State of the State in TB Control

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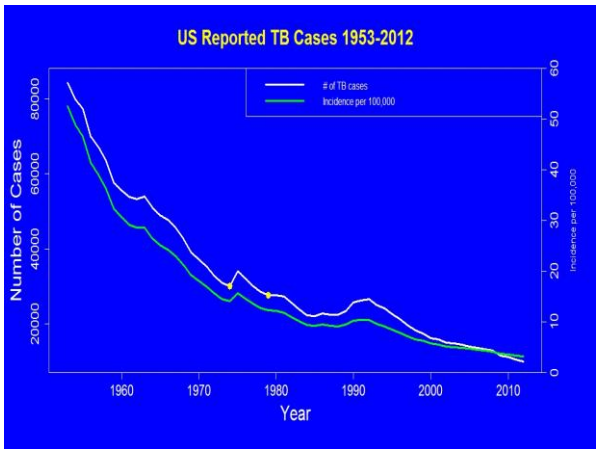
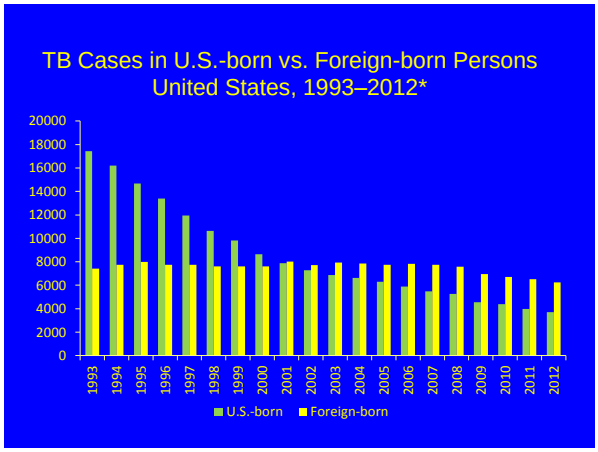
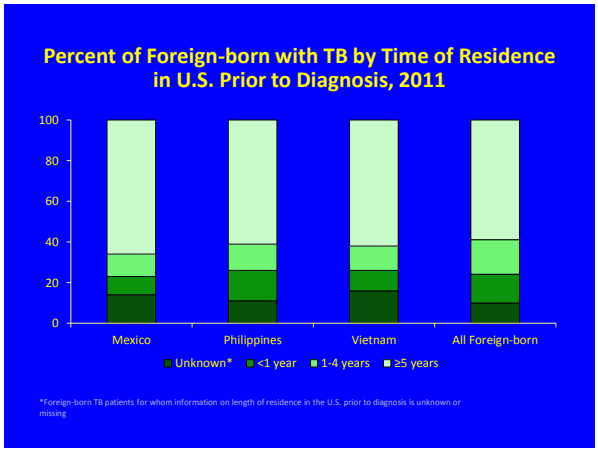
In 2012 the World Did End,
Oops, those Mayans, wrong again.
TB was at an all-time low,
Not ten thousand US cases showed.
Combining HIV, TB, and syph,
Was a great burden for us to lift.
But in these efforts we did great,
Because we are a PCSI state.
To greater challenges we will go,
Can you say, "Cover your cough" in Igbo?

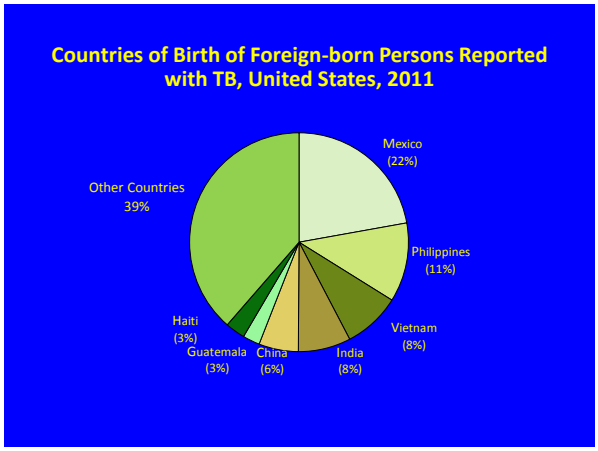
TB News in 2012

- Continued decline in cases
- Continued decline in funding to treat cases
- Evolution of TB epidemiology
- New understanding of transmission
- New data in debate about TB and pregnancy
- New data on monitoring of TB rx
- New drugs





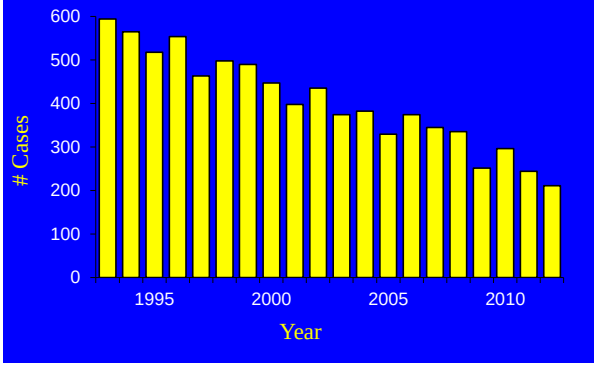




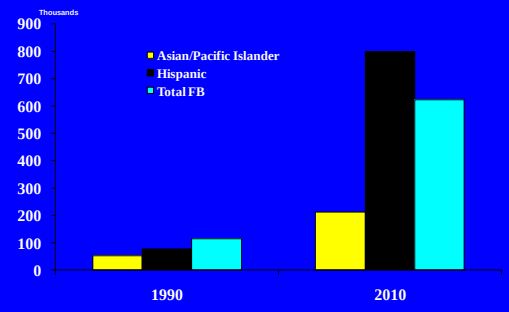
TB in NC

- US rate (2012) 3.2/100K vs NC 2.5 100/K
- #29 for incidence rate, #13 for total cases
- TB is not “someone else’s problem”

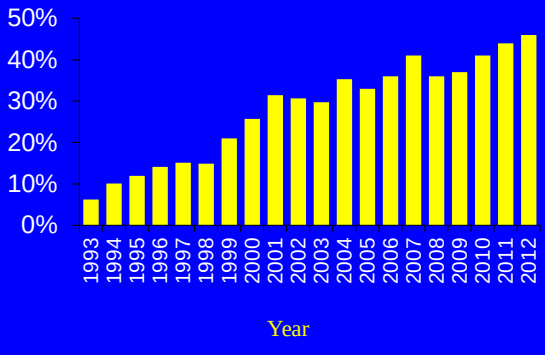
NC TB cases 1993-2012



NC Demographics 1990-2010



Foreign-born TB Cases in NC 1993-2012



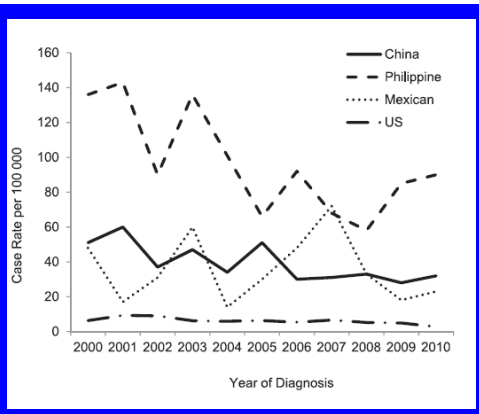
Implications of More FB-TB

- Foreign-born are traditionally infected abroad and reactivate
- In many studies FB transmit less than US-born persons
- FB persons may present differently than US-born persons

Molecular Epi of TB in San Francisco

- Study of culture-confirmed, genotyped TB cases reported in San Francisco between 1991-2010 (n=2419)
- Examined differences among 4 groups:
  - FB Chinese
  - FB Philippino
  - FB Mexican
  - US-born

Am J Resp Crit Care Med 2013; 187: 998-1006



Am J Resp Crit Care Med 2013; 187: 998-1006

Molecular Epi of TB in San Francisco

Characteristic	Chinese	Philippines	Mexico	US
Median age	66	55	33	31.5
TB site				
Pulm only	75.0%	76.8%	64.5%	68.9%
Pulm + EP	7.2%	5.9%	18.3%	15.7%
EP only	17.8%	17.3%	17.3%	15.4%
Smear-positive	31.1%	33.8%	38.4%	44.0%
Cavitary	10.7%	18.3%	19.6%	13.8%
HIV-positive	0.3%	4.3%	20.8%	37.0%
Homeless	0.2%	2.4%	30.8%	40.2%
EtOH abuse	2.9%	4.9%	36.3%	32.8%
INH-resistant	9.8%	15.4%	6.0%	5.1%
MDR	1.5%	2.3%	1.3%	0.8%

Am J Resp Crit Care Med 2013; 187: 998-1006

Molecular Epi of TB in San Francisco

TABLE 2. FREQUENCY OF *Mycobacterium tuberculosis* LINEAGES BY PLACE OF BIRTH FOR THE FOUR GROUPS OF INTEREST (n = 1,814)*

	Birthplace			
	China [*n* (%)]	The Philippines [*n* (%)]	Mexico [*n* (%)]	United States [*n* (%)]
n	559	399	125	731
Lineage 2 (East Asian)	383 (68.5%)	20 (5.0%)	7 (5.6%)	85 (11.6%)
Lineage 4 (Euro-American)	136 (24.3%)	24 (6.0%)	113 (90.4%)	595 (81.4%)
Lineage 1 (Indo-Oceanic)	40 (7.2%)	355 (89.0%)	5 (4.0%)	51 (7.0%)
Allopatric association	178 (31.8%)	45 (11.3%)	12 (9.6%)	134 (18.3%)
P value	<0.001	0.002	0.02	1.00

*Excluding 605 patients born elsewhere.

Molecular Epi of TB in San Francisco

- Secondary cases were more likely to be infected with sympatric strains
- Possibly a reflection of association
- Hypothesis that coevolution of TB and host may also have played a role

Am J Resp Crit Care Med 2013; 187: 998-1006

Cough Aerosols and Transmission

- Traditionally infectiousness is assessed with the use of AFB sputum smears
  - Smear-positive=more infectious
  - Smear-negative=less infectious
- But it is know that there is wide variation in infection rates among persons with the same smear status
- Why?

Cough Aerosols and Transmission

- CASS (Cough Aerosol Sampling System) is a method to quantitate number of infectious particles in a cough

Am J Resp Crit Care Med 2012; 186: 450-457

Figure 1. Cough Aerosol Sampling System. View inside of chamber with two Andersen cascade impactors and settle plate (*left*) and set up in procedure room ready for use (*right*).

Am J Resp Crit Care Med 2012; 186: 450-457

Cough Aerosols and Transmission

- Recruited smear-positive TB pts in Uganda, within 7 days of diagnosis
- Patients coughed into the CASS system during 2 5-minute periods
- No sputum induction used; if sputum came up, it was cultured
- 40 subjects asked to repeat the CASS on 2 consecutive days (to assess reproducibility)

Am J Resp Crit Care Med 2012; 186: 450-457

Cough Aerosols and Transmission

- 101 subjects participated
  - Median age 32 yrs
  - 70% male
  - 58% HIV+ with median CD4+ count 112
  - 63% with cavitary disease
  - 74% with high-grade smear positivity (3-4+)

Am J Resp Crit Care Med 2012; 186: 450-457

Cough Aerosols and Transmission

- Only 28 of 101 (27.7%) produced infectious aerosols from the first CASS study
- Results from first and second 5 minute specimens were tightly correlated, but more likely to get infectious aerosol from 1st specimen
- Among the 40 pts who came in for a second day, reasonable concordance among specimens

Am J Resp Crit Care Med 2012; 186: 450-457

Cough Aerosols and Transmission

- In multivariable analysis, 2 factors associated with infectious aerosols:
  - Salivary or mucosalivary appearance of sputum (OR 4.42, 95% CI 1.23-21.4)
  - Lower BACTEC time to detection (OR 1.17/day decrease, 95% CI 1.05-1.33)
- Other factors significant in univariate but not multivariate analysis: stronger cough, higher Karnofsky score, higher smear grade, fewer days of rx prior to recruitment

Am J Resp Crit Care Med 2012; 186: 450-457

Cough Aerosols and Transmission

- Followup study examined whether these cough aerosols predict rate of infection in household contacts
- Examined smear-positive TB pts presenting to the same clinic in Uganda who lived with at least 3 other persons
- Recruited 96 patients who had 442 household contacts

Am J Resp Crit Care Med 2013; 187: 1007-1015

Cough Aerosols and Transmission

- Collected 2 CASS specimens at baseline (5 minutes each)
- Did TST and Quantiferon Gold in-tube® on contacts
- Source cases were young (median age 28.9 yrs), had a median 12 wks of cough prior to presentation, and 22% were HIV+ with median CD4 of 264

Am J Resp Crit Care Med 2013; 187: 1007-1015

Cough Aerosols and Transmission

- CASS results:
  - 55% produced no infectious aerosols
  - 19% produced infectious aerosols with low numbers of organisms (1-9 CFU)
  - 26% produced infectious aerosols with high numbers of organisms (10+ CFU)

Am J Resp Crit Care Med 2013; 187: 1007-1015

Cough Aerosols and Transmission

CASS result	% of contacts newly infected	OR
No infectious aerosol	20/66 (30%)	1 (reference)
Low infectious aerosol	7/28 (25%)	0.77 (0.27-2.17)
High infectious aerosol	18/26 (69%)	5.17 (1.52-17.61)

- Smear status, sleeping in the same room with the source case, time to growth were not predictive of TST conversion
- Using IGRA vs. TST did not significantly change the result (perhaps slightly stronger with IGRA)

Am J Resp Crit Care Med 2013; 187: 1007-1015

TB and Pregnancy

- Longstanding debate over risk of active TB during pregnancy
- Pregnancy increases risk for a number of other infections requiring T-cell function for control (e.g. Listeria)
- Challenging to control for all relevant factors

Am J Resp Crit Care Med 2012; 185: 779-784

TB and Pregnancy

- Study examined risk of TB among women attending general practices in Great Britain
- Used the U.K. General Practice Research Database, which contains data on 5.5% of the population
- Data are representative of the wider country

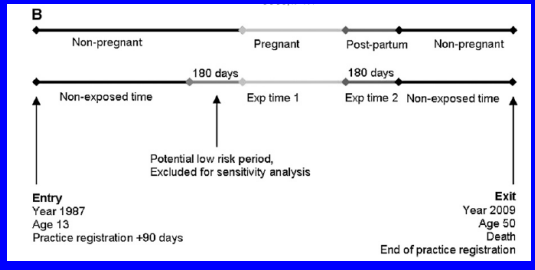
Am J Resp Crit Care Med 2012; 185: 779-784

TB and Pregnancy

- Examined all women with pregnancies 1996-2008 (inclusive)
- Included all pregnancies regardless of outcome (delivery, miscarriage, etc.)
- Looked at risk of TB during and 6 mos after pregnancy compared with TB risk at other times

Am J Resp Crit Care Med 2012; 185: 779-784

TB and Pregnancy



Am J Resp Crit Care Med 2012; 185: 779-784

TB and Pregnancy

Time period	TB Incidence	Risk ratio
Outside of pregnancy	9.11 (95% CI 7.63-10.8)	1 (referent)
During pregnancy	12.81 (8.03-19.39)	1.29 (0.82-2.03)
Postpartum (0-6 mos)	19.15 (12-29)	1.95 (1.24-3.07)

TABLE 3. ANALYSIS OF SELF-CONTROLLED CASE SERIES SHOWING INCIDENCE RATE RATIOS FOR TUBERCULOSIS

	TB Events	Person-Years	IRR	95% CI	*P* Value
Outside of pregnancy*	133	1,448	1	Reference category	
During pregnancy	22	167	1.03	0.64–1.65	0.91
6 mo postpregnancy	22	113	1.62	1.01–2.58	0.04
Age, 20–29 yr*	80	681	1.00	Reference category	
Age, up to 19 yr	11	125	0.81	0.32–2.06	0.67
Age, 30–39 yr	74	742	0.79	0.44–1.42	0.43
Age, 40–49 yr	12	179	0.68	0.23–2.04	0.49
Before year 2000*	53	555	1.00	Reference category	
Years 2000–2005	77	676	0.83	0.52–1.34	0.45
Years 2006–2010	47	497	0.59	0.30–1.14	0.12

TB and Pregnancy

- Authors speculated that TB risk is actually increased in pregnancy, but diagnostic delay causes this increase to be picked up postpartum
- Regardless, reinforces the potential opportunities for TB screening and maybe LTBI rx in pregnancy

Monitoring Active TB Rx

- NC and ATS/CDC/IDSA guidelines recommend baseline and monthly LFTs for "high risk" pts
  - On hepatotoxic meds
  - HIV
  - Alcoholism
  - Viral hepatitis
- Data to support this practice are negligible

Monitoring Active TB Rx

- Prospective, observational study of active TB pts (>16 yrs) at St. Mary's Hospital 1/07-9/09
- Checked ALT, bili, PT in all pts at baseline and 2 wks
- If ALT abnormal, checked weekly until normalized
- Also checked if pts had symptoms of liver toxicity

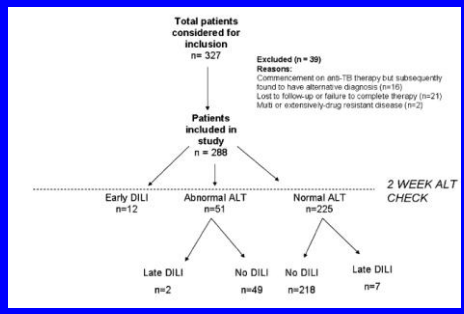
Am J Resp Crit Care Med 2012; 185: 653-659

Monitoring Active TB Rx

- Drug-induced liver injury defined as:
  - ALT>3x ULN with symptoms OR
  - ALT>5x ULN regardless of symptoms
  - And normalization of LFTs after TB meds stopped

Am J Resp Crit Care Med 2012; 185: 653-659

Monitoring Active TB Rx



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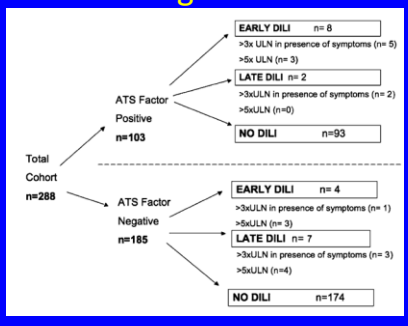
Monitoring Active TB Rx



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Monitoring Active TB Rx

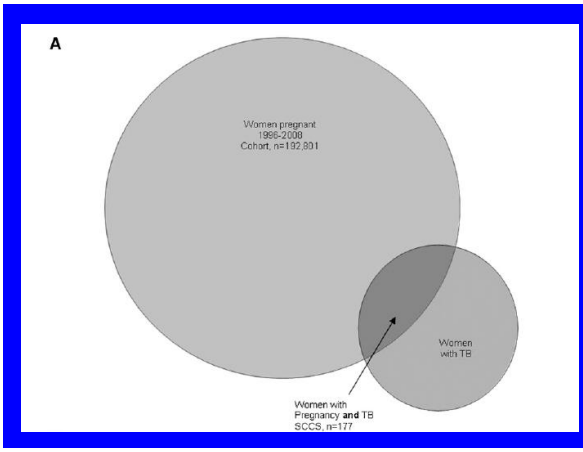
- Authors recommended checking ALT at 2 wks for all pts on TB rx
- Small study, not clear that this strategy is superior
- Bottom line: both strategies miss patients who will have liver toxicity from TB meds, and frequent monitoring will pick up many people with clinically insignificant ALT elevations

Am J Resp Crit Care Med 2012; 185: 653-659

Monitoring Active TB Rx

- 288 pts included
  - 21 (7.3%) had drug-induced liver injury
    - 11 had ALT>3x ULN with symptoms
    - 10 had ALT>5x ULN without symptoms
  - 12/21 (57.1%) had elevated ALT at 2 weeks
  - The other 9 developed liver toxicity later
    - Median time of onset day 50 (IQR 36.5-87.5 days)
    - 3 presented with symptoms
    - 4 had LFTs checked for other reasons
    - 2 had abnormal 2-wk LFTs and were followed

Am J Resp Crit Care Med 2012; 185: 653-659



Investigational Drugs

ATP synthase inhibitors
- Bedaquiline(TMC207)(J)

Ethylenediamines
- SQ109 (Q)

Nitroimidazoles
- Delamanid (OPC-67683)
- PA-824 (Pa)

Oxazolidinones
- Sutezolid (PNU-100480)(U)

Bedaquiline Phase II for MDR

- 8-week randomized, placebo-controlled study
- Bedaquiline added to "optimized background regimen"
- Primary endpoint: time to culture conversion in liquid media

NEJM 2009; 360: 2397

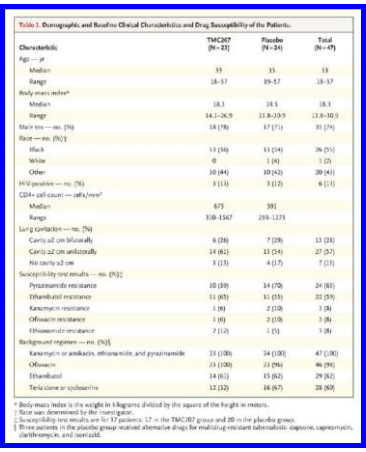
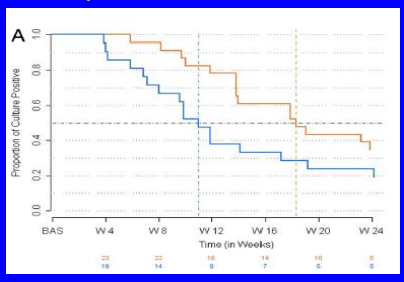


Table 1. Demographic and Baseline Clinical Characteristics and Drug Susceptibility of the Patients.

Characteristic	TMC207 (N = 23)	Placebo (N = 24)	Total (N = 47)
Age — yr			
Median	33	35	33
Range	18–57	19–57	18–57
Body-mass index*			
Median	18.1	18.5	18.3
Range	14.1–26.9	13.8–30.9	13.8–30.9
Male sex — no. (%)	18 (78)	17 (71)	35 (74)
Race — no. (%)†			
Black	13 (56)	13 (54)	26 (55)
White	0	1 (4)	1 (2)
Other	10 (44)	10 (42)	20 (43)
HIV-positive — no. (%)	3 (13)	3 (12)	6 (13)
CD4+ cell count — cells/mm³			
Median	675	391	
Range	338–1367	269–1273	
Lung cavitation — no. (%)			
Cavity ≥2 cm bilaterally	6 (26)	7 (29)	13 (28)
Cavity ≥2 cm unilaterally	14 (61)	13 (54)	27 (57)
No cavity ≥2 cm	3 (13)	4 (17)	7 (15)
Susceptibility test results — no. (%)‡			
Pyrazinamide resistance	10 (59)	14 (70)	24 (63)
Ethambutol resistance	11 (65)	11 (55)	22 (59)
Kanamycin resistance	1 (6)	2 (10)	3 (8)
Ofloxacin resistance	1 (6)	2 (10)	3 (8)
Ethionamide resistance	2 (12)	1 (5)	3 (8)
Background regimen — no. (%)§			
Kanamycin or amikacin, ethionamide, and pyrazinamide	23 (100)	24 (100)	47 (100)
Ofloxacin	23 (100)	23 (96)	46 (98)
Ethambutol	14 (61)	15 (62)	29 (62)
Terizidone or cycloserine	12 (52)	16 (67)	28 (60)

* Body-mass index is the weight in kilograms divided by the square of the height in meters.
† Race was determined by the investigator.
‡ Susceptibility test results are for 17 patients: 17 in the TMC207 group and 20 in the placebo group.
§ Three patients in the placebo group received alternative drugs for multidrug-resistant tuberculosis: dapsone, capreomycin, clarithromycin, and isoniazid.

Bedaquiline Phase II MDR



Discontinuation=failure to convert analysis at 24 weeks:
- Time to 50% culture conversion 78 vs. 129 days
- 81% vs. 65% culture conversion at 24 weeks

Diacon *et al.* (2009) NEJM; Diacon *et al.* (2012) AAC

Bedaquiline Drug Interactions

With rifamycins (based on single-dose data):
- J concentrations reduced ≥ 50% by RIF or RPT
- DMID-sponsored study of RBT + J DDI in healthy volunteers fully-enrolled, results expected soon

With ARVs (based on single-dose data):
- EFV reduces J concentrations ≥ 20%
- AUC with and without NVP were similar, Cmax reduced 20%
- LPV/r increases J AUC about 22%

With fluoroquinolones:
- Potential for combined effect on QT (overlapping toxicity)

Does Bedaquiline Kill People?

Outcome	Placebo	Bedaquiline
Week 24 cx conv (mITT) (S2)	38/66 (57.6%)	52/66 (78.8%) (p=0.008)
Week 72 cx conv (mITT) (S2)	37/66 (56.1%)	47/66 (71.2%) (p=0.069)
Isolate became pre-XDR or XDR	4 in Stage 1 7 in Stage 2	1 in Stage 1 0 in Stage 2
Grade 3+ AEs (Stage 1 and 2)	0/105 (0%)	5/102 (4.2%) 1 headache, 2 elevated transaminases, 2 arthralgias
Death (combined) Stage 1 Stage 2	4/105 (3.8%) 2/24 (8.3%) 2/81 (2.5%)	12/102 (11.8%) 2/24 (8.3%) 10/79 (12.7%)

From FDA submission for bedaquiline

C208 Death By Arm

Time since last J/Placebo dose	Placebo	Bedaquiline
2 days (considered on rx)		EtOH poisoining
86 days		Hepatitis/cirrhosis
105 days	Hemoptysis	
115 days		Acute MI
262 days		TB (relapse)
267 days	TB (XDR)	
281 days		TB (relapse)
314 days		TB (relapse, XDR)
344 days		TB (relapse)
427 days	TB (XDR)	
504 days		TB (XDR)
513 days		Sepsis/peritonitis
556 days		Stroke
709 days	TB	
787 days		TB
911 days		Car accident (but TB relapsed)

Bedaquiline

- Now FDA-approved for MDR treatment
- Special access program through the company only
- Very expensive
- Phase 3 study ongoing to better understand safety/efficacy issues

Delaminid Phase II for MDR

- 8-week randomized, double-blind, placebo-controlled study
- Multinational
- Delaminid added to "optimized background regimen" at 2 different doses (100 bid or 200 bid)
- Primary endpoint: proportion with sputum culture conversion in liquid media at 8 wks

NEJM 2012; 360: 2397

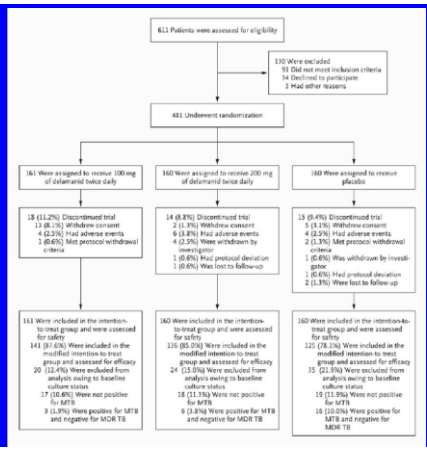
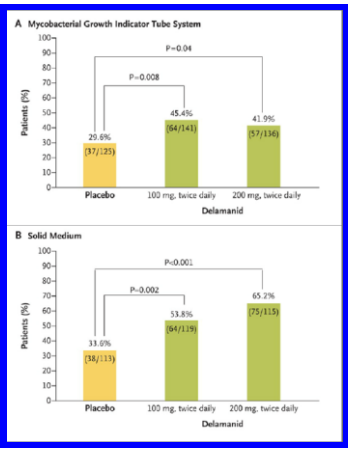


Table 1. Demographic and Baseline Clinical Characteristics of the Modified Intention-to-Treat Population for the Primary Efficacy Analysis.*

Characteristic	Delamanid, 100 mg Twice Daily (N=141)	Delamanid, 200 mg Twice Daily (N=136)	Placebo (N=125)	Total (N=402)
Age — yr				
Median	36	33	35	35
Range	19–63	18–63	18–63	18–63
Male sex — no. (%)	91 (64.5)	95 (69.9)	89 (71.2)	275 (68.4)
Body-mass index†				
Median	19.8	19.5	19.5	19.6
Range	12–31	12–40	12–31	12–40
Region — no. (%)‡				
Americas	39 (27.7)	38 (27.9)	39 (31.2)	116 (28.9)
Southeast Asia	43 (30.5)	47 (34.6)	45 (36.0)	135 (33.6)
Northeast Asia	29 (20.6)	28 (20.6)	25 (20.0)	82 (20.4)
Eastern Europe or Mediterranean	30 (21.3)	23 (16.9)	16 (12.8)	69 (17.2)
Lung cavities — no. (%)				
Absent	44 (31.2)	43 (31.6)	38 (30.4)	125 (31.1)
Unilateral	60 (42.6)	56 (41.2)	60 (48.0)	176 (43.8)
Bilateral	37 (26.2)	37 (27.2)	27 (21.6)	101 (25.1)
Previous treatment — no. (%)				
<30 days before randomization	11 (7.8)	14 (10.3)	12 (9.6)	37 (9.2)
≥30 days before randomization	130 (92.2)	122 (89.7)	113 (90.4)	365 (90.8)
First-line only	72 (51.1)	73 (53.7)	68 (54.4)	213 (53.0)
Second-line with or without first-line	40 (28.4)	27 (19.9)	23 (18.4)	90 (22.4)
Third-line with or without first-line or second-line	18 (12.8)	22 (16.2)	22 (17.6)	62 (15.4)



Delaminid Phase II

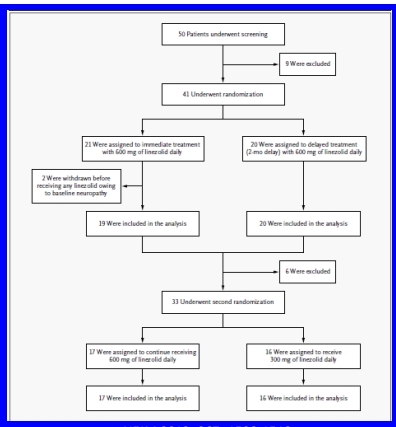
- Only adverse effect more common in delaminid group was QT prolongation
  - 3.8% in placebo group
  - 9.9% in 100 bid group
  - 13.1% in 200 bid group
- All asymptomatic, no clinical events
- Pk substudy demonstrated nonlinear AUC increase with dose increase

Linezolid for XDR TB

- MDR TB=TB resistant to isoniazid + rifampin
  - Treatment duration goes from 6→18-24 mos
  - Cure rate goes from >95% to 60-80%
- XDR TB=MDR resistant to FQ, injectable
  - Unknown treatment duration
  - Cures reported 30-60%, often with surgery
- Treatment of XDR is not standardized, not sure what really works

Linezolid for XDR TB

- Linezolid is an oxazolidinone antibiotic
- Inhibits protein synthesis
- Active against many gram-positive bacteria
- Active *in vitro* against TB
- Very expensive, fairly toxic



NEJM 2012; 367: 1508-1518

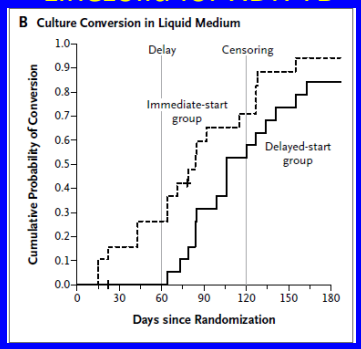
Linezolid for XDR TB

Table 1. Baseline Characteristics of the Study Participants According to Treatment Group.*

Characteristic	Immediate-Start Group (N = 19)	Delayed-Start Group (N = 20)	Total (N = 39)
Age — yr			
Mean	42.1	40.4	41.2
Range	20–64	23–63	20–64
Male sex — no. (%)	12 (63)	16 (80)	28 (72)
Body-mass index†			
Mean	19.6	20.5	20.0
Range	14.9–25.7	14.4–28.1	14.4–28.1
Diabetes mellitus — no. (%)	7 (37)	7 (35)	14 (36)
BCG vaccination scar — no. (%)	14 (74)	17 (85)	31 (79)
Radiographic findings — no. (%)			
Far advanced tuberculosis‡	15 (79)	15 (75)	30 (77)
Cavitary tuberculosis	9 (47)	8 (40)	17 (44)
Bilateral lesions	18 (95)	20 (100)	38 (97)
No. of previous treatment episodes for tuberculosis			
Median	5.0	5.0	5.0
Interquartile range	3.0–8.5	4.0–7.0	3.0–7.3
No. of resistant drugs§			
Mean	11.6	10.4	11.0
Range	8–15	6–14	6–15

NEJM 2012; 367: 1508-1518

Linezolid for XDR TB



NEJM 2012; 367: 1508-1518

Linezolid for XDR TB

- 34/38 (89%) of pts who received linezolid converted cultures on solid media at 6 mos
- Toxicity was common— 31 (82%) had adverse events potentially due to linezolid
  - 2 pts discontinued permanently due to optic neuropathy, 1 due to anemia
  - Total 7 cases optic neuropathy, 21 peripheral neuropathy, 7 myelosuppression, 1 rhabdomyolysis

NEJM 2012; 367: 1508-1518

Linezolid for XDR TB

- 4 pts failed or relapsed, all with mutations suggestive of linezolid resistance
- Bottom line: linezolid helpful for XDR (along with background regimen), but expensive and toxic

NEJM 2012; 367: 1508-1518

Combinations of New Drugs

- Need not just new drugs, but new regimens
- With several new drugs on the horizon, need to understand which combinations are most promising

Combinations of New Drugs

- Randomized trial looking at 14-day activity of combinations of several drugs:
  - Moxifloxacin
  - Bedaquiline
  - Pyrazinamide
  - Moxifloxacin

Lancet 2012; 380: 986-993

Combinations of New Drugs

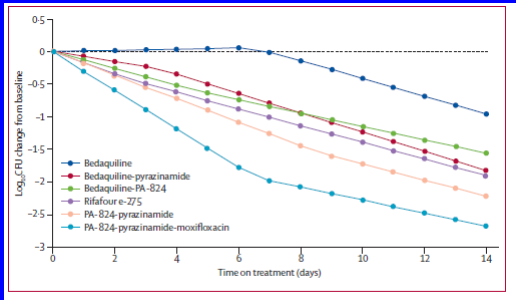


Figure 2: **Bilinear regression showing the fall in mean log_{10}CFU from baseline**
CFU=colony forming unit.

Lancet 2012; 380: 986-993

Is Spending Money on TB Good Value?

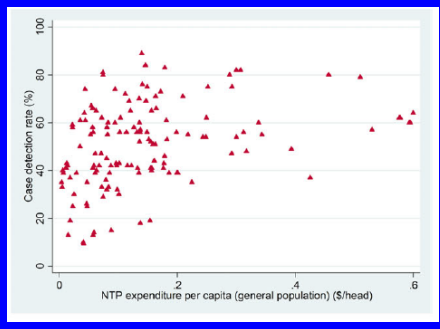
- Money is tight in the US
- Similarly tight across the world
- 80% of world TB occurs in 22 high-prevalence countries, generally low-income

Is Spending Money on TB Good Value?

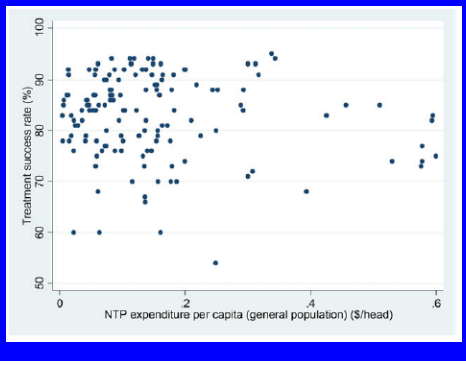
- Study examined relationship between national TB program expenditures and changes in TB prevalence in the 22 high-burden countries
- Looked at time period 2002-2009

Journal of Infectious Diseases 2012; 205: S284-S292

Is Spending Money on TB Good Value?



Is Spending Money on TB Good Value?



Is Spending Money on TB Good Value?

- Authors estimated that a $1 per capita increase in NTP budget was associated with a 1.9% annual increase in case detection rate
- NTP budget was not associated with any change in treatment success rate
- Higher case detection rate was associated with lower TB incidence and death rates the following year

Conclusions

- TB is still declining in the US
- Still a big global problem, some exciting new interventions on the way
- Potential for better targeting control strategies
  - Understanding differences among population subgroups
  - Figuring out who is most infectious
  - Better understanding risk factors like pregnancy