Tuberculosis and Biologic Therapies

Risk and Prevention

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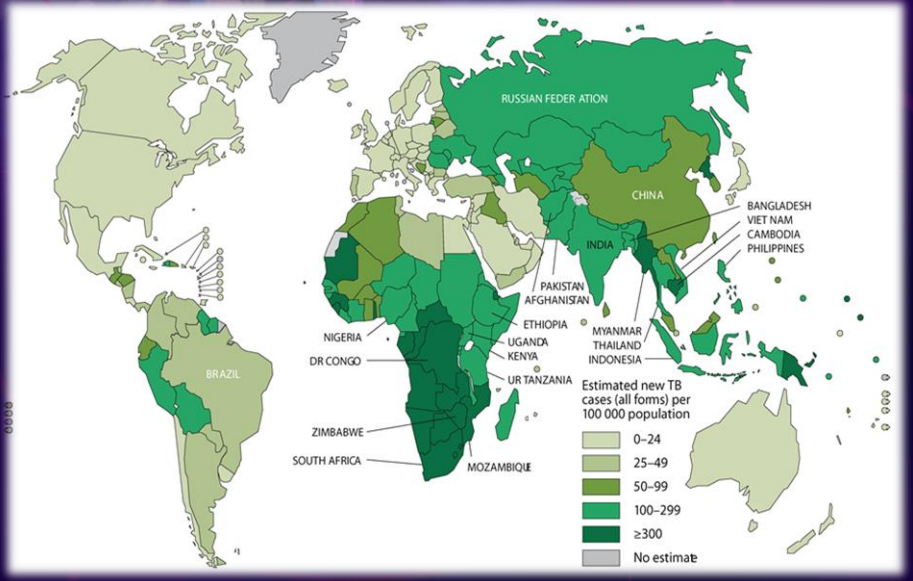
Disclosures

- **Research funding from Pfizer**
- **Scientific consultant work for Abbvie, Pfizer, UCB, Genentech, Regeneron**
- **Data safety monitoring boards for RCTs conducted by UCB, Roche, Abbvie, Astellis, Janssen, Biogen, Galapagos, Lilly, EMD Merck-Serono**

Global TB Epidemiology

World Health Organization

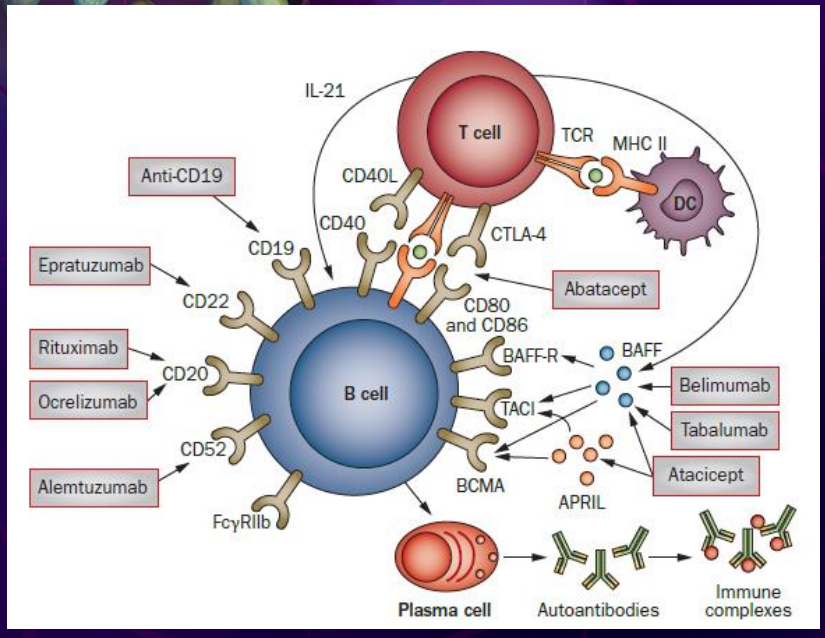


TB Pathogenesis

- Transmitted by inhalation (or ingestion) of *M. tuberculosis* bacilli
  - Alveolar macrophage
  - Bacilli replication
  - Brief hematogenous dissemination
- Cytokine and cellular activation
- Immune system attempts to limit spread of infection
  - Granuloma formation around bacilli
  - Intracellular killing of bacilli

IMID Biologic Therapies

- TNF-α inhibition
  - **Infliximab, adalimumab,** golimumab, certolizumab (monoclonal antibodies)
  - **Etanercept (soluble p75 receptor)**
- Other
  - CD4 co-stimulation modulator: abatacept
  - B-cell (CD20+) antibody: rituximab
  - Anti-IL-6 receptor antibody: tocilizumab
  - Anti- IL12/IL23 antibody: ustekinumab
- JAK 1/3 inhibitor: tofacitinib



Burmester GR, et al. *Nature Reviews Rheumatology* 2014

Prednisone and Tuberculosis

- *Jick et al. Arthritis Rheum 2006*
- General Practice Research Database, UK
- TB cases 1990-2001 and controls†
- Current glucocorticoid use *OR 4.9 (2.9-8.3)

  ≤15mg/day *OR 2.8 (1.0-7.9)

  ≥15mg/day *OR 7.7 (2.8-21.4)

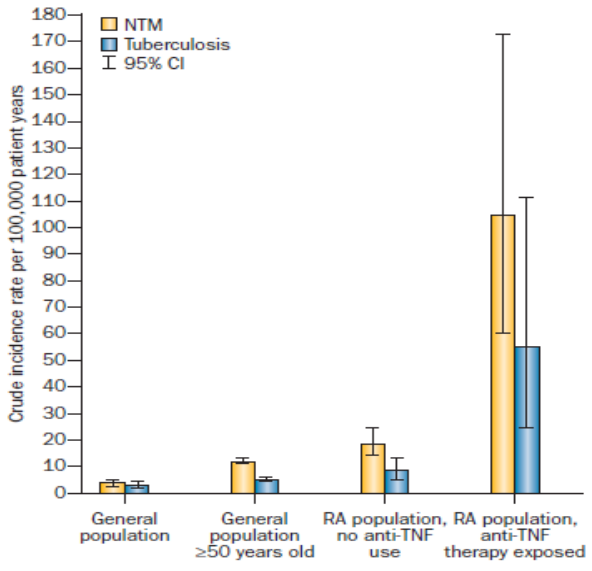
*Adjusted for smoking, BMI, lung disease, diabetes, anti-rheumatic therapy, other TB risk factors
†Controls matched for age, sex, residence, time clinically followed

Risk of TB

Country/Year	Mycobacteria disease	Crude Incidence per 100,000 pt-yrs. Anti-TNF treated		Crude Incidence per 100,000 pt-yrs. Non-biologic comparator	Adj. RR¥ (95% CI
[38]UK, 2010	Tuberculosis	95¥		0¥	UNDEF
		Etanercept users	39¥		
		Infliximab users	136¥		
		Adalimumab users	144¥		
[76]France, 2011	Tuberculosis	117*		NR	NR
[24]US, 2011	Tuberculosis	56¥		9¥	NR
		Etanercept users	17		
		Infliximab users	83		
		Adalimumab users	91		

Winthrop KL, Nature Prac Rheum (In Press)

Figure 2

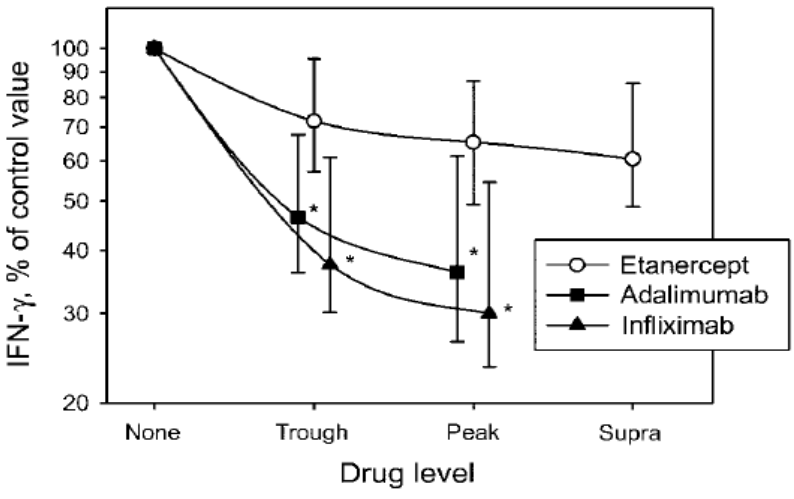


Winthrop KL et al. Ann Rheum Dis 2012; Winthrop KL Nat Rheum Rev, in press

More TB Risk with Monoclonals?

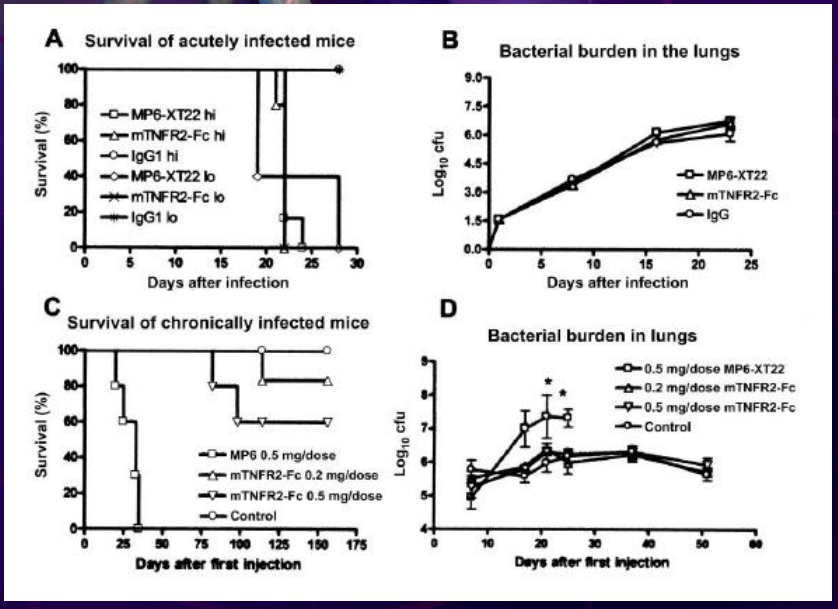
- Drug mechanisms differ
- Greater TNF-α binding
  - Transmembrane and soluble TNF-α
  - Forms stable complex
- ~~Longer half-life~~
- Apoptosis of monocytes and ~~T lymphocytes~~
- Interferon-gamma down-regulation
- Differential granuloma penetration

Interferon-γ Downregulation



Saliu et al. JID 2006

Granuloma Penetration



Plessner HL et al JID 2007

Granuloma Penetration

- Acute TB infection (mouse)
  - Large bacillary load and death
  - No difference between anti-TNFs
- Chronic TB infection (mouse)
  - Monoclonal antibodies = death (1 month)
  - Etanercept = 60% alive at 6 months
  - Lung path: etanercept with less penetration of granulomas

Plessner et al JID 2007

Downregulation of CD8+ Cells

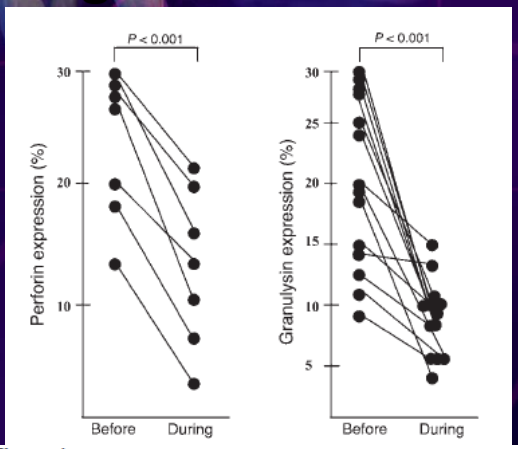


Figure 1
Decreased expression of lytic and antimicrobial effector molecules in patients treated with infliximab. PBMCs from patients with active RA or AS were stained for perforin ($n = 7$) or granulysin ($n = 17$) before and 2 weeks after beginning therapy. The percentage of granulysin+ and perforin+ lymphocytes was determined by flow cytometry. Shown are results from all individual donors tested.

Bruns H et al. *J Clin Invest* 2009

LTBI Screening

Table 1. Summary of selected recommendations for tuberculosis screening prior to anti-TNF therapy

Agency/Region	Year	Regional BCG use±	Regional TB prevalence (cases/100,000) *	Risk assessment	Initial screening test	Chest radiograph	Other
BTS[26]	2005	Yes	Low (12)	Yes	None£	Yes¥	Empiric INH for those from highly prevalent regions
Switzerland[37]	2008	Yes	Low (4.9)	Yes	IGRA	Yes¥	
France[39]	2006	Yes	Low (6.2)	Yes	IGRA	Yes¥	
Spanish[11]	2004	Yes	Low (17)	Yes	TST (two-step)	Yes	
Germany[38]	2009	Yes	Low (5.1)	Yes	IGRA	Yes¥	
ACR[28]	2008	No	Low (4.8)	Yes	TST	Yes+	
CDC[27]	2005	No	Low (4.8)	Yes	TST	Yes+	
Canada[29]	2008	No	Low (5)	Yes	TST	Not specified	IGRA in those with negative TSTs but risk factors

American College of Rheumatology (ACR); British Thoracic Society (BTS); National Institute for Health and Clinical Excellence (NICE); US Centers for Disease Control or Prevention (CDC).

Winthrop KL Intl J Rheum 2010

Interferon-gamma Release Assays (IGRAs)

T-SPOT.TB 96

Oxford Immunotec
Harnessing the power of T cell measurement

17

Relative Sensitivity of IGRA

- Case-control study, Peru
- 80% BCG use in both groups
- High prednisone use among RA group

	RA (n = 101)	Controls (n = 93)
TST+	27 (27%)[a]	61 (66%)
QFT-IT+	45 (45%)	55 (59%)

Ponce de Leon D et al. J Rheumatol. 2008;35:776-781

German Experience

TST > 15mm (n=71)

40% = IGRA negative, no BCG

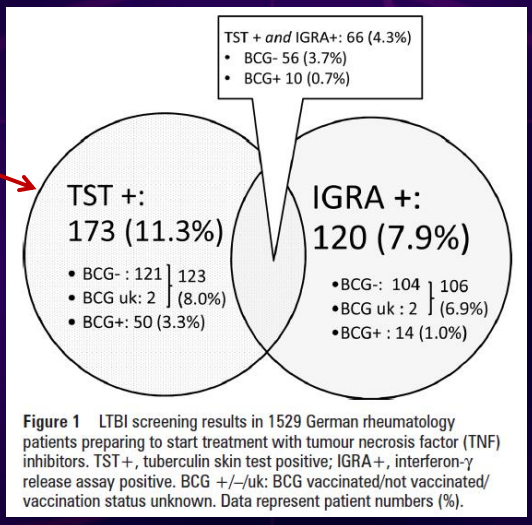


Figure 1 LTBI screening results in 1529 German rheumatology patients preparing to start treatment with tumour necrosis factor (TNF) inhibitors. TST+, tuberculin skin test positive; IGRA+, interferon-γ release assay positive. BCG +/–/uk: BCG vaccinated/not vaccinated/ vaccination status unknown. Data represent patient numbers (%).

Kleinert S, et al. *Ann Rheum Dis* 2012

French Experience

- 392 screened with TST, T-SPOT, AND QFT-IT
  - 66%-95% with BCG history
  - AS, RA, IBD
- Agreement between IGRAs
  - 91% (Kappa 0.61 [0.5-0.7])
- TST > 10mm
  - 2/3 were negative by both IGRA
  - Most given TNFi without INH = no TB at one year

Golimumab and TB

- N= 2,282 RA, PsA, AS development program
- Screened with TST and QFT-IT
- 5 patients developed active TB
  - All 5 screened negative at baseline
  - 2 with TST of 5mm or 15mm (negative by local standards)
- 317 screened positive
  - INH and golimumab
  - No TB cases

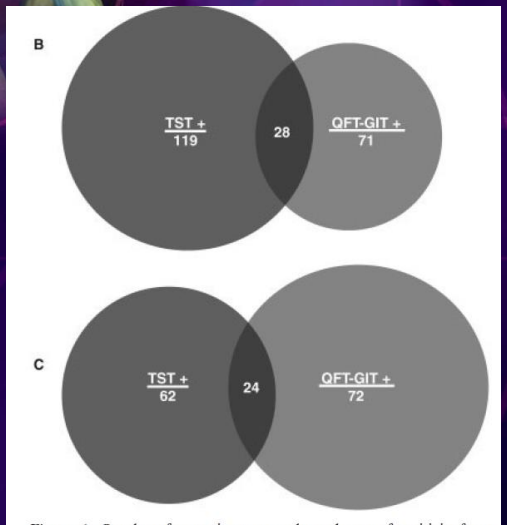
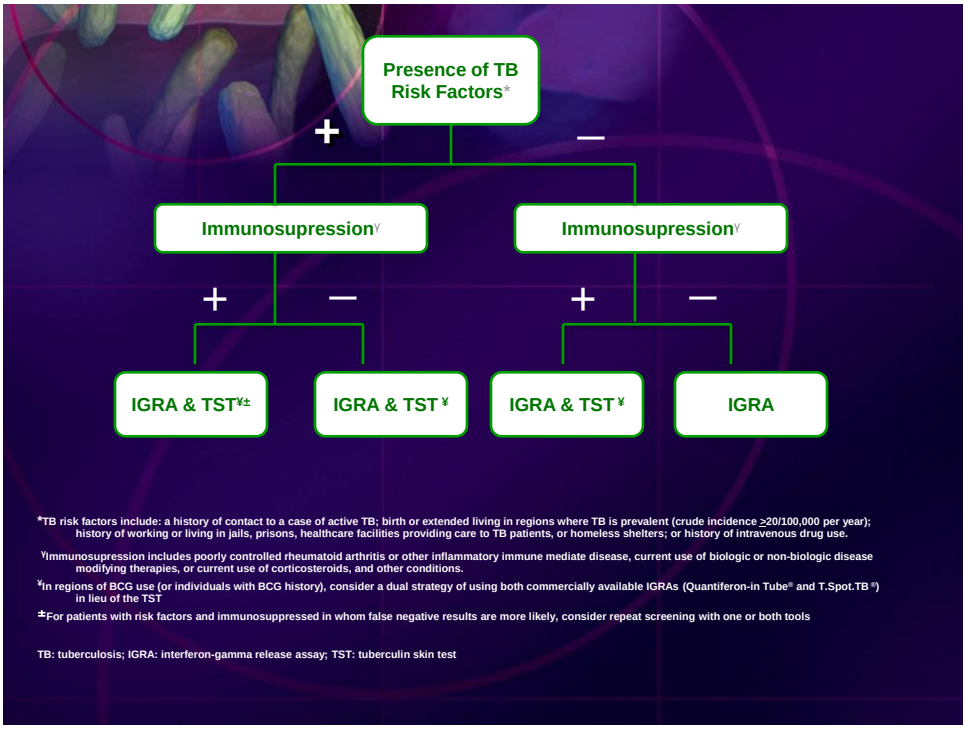


Figure 1. Overlap of screening test results and rates of positivity from the tuberculin skin test (TST) and an interferon-γ release assay (i.e., the QuantiFERON-TB Gold In-Tube [QFT-GIT] test) for the detection of latent tuberculosis infection in all patients (**A**), bacillus Calmette-Guérin (BCG)–vaccinated patients (**B**), and non–BCG-vaccinated patients (**C**).

Hsia E et al. Arth Rheum 2012



*TB risk factors include: a history of contact to a case of active TB: birth or extended living in regions where TB is prevalent (crude incidence ≥20/100,000 per year); history of working or living in jails, prisons, healthcare facilities providing care to TB patients, or homeless shelters; or history of intravenous drug use.

¥Immunosupression includes poorly controlled rheumatoid arthritis or other inflammatory immune mediate disease, current use of biologic or non-biologic disease modifying therapies, or current use of corticosteroids, and other conditions.

¥In regions of BCG use (or individuals with BCG history), consider a dual strategy of using both commercially available IGRAs (Quantiferon-in Tube® and T.Spot.TB®) in lieu of the TST

±For patients with risk factors and immunosuppressed in whom false negative results are more likely, consider repeat screening with one or both tools

TB: tuberculosis; IGRA: interferon-gamma release assay; TST: tuberculin skin test

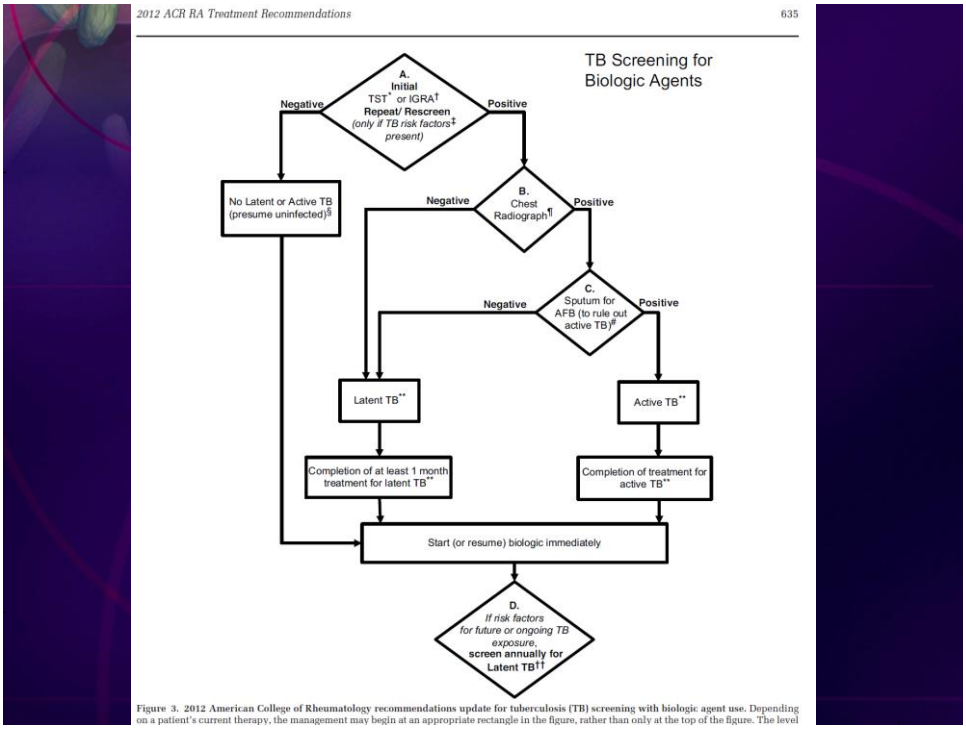
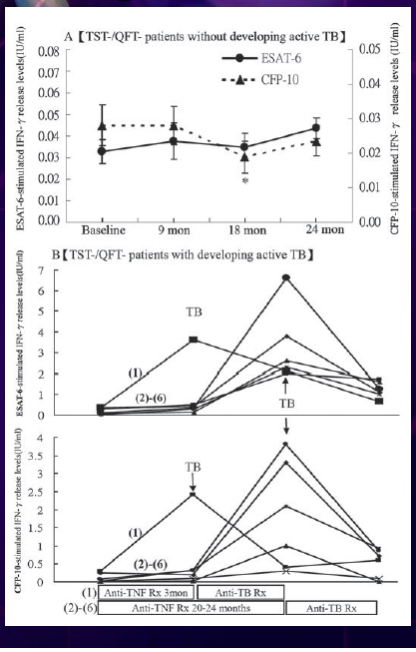


Figure 3. 2012 American College of Rheumatology recommendations update for tuberculosis (TB) screening with biologic agent use. Depending on a patient's current therapy, the management may begin at an appropriate rectangle in the figure, rather than only at the top of the figure. The level

Serial Screening in Endemic Areas?

Taiwan RA (n=242)



Chen DY, et al *Ann Rheum Dis* 2012

LTBI Treatment

- Begin treatment before starting anti-TNF therapy
  - 9 months isoniazid (INH) preferred
  - 4 months rifampin is alternative
- Start INH 1 month prior to anti-TNF initiation
  - 83% reduction in INF-associated cases in Spain[1]
  - Ensure INH compliance and tolerance
- Liver function testing
  - Many patients taking methotrexate

MTX, methotrexate.

1. Carmona L et al. *Arthritis Rheum.* 2005;52:1766-1772.

New Therapy Option

- INH and Rifapentine
  - 3 months, once weekly (directly observed?)

Table 2. Number of Subjects with Tuberculosis and Event Rates.*

Population and Study Group	No. of Subjects	Subjects with Tuberculosis			Difference in Cumulative Rate†	Upper Limit of 95% CI for Difference in Cumulative Rate
		no.	no. per patient-yr	cumulative rate	percentage points	
Modified intention-to-treat analysis						
Isoniazid only	3745	15	0.16	0.43	−0.24	0.01
Combination therapy	3986	7	0.07	0.19		
Per-protocol analysis						
Isoniazid only	2585	8	0.11	0.32	−0.19	0.06
Combination therapy	3273	4	0.05	0.13		

* Combination therapy consisted of 3 months of directly observed once-weekly therapy with rifapentine (900 mg) plus isoniazid (900 mg). Isoniazid-only therapy consisted of 9 months of self-administered daily isoniazid (300 mg). Data are shown for a period up to 33 months after study enrollment.
† The difference is the rate in the combination-therapy group minus the rate in the isoniazid-only group.

Sterling T et al. NEJM 2011

Rheumatologists are Smartest

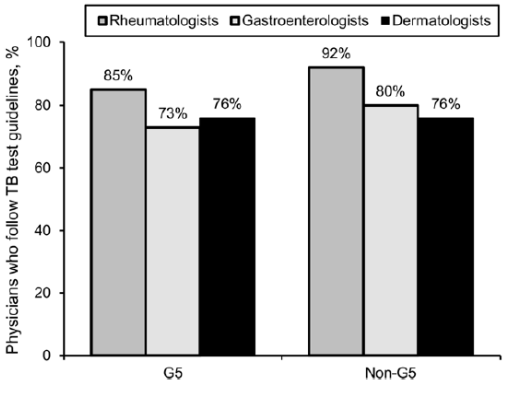


Figure 2 Percentage of rheumatologists, gastroenterologists and dermatologists who reported following guidelines for TB testing of their patients prior to prescribing anti-TNF agents: G5 vs. non-G5 EU member countries, 2010. TB = tuberculosis; G5 = the five foremost industrialized economies; TNF = tumor necrosis factor; EU = European Union.

Smith MY et al. IJTLD 2012

Rituximab

- Peripheral B cell depletion
  - No TB in RA clinical trials or in lymphoma use
- US ID specialist survey
  - 8 TB/NTM cases with rituximab
  - All cases also on prednisone
- Animal data
  - B cell importance to granuloma/survival in murine model of TB*

*Maglione et al. *J Immunol* 2007

Abatacept

- CTLA-4 ligand that mitigates CD4 cell proliferation
- At least 12 human cases reported (rate 90/100,000) £
- Tuberculosis risk unknown
  - Screened in clinical trials
  - Should screen in practice
- Murine chronic TB not affected by abatacept*
  - Mortality, T cell, B cell, INF-γ production in lung, and bacillary load

*Bigbee et al. Arth Rheum 2007; £Allen R et al Arth Rheum 2014

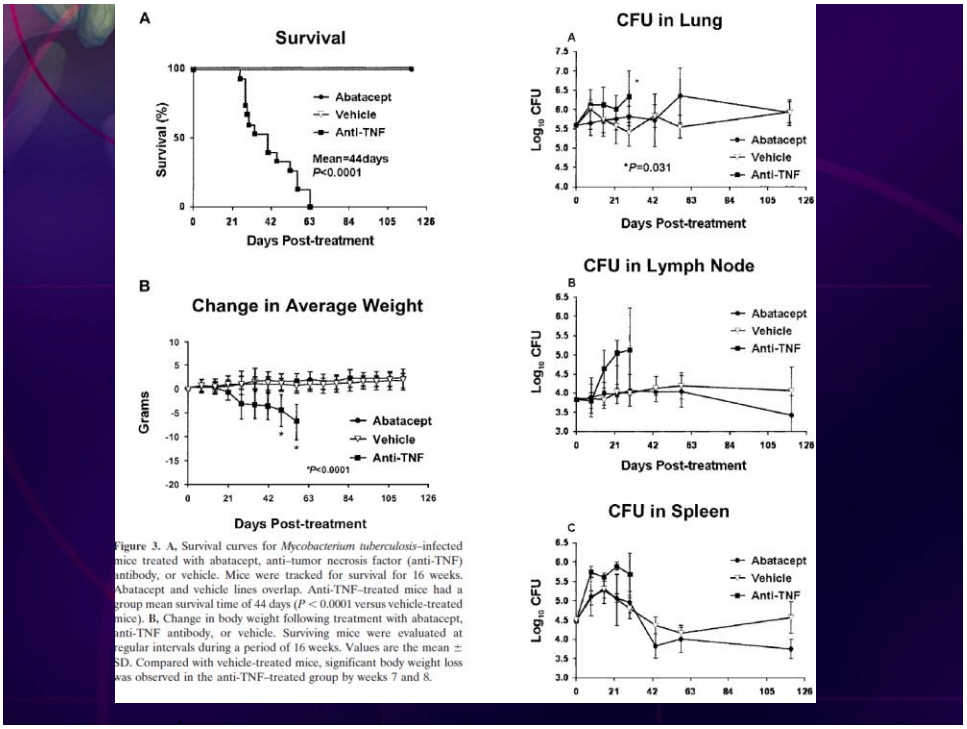


Figure 3. A, Survival curves for *Mycobacterium tuberculosis*–infected mice treated with abatacept, anti–tumor necrosis factor (anti-TNF) antibody, or vehicle. Mice were tracked for survival for 16 weeks. Abatacept and vehicle lines overlap. Anti-TNF–treated mice had a group mean survival time of 44 days ($P < 0.0001$ versus vehicle-treated mice). **B,** Change in body weight following treatment with abatacept, anti-TNF antibody, or vehicle. Surviving mice were evaluated at regular intervals during a period of 16 weeks. Values are the mean ± SD. Compared with vehicle-treated mice, significant body weight loss was observed in the anti-TNF–treated group by weeks 7 and 8.

Abatacept versus Infliximab

RCT, 12 month safety endpoint

	Abatacept + MTX (N=156)	Infliximab + MTX (N=165)
Serious infection	**3 (1.9%)***	**14 (8.5%)***
†Opportunistic infection	**0**	**5 (3%)**

***p=0.01**

†Tuberculosis (n=2), PCP, HSV encephalitis, pseudomonas pneumonia

Schiff M et al, *Ann Rheum Dis* 2008

IL-6 Importance

- Upstream, pleiotropic cytokine
- Secreted by T cells, macrophages, endothelial cells
- Stimulate TH17 development, B cell development, other

TB and IL-6 mouse

Table 4 Susceptibility to bacterial, parasitic, fungal, and viral infections in interleukin-6 knockout mice in comparison to wild type mice

Pathogen	Pathogen burden	Survival
Chlamydia trachomatis	Increased[c]	Reduced[c]
Escherichia coli	Increased[c,b]	Reduced[c,b]
Helicobacter felis	No difference[c]	NA
Listeria monocytogenes	Increased[a,c]	NA[a], reduced[c]
Mycobacterium bovis BCG	No difference[c]	NA
Mycobacterium tuberculosis	No difference[b], increased[c,b]	NA[b], no difference[b], reduced[c]
Rhodococcus aurantiacus	No difference[b]	NA
Staphylococcus aureus	No difference[d]	No difference[d]
Giardia lamblia	Increased[c]	NA
Leishmania major	No difference[c]	NA
Schistosoma mansoni	Reduced[b]	NA
Taenia crassiceps	Increased[a], reduced[b]	NA
Toxoplasma gondii	Increased[a]	No difference[a]
Trypanosoma cruzi	Increased[c]	Reduced[c]
Aspergillus fumigates	Increased[b]	NA
Candida albicans	Increased[b]	Reduced[b]
Cryptococcus neoformans	NA	Reduced[c]
Friend retrovirus	Increased (only during acute phase)[c]	NA
Herpes simplex virus type 1	No difference[b]	Reduced[b]
Influenza virus	No difference[c]	No difference[c]
Murine gammaherpesvirus-68	No difference[c]	No difference[c]

Tocilizumab and Opportunistic Infection

- Schiff et al meta-analysis clinical trial data
  - 230/100,000 (TB/NTM, candida, crypto, pneumocystis)
  - No cases in control groups (n=1,550)
- Japan observational study
  - TB, 220/100,000
  - Pneumocystis, 280/100,000
  - Zoster, 6.1/1,000
- HBV?
  - Only two case reports in literature

Interferon-gamma downregulation

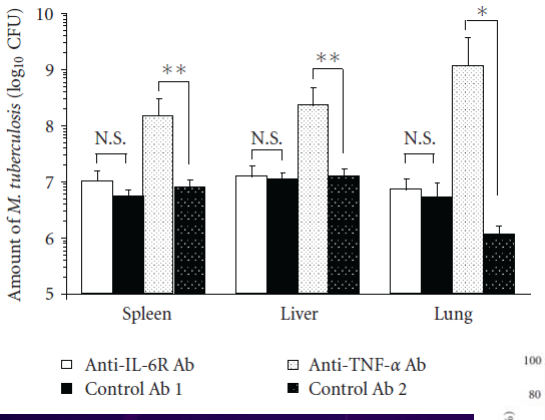
Table 1 Interferon gamma (IFN-γ) production from *Mycobacterium tuberculosis* (MTB) antigens stimulated whole-blood cells from patients with active TB

	ESAT-6 ($n = 23$)	CFP-10 ($n = 16$)
No biologic	1.30 ± 1.95	1.47 ± 1.60
Tocilizumab (TCZ)	1.56 ± 1.88	1.51 ± 1.77
Etanercept (ETA)	0.99 ± 1.74*	0.91 ± 0.99*
Infliximab (INF)	0.75 ± 1.66**	0.72 ± 0.88**

IFN-γ (IU/ml) production was significantly inhibited by ETA and INF but not TCZ

*$P < 0.005$ compared with no biologic; ** $P < 0.0001$ compared to no biologic

A Ogata et al, *Mod Rheumatol* 2010



Would chronic TB model yield different result?

Okada M et al. *Clin Develop Immunology* 2011

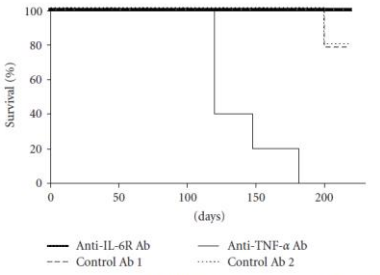
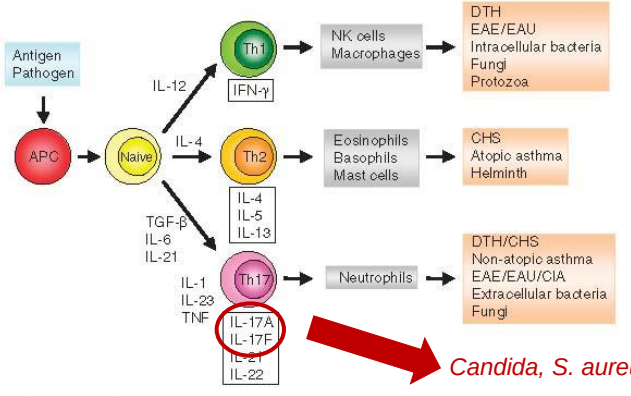


FIGURE 2: Survival of TB-challenged BALB/c mice treated with antibodies to TNF-α and IL-6R. Mice were injected with TB and antibodies, as shown in Figure 1, and monitored daily for survival. Each group consisted of 5 mice.

IL12 and IL23 (they share p40 subunit)



Candida, S. aureus

Fig. 1. Effector function of Th-cell subsets.

Iwakura et al *Immunological Reviews* 2008; Kagami S, et al. *J Immunol* 2010; Cho et al, *J Clin Invest* 2010

Human IL12-23 defects

Table 1 Affected cytokine (receptor) proteins and the pathogens to which humans with defects in these genes show extreme susceptibility

Affected protein	Pathogens causing severe infection or observed more than once	Sporadic pathogens
IFN-γR1 chain of the IFN-γ receptor	*Mycobacterium bovis* BCG *Mycobacterium tuberculosis* *Mycobacterium avium* *Mycobacterium fortuitum* *Mycobacterium chelonei* *Mycobacterium smegmatis* *Mycobacterium kansasii* *Mycoplasma pneumoniae* Cytomegalovirus	*Mycobacterium szulgai* *Mycobacterium peregrinum* *Mycobacterium gordonae* *Mycobacterium mageritense* *Listeria monocytogenes* *Legionella sp* *Salmonella enteritidis* Herpes simplex virus Parainfluenza virus Respiratory syncytial virus Human herpes virus-8
IFN-γR2 chain of the IFN-γ receptor	*Mycobacterium bovis* BCG *Mycobacterium avium* *Mycobacterium fortuitum* *Mycobacterium abscessus*	*Serratia marcescens* Herpes simplex virus
IL12p40 subunit of IL-12 and IL-23	*Mycobacterium bovis* BCG *Mycobacterium tuberculosis* *Mycobacterium chelonae* *Salmonella gallinarum* Varicella zoster virus	*Salmonella enteritidis* *Salmonella paratyphi* *Salmonella typhimurium* *Nocardia asteroides*
IL-12Rβ1 chain of the IL-12 and IL-23 receptors	*Salmonella typhimurium* *Salmonella enteritidis* *Salmonella paratyphi* *Salmonella typhi* *Salmonella dublin* *Mycobacterium bovis* BCG *Mycobacterium avium* *Mycobacterium tuberculosis* *Mycobacterium chelonae*	*Salmonella typhi* *Mycobacterium fortuitum* *Mycobacterium triplex* *Mycobacterium genavense* *Pseudomonas aeruginosa* *Streptococcus pneumoniae* *Kingella kingae* *Leishmania sp*

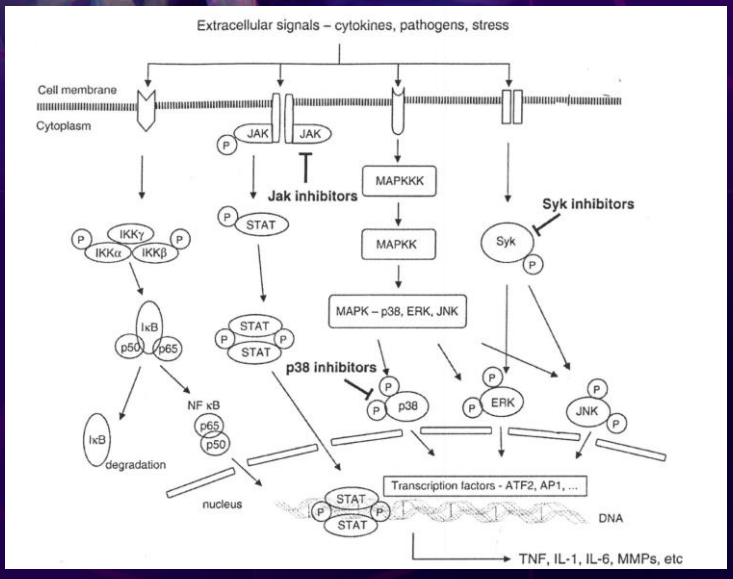
Van de Vosse, Curr Opin Rheumatol 2007

Ustekinumab

- Blocks p40 subunit present on IL12 and IL23
- Approved for Psoriasis
- Meta-analysis of RCT and open-label
  - 3,117 treated patients
  - SAEs (45 mg: 6.8/100 patient-yrs; 90 mg: 8.2/100 patient-yrs over 3 years)
  - No cases TB (patients screened at entry)
- Can treat LTBI concomitantly with INH

Lebwohl M. et al, J *Am Acad Dermatol* 2011; Tsai et al Br J Derm 2012

Brave New World



L Senolt et al., *Autoimmunity Reviews* 2009

Tofacitinib in RA

- JAK 1/3 inhibition
- Tuberculosis rate = 173/100,000
  - 37/100,000 (North America/Western Europe)
  - Most cases at 10mg BID dose
  - All cases screened negative prior to trial entry
- Mechanism?
  - Macrophage control of TB
  - Interferon signalling?

Winthrop et al abstract, American College of Rheumatology (ACR), Washington DC, Nov 2012

Figure 2. The majority of reported cases of TB occurred in geographic locations with a high endemic incidence of TB

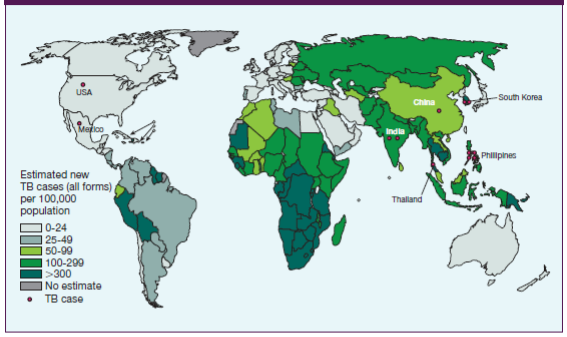


Table 3. TB incidence rates for tofacitinib patients by background country incidence rates (Phase 3 and LTE studies)

Background country IR[a] (events/100 pt-yrs)	No. of TB cases with tofacitinib	Tofacitinib exposure (pt-yrs)	TB IR (events/100 pt-yrs) (95% CI)
Low (≤0.01)	1	2712	0.037 (0.005, 0.261)
Medium (>0.01 and ≤0.05)	1	2930	0.034 (0.005, -0.242)
High (>0.05)	10	1280	0.781 (0.420, 1.452)

[a]TB background country incidence rate categories from World Health Organization, 2011 report for year 2010[9]
CI, confidence interval; IR, incidence rate; pt-yrs, patient-years; TB, tuberculosis
Low TB IR region: total tofacitinib study enrollment, n=1234 in the Phase 3 studies:
United States (n=543), Canada (n=57), Australia (n=100), Austria (n=27), Belgium (n=8) Czech Republic (n=248), Denmark (n=11), Finland (n=16), France (n=10), Germany (n=198), Greece (n=6), Ireland (n=3), Italy (n=13), Sweden (n=4)
Medium TB IR region: total tofacitinib study enrollment, n=1212 in the Phase 3 studies:
Brazil (n=177), Bulgaria (n=99), Chile (n=69), Columbia (n=77), Costa Rica (n=16), Croatia (n=16), Japan (n=118), Mexico (n= 128), Poland (n=175), Slovakia (n=76), Spain (n=85), UK (n=169), Venezuela (n=7)
High TB IR region: total tofacitinib study enrollment, n=976 in the Phase 3 studies:
Bosnia-Herzegovina (n=6), China (n=216), Dominican Republic (n=22), India (n=121), South Korea (n=205), Malaysia (n=42), Philippines (n=46), Taiwan (n=30), Thailand (n=49), Russia (n=26), Ukraine (n=111)

LTBI Treatment during Tofacitinib

- 209 patients diagnosed with LTBI
  - INH X 9 months during trial
  - No cases of TB
  - No hepatotoxicity noted
- INH is therapy of choice
  - Drug-drug interaction with Rifampin

Biological Conclusion

- TB risk with anti-TNF therapies is clear
- Newer biologics---TB risk relative to anti-TNF?
  - Animal data suggest less risk for tocilizumab and abatacept
  - Limited human data suggest similar risk for tocilizumab, but less risk for abatacept or rituximab
  - JAK inhibitors with risk
- Screening prior to immunosuppression!

Screening in the Biologics Setting
Words to Live By

- A priori probability reigns supreme
  - If they should be positive, then they probably are
  - If they shouldn't be positive, they probably aren't
- If risk factors, then use two screening tests
  - Maximize sensitivity
- If you don't believe your test result, REPEAT it!

Drug	Mechanism/target	Trial	Indication
NNC0109-0012	Anti-IL-20	Phase 2 recruiting	Rheumatoid arthritis
NNC114-0005	Anti-IL-21	Phase 1 completed	Rheumatoid arthritis
BMS-945429	Anti-IL-6	Phase 2 recruiting	Psoriasis
PF-04236921	Anti-IL-6	Phase 2 recruiting	Crohn's disease
LY3074828	Anti-Il-23	Phase 1 recruiting	Psoriasis
AMG 181	Anti-α4 β7 antibody (blocks interaction with MAdCAM-1)	Phase 2 recruiting	Ulcerative Colitis
TNF kinoid	Recombinant anti-TNF-α conjugated toKLH	Phase 1/2 completed Phase 2 recruiting	Crohn's disease Rheumatoid arthritis
Fostamatinib (R935788)	Spleen tyrosine kinase (Syk) inhibitor	Phase 2 completed	Rheumatoid arthritis
ABT-494	JAK 1 inhibitor	Phase 2 recruiting	Rheumatoid arthritis
Baricitinib	JAK 1 and JAK 2 inhibitor	Phase 3 recruiting	Rheumatoid Arthritis
VX-509	JAK 3 inhibitor	Phase 2 completed	Rheumatoid arthritis
Ixekizumab	Anti-IL-17	Phase 2 completed Phase 3 recruiting	Rheumatoid arthritis Psoriasis
Secukinumab	Anti-IL-17	Phase 3 recruiting Phase 3 recruiting	Rheumatoid arthritis Psoriasis
BIIB023	Inhibitor of TWEAK (TNF-related weak inducer of apoptosis)	Phase 2 recruiting	Systemic lupus erythematosus/lupus nephritis
NI-071	Infliximab biosimilar	Phase 3 recruiting	Rheumatoid arthritis
MEDI-546	Anti-Interferon-α Receptor Antibody	Phase 2 recruiting	Systemic lupus erythematosus
TNF-Kinoid	Recombinant TNF carrier (self-immunization)	Phase 2 recruiting	Rheumatoid arthritis
Ala-Cpn10	Modified version of the natural human protein, chaperonin10	Phase 2 recruiting	Systemic lupus erythematosus
MOR103	Anti-GMCSF	Phase 1 and 2 completed	Rheumatoid arthritis
Mavrilimumab	Anti-GMCSF receptor	Phase 2	Rheumatoid arthritis

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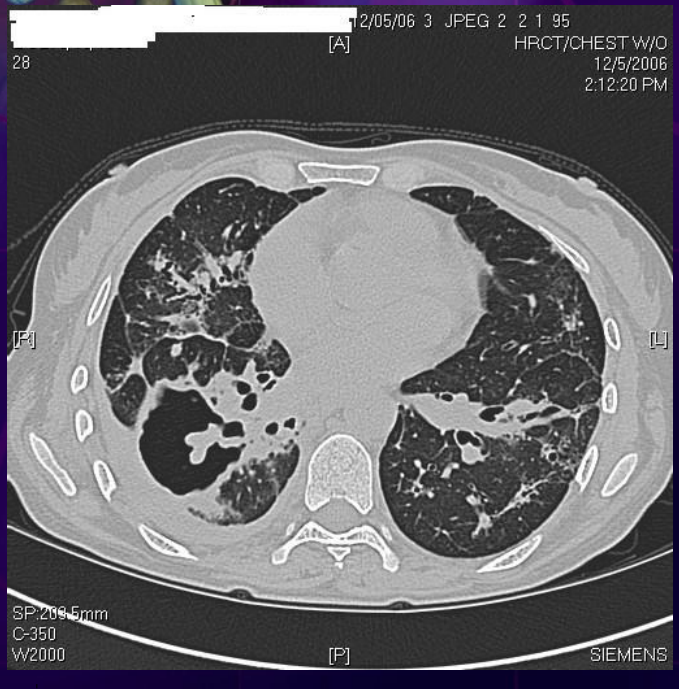

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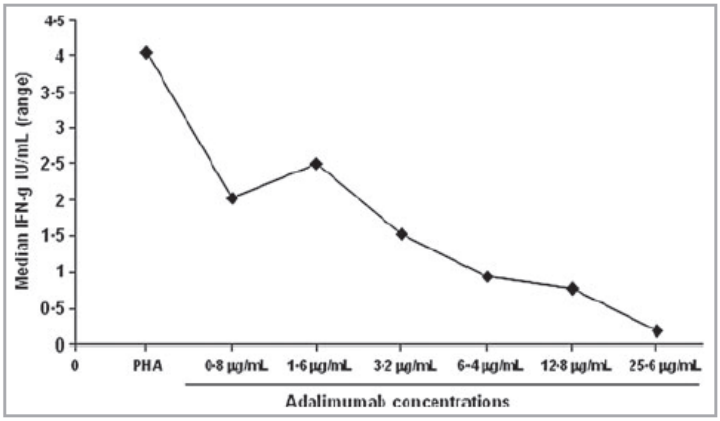
  - KPNC
  - UAB

TNFi Can Downregulate IGRA response



Sauzullo I, et al. *Abritish J Derm* 2013

Positive Predictive Value for LTBI

	QFT-IT	QFT-IT	TST
Prevalence	**1%**	**4%**	**1%**
Sensitivity	85%	85%	80%
Specificity	99%	99%	90%
PPV	**0.46**	**0.78**	**0.08**

US Comparison Studies

- **179 patients, TST vs. TSPOT.TB**
  - **Boston, US born women, 80% with RA**
  - **Taking TNF and/or DMARD +/- steroids**

TST +	TSPOT +
2 (1%)	10 (6%)

- **No concordance among positives**
  - **Few to no TB risk factors among the TSPOT+**
- **False versus true positive TSPOT?**

Behar et al. J of Rheum 2009;36:546-551

TABLE 2. ESTIMATED LATENT TUBERCULOSIS INFECTION PREVALENCE IN THE U.S. POPULATION BORN IN THE UNITED STATES, AND THE FOREIGN-BORN U.S. POPULATION, 1999–2000

	U.S.-born Population			Foreign-born Population		
Characteristics	LTBI Prevalence % (95% CI)	Population with Characteristic No. × 1,000	Estimated No. with LTBI No. × 1,000 (95% CI)	LTBI Prevalence % (95% CI)	Population with Characteristic No. × 1,000	Estimated No. with LTBI No. × 1,000 (95% CI)
All participants	1.8 (1.3–2.4)	231,227	4,154 (3,073–5,607)	18.7 (13.5–25.2)	37,057	6,888 (4,993–9,292)
Sex						
Female	1.5 (1.0–2.2)	112,019	1,761 (1,202– 2,575)	14.4 (8.7–23.0)	19,033	2,596 (1,565–4,138)
Male	2.1 (1.3.3.4)	119,208	2,380 (1,482–3,802)	22.7 (16.3–30.5)	18,023	4,313 (3,109 5,812)
Age group, yr						
1–14	0.3 (0.1–1.1)*	53,781	173 (49–610)	11.9 (5.2–24.8)*	3,480	413 (182–861)
15–24	0.6 (0.2–1.6)*	33,597	193 (68–540)	12.8 (5.1–28.4)*	5,755	735 (295–1,636)
25–44	1.2 (0.7–2.2)	68,841	826 (453–1,500)	20.6 (14.6–28.1)	15,965	3,281 (2,330–4,492)
45–64	3.4 (2.0–5.8)	48,189	1,650 (963–2,797)	25.3 (17.6–35.1)	8,266	2,094 (1,454–2,897)
≥65	4.8 (2.8–8.0)	26,819	1,288 (762–2,148)	11.9 (5.2–24.8)*	3,590	427 (188–899)
Race/ethnicity						
Non-Hispanic white	1.1 (0.6–2.0)	17,441	1,960 (1,120–3,418)	17.9 (11.4–26.8)	8,333	1,489 (953–2,236)
Non-Hispanic black/African American	5.7 (4.2–7.8)	29,193	1,661 (1,212–2,263)	20.0 (13.7–28.4)	2,842	570 (388–808)
Mexican/Mexican American	2.5 (1.6–3.8)	12,372	307 (200–470)	19.1 (16.2–22.5)	8,443	1,616 (1,366–1,900)
Other	1.5 (0.4–5.2)*	15,249	221 (60–794)	18.6 (10.9–29.9)	17,438	3,241 (1,900–5,211)
Poverty income index						
Poverty income index ≥1	1.4 (1.0–2.1)	171,561	2,469 (1,714–3,550)	16.5 (11.8–22.7)	23,936	3,950 (2,813–5,428)
Poverty income index <1	2.8 (1.9–4.0)	3,751	1,052 (728–1,516)	20.3 (13.0–30.3)	8,295	1,687 (1,082–2,514)
Education level						
<High school	2.5 (1.7–3.5)	81,900	2,003 (1,391–2,874)	19.2 (14.9–24.4)*	18,392	3,527 (2,734–4,483)
High school graduate	1.6 (0.9–2.8)	46,842	740 (413–1,316)	17.9 (8.9–32.7)	5,837	1,046 (520–1,911)
Beyond high school	1.6 (1.0–2.7)	85,094	1,371 (824–2,273)	18.3 (9.5–32.1)	12,220	2,230 (1,164–3,923)

For definition of abbreviations, *see* Table 1.

* Estimates and 95% CIs are unstable and may not accurately reflect the true proportion because of the small number of individuals in the subgroup.