RELATIONSHIP BETWEEN USE OF TNF-ALPHA BLOCKERS AND TUBERCULOSIS IN MARYLAND

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Background & Rationale

- Maryland is ranked as a "high-incidence" state for TB
  - Maryland case rate: 4.8 cases per 100,000 residents
  - National case rate: 4.4 cases per 100,000 residents
- Anecdotal reports of active TB cases in patients taking TNF-alpha blockers have not been systematically studied

Objectives

- Primary objective:
  - To describe the epidemiology of TB in patients taking TNF-alpha blocker medications
  - To identify tuberculosis testing activities of rheumatologists and dermatologists who are prescribing TNF-alpha blocker medications
- Secondary objective:
  - To develop relevant public health recommendations related to TB screening and treatment for patients who need to take TNF-alpha blocker medications

Tuberculosis

- Communicable bacterial infection caused by *Mycobacterium Tuberculosis*
- Airborne transmission
- Primarily affects lungs, although bacteria can spread systemically
- 90% of infected develop latent TB
- 5-10% of individuals with LTBI develop active TB
- Immunosuppression increases risk of progression to clinically active disease

TNF-alpha blocker medications

- Immunosuppressive
  - Inhibit the activity of TNF-alpha, an inflammatory cytokine
- Highly effective for treating inflammatory and autoimmune conditions:
  - Rheumatoid arthritis
  - Crohn's disease
  - Psoriasis
  - Ankylosing spondylitis
- First used in 1998
- Humira, Remicade, Enbrel, Cimzia

Relationship between TB and TNF-alpha blocker medications

- Serious side effect: reactivation of latent TB
- TB in patients taking TNF-alpha therapy often have extra-pulmonary or disseminated TB

Standard of care

- Perform TB screening for patients prior to initiation of immunosuppressive drugs
  - 2-step TST recommended to rule out false negative due to waning TB antibodies
- Treat TST positive patients for 9 months on isoniazid (INH)
- Repeat TST annually while patient is taking immunosuppressive drug

TB in patients taking TNF-alpha blocker medications…

Methods – Subject selection

- Cases who were treated at Maryland local health departments from 1998-2007 were included
- Cases identified by:
  - Investigating anecdotal reports
  - Interviewing TB controllers

Methods – Data collection

- Medical chart abstraction
- Interviews with case managers and county TB controllers
- Routine surveillance data
  (MD DHMH TIMS database)

Patient demographics

- 9 cases total
- Average age: 62 years (range 51-71)
- 3 male; 6 female
- 5 White; 2 Asian; 2 African American
- Cases identified in 7 jurisdictions

Distribution of TB cases by county

	TB cases taking TNF-alpha blockers		All TB cases in Maryland	
County	# of cases	% of total	# of cases	% of total
Montgomery	2	22.2	780	27.3
Prince George's	0	0	634	22.2
Baltimore City	1	11.1	610	21.4
Baltimore	1	11.1	258	9.0
Anne Arundel	1	11.1	142	5.0
Howard	2	22.2	104	3.6
Carroll	1	11.1	17	0.6
Kent	1	11.1	3	0.1
All others	0	0	308	10.8
Total	9	100%	2,856 (in MD)	100%

MD TB surveillance1998-2007

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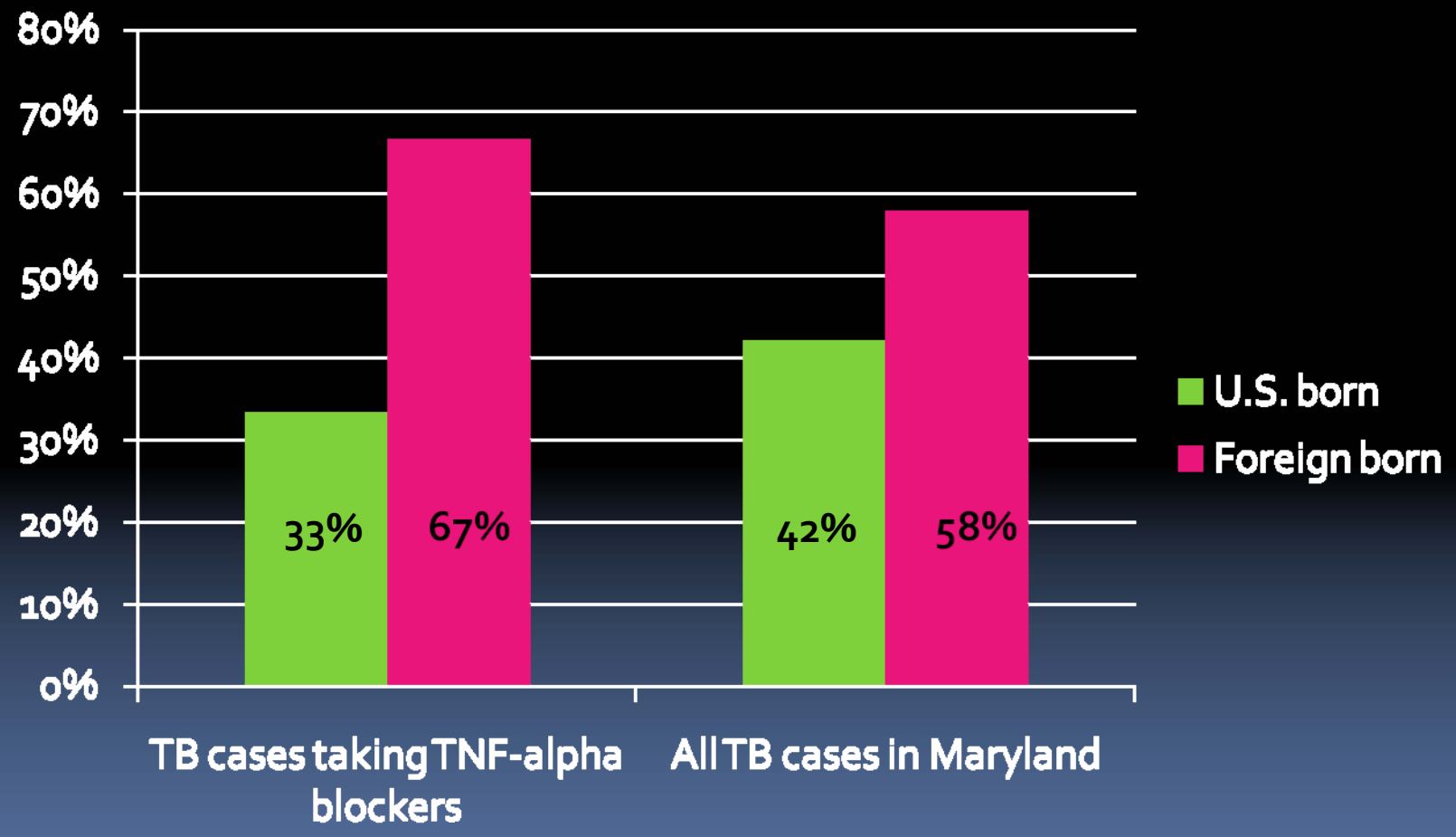
MD TB surveillance1998-2007

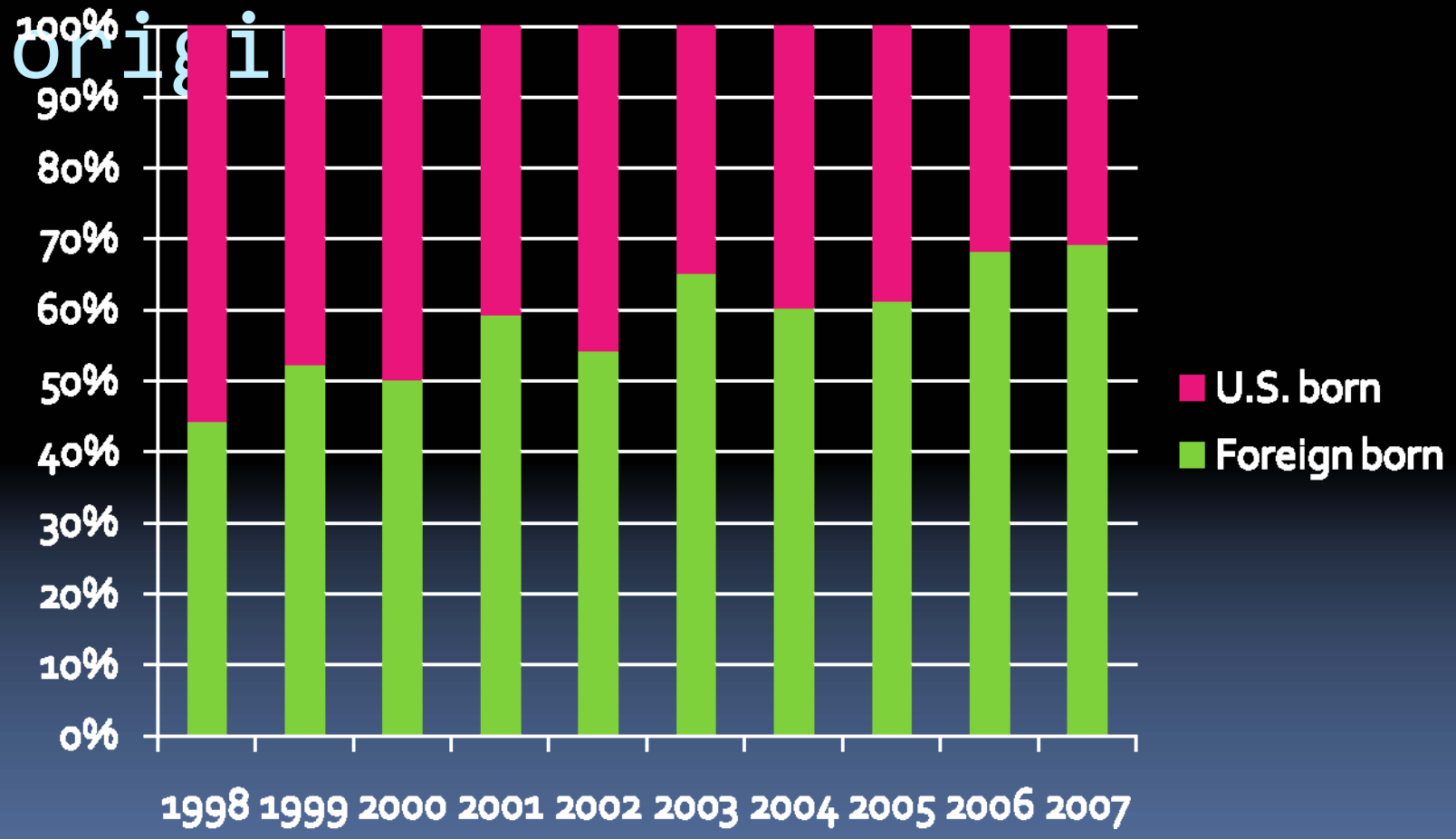
Patient country of origin: 1998-2007

3 out of 9 patients with TB and taking TNF-alpha blocker medications were foreign born



MD TB surveillance 1998-2007

Maryland TB cases: 1998-2007 Proportion of cases by origin



Patient medical history

- All 9 cases took Remicade, Humira, or Enbrel for rheumatoid arthritis
- Concomitant medications: prednisone, methotrexate
- None had prior TB diagnosis
- All HIV negative
- Standard procedures for excluding TB disease were completed, depending on patient's clinical presentation.
  - TST
  - Sputum smear
  - Sputum culture
  - Culture of other sites (i.e. bronchus, lymph node)
  - Chest x-ray

Sites of TB infection

- 4 patients had pulmonary TB; 4 patients had extra-pulmonary TB; 1 patient had both
- 76% (211 cases) of TB cases in MD in 2008 had pulmonary TB
- Cases of extra-pulmonary TB:
  - Pericardial
  - Pleural
  - Lymphatic
  - Brain

TB Treatment Outcomes 1998-2007

Reason	Patients taking TNF-alpha blocker	Patients not taking TNF-alpha blocker	All TB patients in Maryland
Completed therapy	7 (77.78%)	2460 (88.14%)	2467 (88.11%)
Died	1 (11.11%)	187 (6.70%)	188 (6.71%)
Moved	0	59 (2.11%)	59 (2.11%)
Lost	0	34 (1.21%)	34 (1.21%)
Uncooperative/ Refused	0	12 (0.43%)	12 (0.43%)
Other	1 (11.11%)	9 (0.32%)	10 (0.36%)
Missing	0	30 (1.07%)	30 (1.07%)
Total	9 (100%)	2791 (100%)	2800 (100%)

DHMH TB Surveillance 1998-2007

Conclusions from case investigations

- TB diagnostic algorithms and treatment methods are effective
  - All cases completed treatment
  - No treatment failures
- However, improvements need to be made in screening procedures to identify high-risk patients so that they enter the health system prior to the development of clinically active disease.

TB screening and treatment practices of dermatologists and rheumatologists…

Methods – Physician selection

- Practicing dermatologists and rheumatologists identified from MedChi (Maryland State Medical Society)
- Random selection of physicians
- Voluntary participation

Methods – Data collection

- Phone interviews
- 15 interviews conducted
  - 8 dermatologists
  - 7 rheumatologists
- Survey completed by physician, designated clinical staff or designated non-clinical staff

Physician demographics

- Average years in practice: 23.5 years (range: 3 to 45)
  - Dermatologists: 22 years (range 3 to 45)
  - Rheumatologists: 25 (range 15 to 40)
- Representative of 8 Maryland jurisdictions:

Montgomery (4)	Baltimore City (2)
Baltimore County (2)	Kent (1)
St. Mary's (1)	Prince George's (1)
Carroll (1)	Queen Anne's (1)
Anne Arundel (1)	Wicomico (1)

Jurisdiction (n)

Physician survey results

* Responses are grouped; no difference between dermatologist and rheumatologist responses

- 7 out of 15 physicians (47%) of physicians perform TST at their practice; all others refer patient to PMD
- Of those who perform TST at their practice, all perform:
  - 1-step TST
  - Test prior to TNF-alpha blocker medication initiation
- Only 50% repeat TST annually, as recommended
  - 1 physician evaluates on case-by-case basis

Results, cont'd

Procedure	# of physicians who perform procedure	# of physicians who refer out	# of physicians who do not complete procedure
TB sputum smear	1	12	2
TB sputum culture	1	12	2
Chest X-ray	4	11	0
Symptom evaluation*	7	8	1

* 1 physician did symptom evaluation at practice *and* referred patients for further evaluation

- The majority of physicians referred patients who required TB follow-up to outside health sources
- Patients were referred to:
  - their primary care physician
  - the local health department or hospital
  - infectious disease specialists & pulmonologists

Results, cont'd

- 5 out of 15 physicians (33%) were aware that TB treatment needed to be completed prior to TNF-alpha blocker medication initiation
- All were aware of sources for guidelines
- Most commonly used sources:

Source	# who used source
CDC recommendations	6
American Academy of Dermatology	4
American College of Rheumatology	3
Medication package insert/ medication representatives	4
Maryland TB Guidelines Handbook	3

Limitations of this project

- Possibility of missing cases:
  - Cases identified by anecdotal report and employee recall
  - Systematic review of *all* TB cases (2,856) not done
- Possibility of missing patient information:
  - Patients transferred to multiple health facilities; chart information incomplete in some cases
  - Inaccurate documentation in charts

Conclusions

- TNF-alpha blocker medications becoming more widely used; Number of TB cases in immigrant populations increasing
- TB screening will be important as more cases are expected
- Currently, majority of physicians are not following recommended screening procedures
- Difficult to place and read a skin test; new technology for TB screening via blood test (QuantiFERON TB-Gold) may improve compliance with TB screening guidelines

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