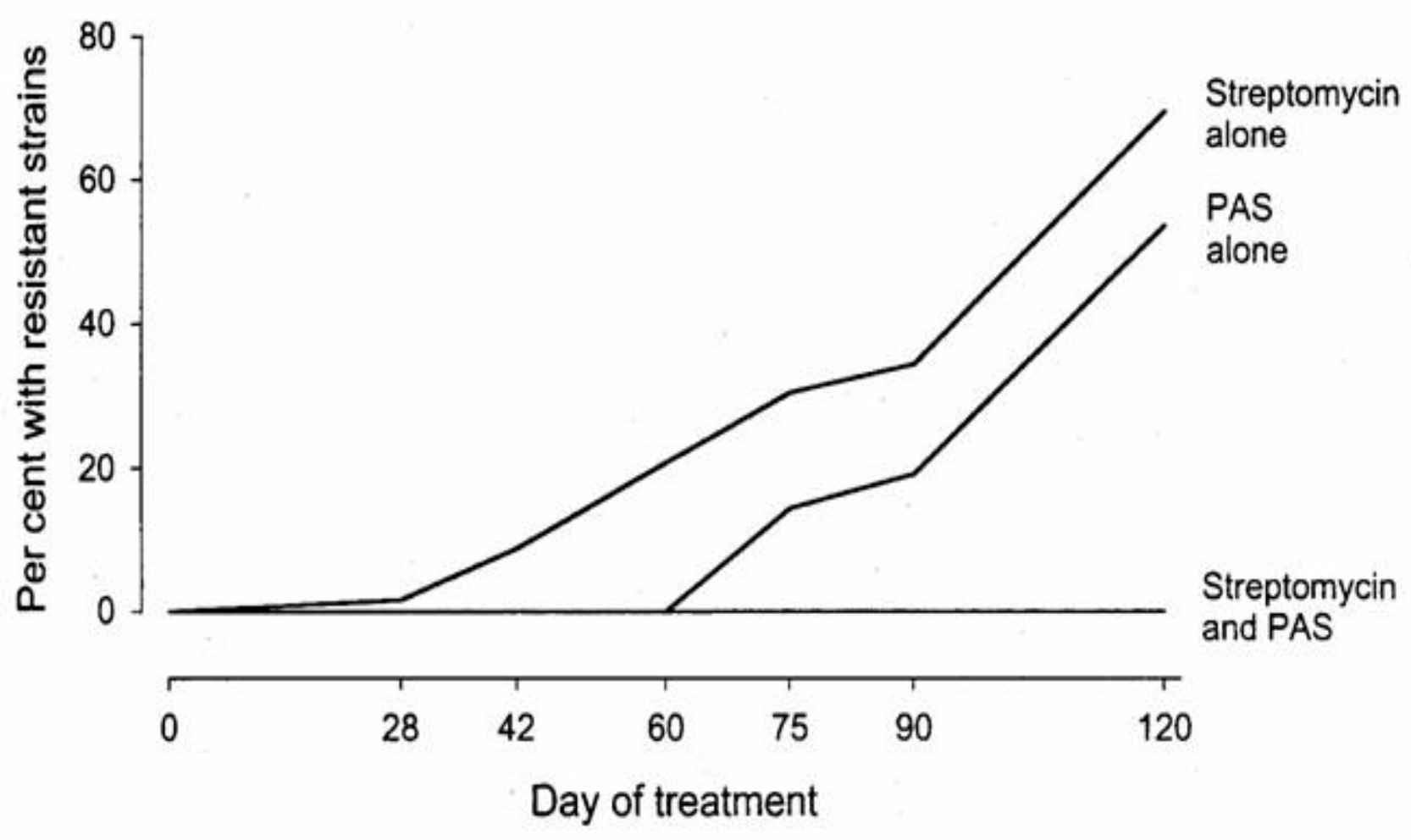
In bacilli

and individual patients

Rate of spontaneous mutations of M Tuberculosis to anti-TB drugs

Streptomycin	**10^{-6}**
Isoniazid	**10^{-6} - 10^{-7}**
Rifampin	**10^{-8} - 10^{-9}**
Ethambutol	**10^{-7} - 10^{-8}**
INH&Rif	**10^{-14}**

Treatment with Streptomycin alone, or PAS alone
% Patients with resistance - Days after Tx started



Source: Rieder, Interventions for TB control, IUATLD.

Summary - What we know about how drug resistance develops

In Populations

Research needed: What causes DR epidemics?

- Don't believe the Dogma – Examples:
  - "Default causes resistance"
  - "INH resistance does not matter"
  - "DR strains are less transmissible"
  - "DOT prevents drug resistance"
- Possible study methods:
  - Modeling
  - Surveillance – with detailed clinical data
  - Case-control and cross-sectional DR-TB vs DS-TB
  - Mol Epi – large scale with complete population coverage

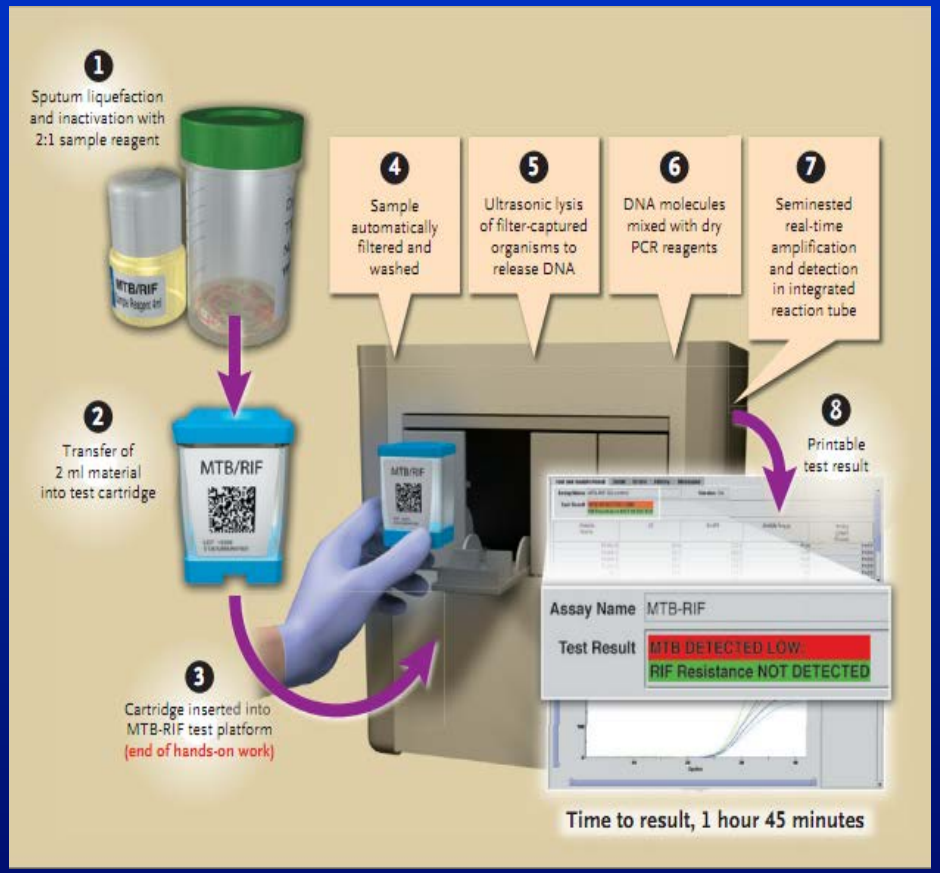
Diagnosis of drug resistance

(Research needs - very briefly)

Cepheid GeneXpert MTB/RIF

Boehme et al. 2010 NEJM

- Automated RT-PCR
- Simple 1-step specimen preparation
- Minimal biohazard risks
- **Results in 2 HOURS!!**
- Demonstration studies (6673 patients, 6 sites):
- **Sensitivity for diagnosis**
  - **99% in smear +**
  - **80% in smear - / culture +**
- **Rifampicin resistance**
  - **95% sensitive**
  - **98% specific**



Current status of diagnostic research - DR-TB?

- GX, Line probe assays, MODS – all have well established and high diagnostic accuracy
- Randomized trials of GX and LPA have also been conducted
  - Individual and cluster randomized
  - Surprisingly little impact
- Needed - Large scale trials/other designs – population impact of new diagnostics on DR-TB epidemiology.

Treatment of DR-TB

MDR-TB

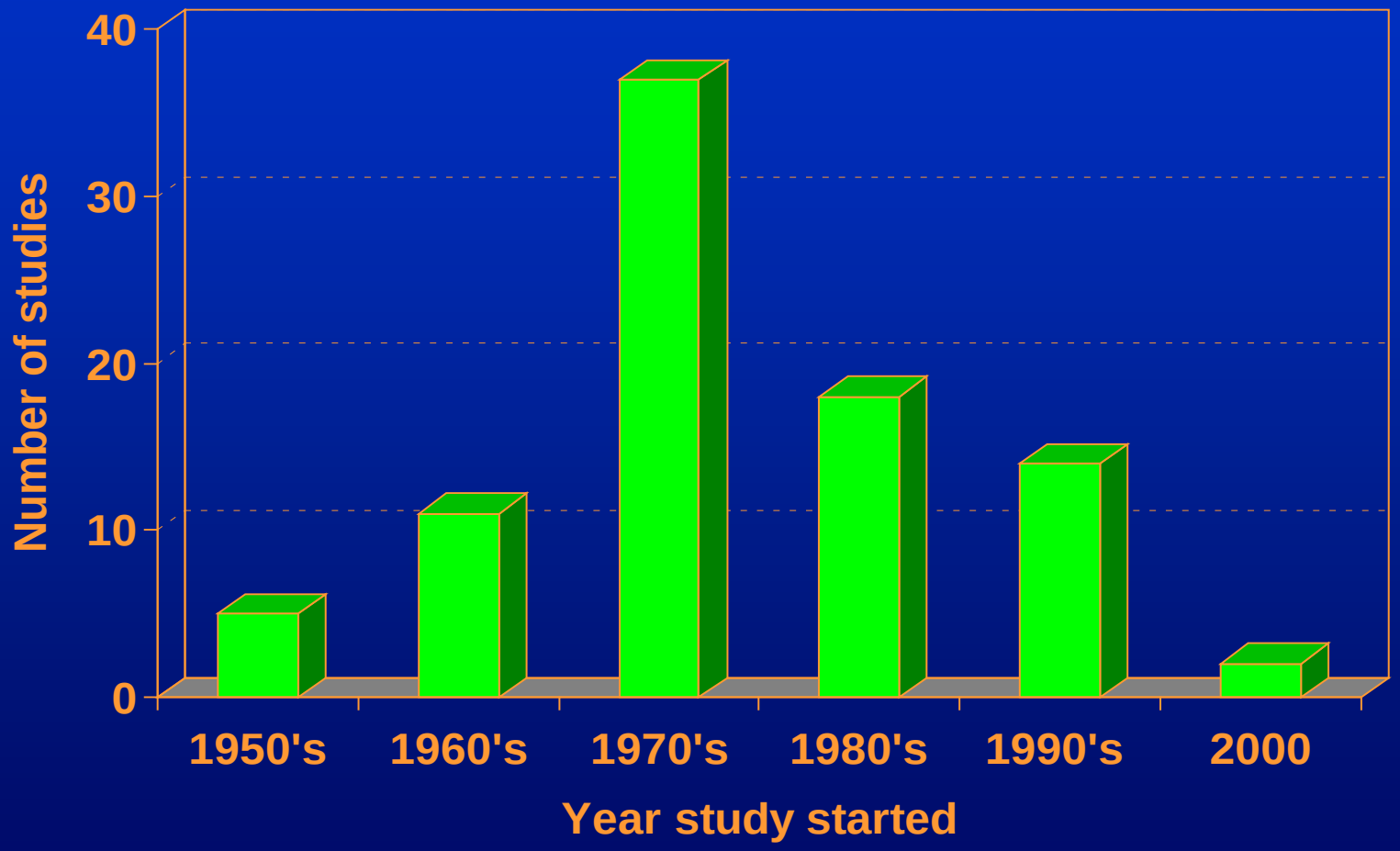
XDR-TB

INH Mono-resistance and other forms

How good is the published evidence for treatment of DR-TB?

Evidence base – Phase 3 RCT in TB

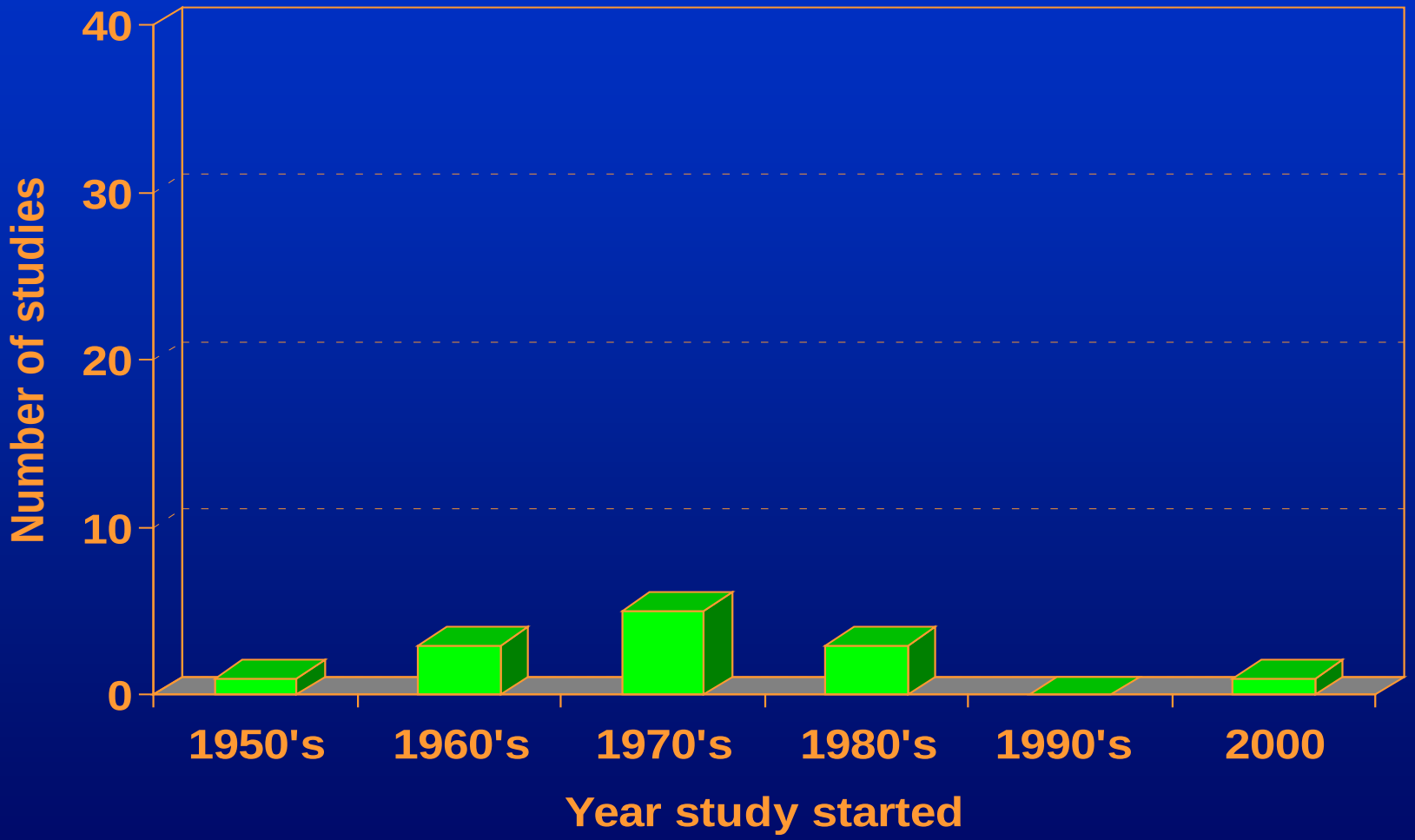
Number of Randomized trials of treatment in New cases by decade when they started enrolment



Note: all but two of the RCT were publicly funded

Evidence base: Phase 3 RCT in Drug resistance / Re-treatment

Number by decade when they started enrolment



To date no published RCT in MDR-TB

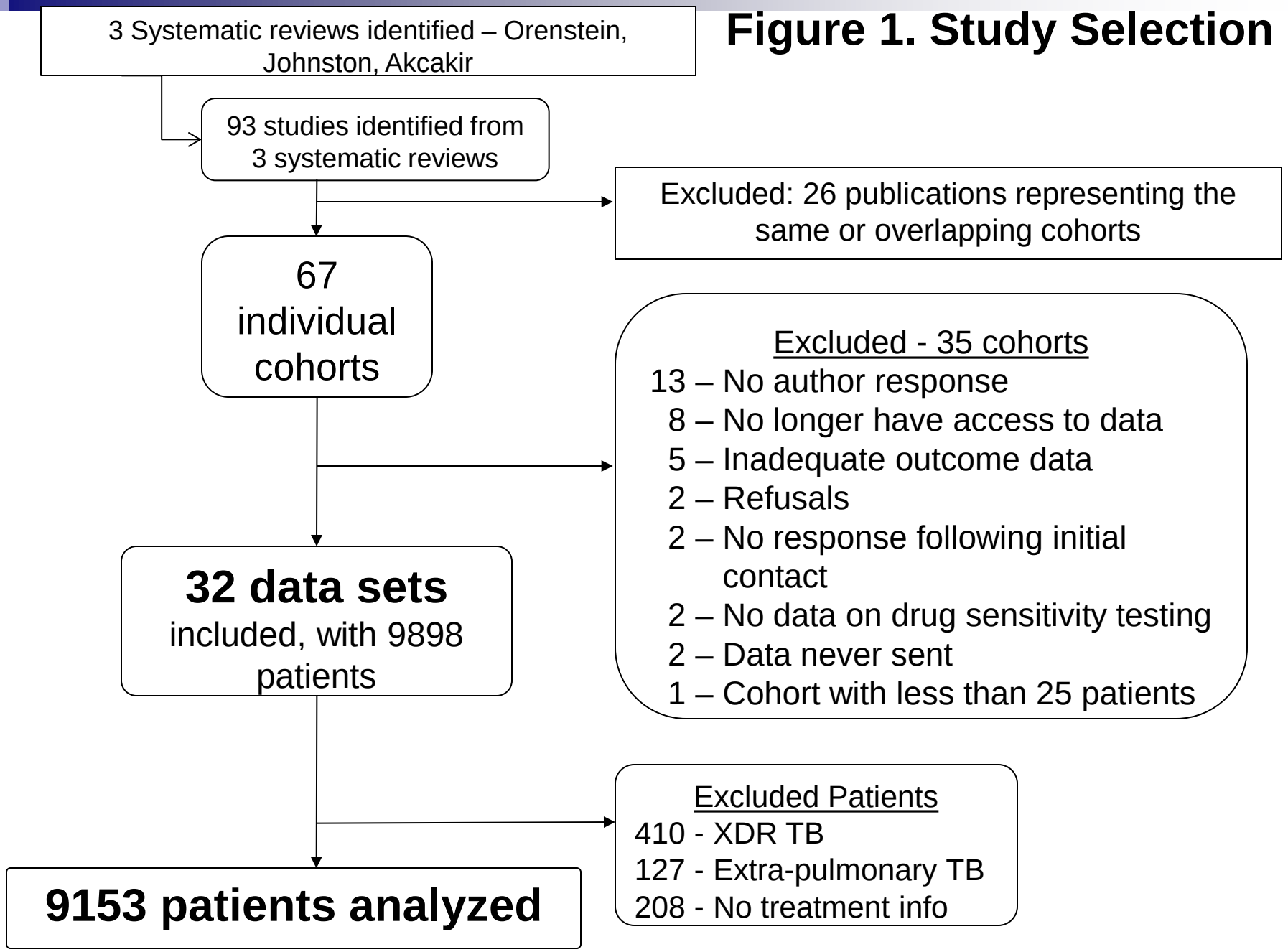
Published randomized trials: DR-TB treatment

- Trials of retreatment
  - N = 4, all published before 1980
- Trials of INH resistant patients
  - N = 5, also older studies
- Trials of current standardized retreatment
  - NONE
- Phase 3 Trials of MDR treatment
  - NONE
  - Two Phase 2 trials – Bedaquiline and Delamanid

Recent research completed: treatment of DR-TB

- MDR-TB – Many observational studies
  - Several aggregate data meta-analyses (traditional)
  - One Individual patient data meta-analysis
  - Two Phase 2 trials
- XDR-TB – Several observational studies
  - Two aggregate data meta-analyses (traditional)
  - One Individual patient data meta-analysis
  - One Phase 2 trial

Figure 1. Study Selection



The Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB

(members in alphabetic order)

D. Ashkin, S.Ahuja, M. Avendano, M. Bauer, M. Becerra, A. Benedetti, M. Burgos, R. Centis, E. Chan, C.Y. Chiang, F. Cobelens, H. Cox, E. Declercq, D. Enarson, D. Falzon, K. Flanagan, J. Flood, J. Furin, L. Garcia-Garcia, N. Gandhi, P. Hopewell, T. Holtz, S. Keshavjee, WJ.Koh, V. Leimane, C.C. Leung, J. Li, A.K. Maug, D. Menzies, G.B. Migliori, C.Mitnick, S.S. Munsiff, M. Narita, E. Nathanson, P. O'Riordan, M. Pai, D. Palmero, G. Pasvol, J. Pena, C. Perez, MID Quelapio, H.T. Quy, A. Ponce-de-Leon, V. Riekstina, J. Robert, S. Royce, M. Salim, H.S. Schaaf, K.J. Seung, L. Shah, K.P. Shean, T.S. Shim, S.S. Shin, Y. Shiraishi, Jose Sifuentes-Osornio, G. Sotgiu, M. Strand, P. Tabarsi, T.E. Tupasi, M. Vargas, M. Van der Walt, T.S. Van der Werf, A. Van Deun, P. Viiklepp, W.W. Yew, J.J. Yim

Recent research completed: treatment of DR-TB

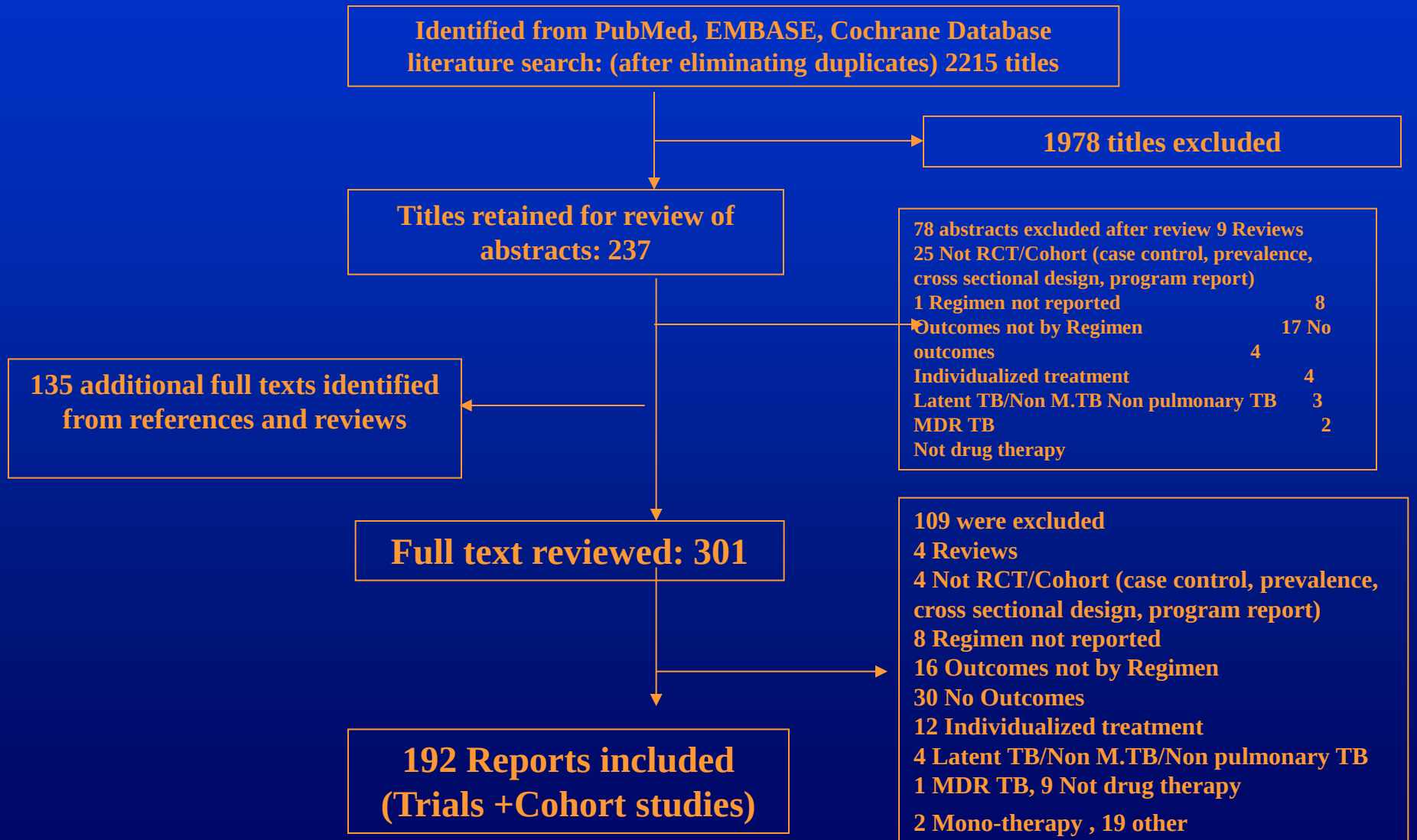
- MDR-TB – Many observational studies
  - Several aggregate data meta-analyses (traditional)
  - One Individual patient data meta-analysis
  - Two Phase 2 trials
- XDR-TB – Several observational studies
  - Two aggregate data meta-analyses (traditional)
  - One Individual patient data meta-analysis
  - One Phase 2 trial
- **What more is needed?**

What research is needed: DR-TB treatment?

- Trials, trials and more trials
- In MDR-TB & XDR-TB
  - How to use the new drugs (DMD, BDQ)
  - Optimal use of existing drugs (FQN, LZD, CFZ)
  - Duration, number of drugs, schedule

- How many trials will be needed?
  - Trials needed for current First line therapy

Summary of study review and selection



How many RCT are needed - example

RCT to address Duration of RIF to prevent Relapse: 57 trials with 16377 subjects

Rifampin duration	Arms (N)	Events/ Subjects	Event rate	(95% CI)
1-2 months	67	373/3545	**10.8%**	**(6.5, 15.1)**
3-5 months	40	198/2732	**6.4%**	**(3.6, 9.3)**
6-7 months	167	364/8611	**3.5%**	**(2.6, 4.4)**
8+ months	20	15/1489	1.0%	(0.3, 1.7)

What research is needed: DR-TB treatment?

- Trials, trials and more trials
- In MDR-TB & XDR-TB
  - How to use the new drugs (DMD, BDQ)
  - Optimal use of existing drugs (FQN, LZD, CFZ)
  - Duration, number of drugs, schedule

- **What else is needed?**
  - What has been largely ignored in past 20 years?

The ignored DR-TB
INH resistance (and other non-MDR)

Global weighted mean, 1994-2007*

- 7.4% in new cases
- 12.4% in previously treated cases

Treatment

- Dogma: “INH-R is of no importance. Treat with standard therapy”
- Evidence – from two systematic reviews
  - Much higher risk of failure (10 times higher)
  - Much higher rate of relapse (8-10%)
  - High risk of acquiring MDR-TB if fail or relapse

Research needs: DR-TB treatment

- Trials, trials and more trials
- In MDR-TB & XDR-TB
  - New drugs, old drugs
  - Duration, number of drugs, schedule
- **But also trials are needed for non-MDR-TB**
  - INH resistance and poly drug resistance
  - “old drugs” (FQN, LZD)
  - Duration, combinations, Schedule
  - Enhancing cure, avoiding drug resistance

Thank you!

Merci!

Gracias!!

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  - Kitty Lambregts, Fuad Myrzayev, Matteo Zignol, Sarah Royce, Jessica Minion, Madhu Pai,