MAJURO

THE MARSHALL ISLANDS TB ELIMINATION EFFORT

TB SCREENING BRIEF REVIEW

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There are no conflicts of interest to declare.

RUSH UNIVERSITY MEDICAL CENTER

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Learning Objectives

At the conclusion of this course participants will be able to:

- Discuss the prognosis and mortality rate of untreated pulmonary TB
- Recall local, state, and national TB data trends; Define whole genome sequencing (WGS) and how it is used in TB epidemiologic and contact investigations.
- Describe steps needed for a mass TB screening; identify appropriate TB test for individual patients.
- Identify strategies to reduce or stop alcohol consumption among patients with TB
- Identify components of nurse care management, as it pertains to tuberculosis and discuss various approaches to challenging situations

To obtain credit you must:

- **Complete an electronic evaluation**
- **After completing the evaluation you can generate your certificate immediately.**

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POPULATION IN MARSHALL ISLANDS (2019)

Year	Population	% Male	% Female	Density (km²)	Population Rank	Growth Rate
2019	53,211	50.38%	49.63%	293.98	211	0.08%
2018	53,167	50.41%	49.61%	293.74	211	0.08%

http://worldpopulationreview.com/countries/marshall-islands-population/cities/

Name	Population
Majuro	25400
Ebaye	15000
Arno	2068
Jabor	1200
Wotje	880
Mili	854
Namdrik	814
Ebon	714
Kili	602
Likiep	482
Ailuk	451
Ujae	448
Aur	438
Utrik	409
Lae	319
Mejit	300
Wotho	160
Lib	115
Jabat	112
Rongelap	19

TB + LEPROSY FREE MAJURO: PRELIMINARY RESULTS

49th Union World Conference on Lung Health Oct 26, 2018

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BACKGROUND

- Republic of the Marshall Islands (RMI)
  - Pacific atoll nation
  - World's 8th highest TB incidence (488/100,000 WHO 2017)
  - Low prevalence of HIV, high prevalence of diabetes
  - No recent cases of DR-TB
- 2017 mass TB screening in Ebeye Island
  - Active TB rate of 846/100,000
  - Expanded local TB program capacity
- June 2018 – October 2018 Majuro Atoll
  - Mass TB screening (leprosy, diabetes) for population of 27,000
  - Mass treatment of latent TB
  - Increased support to local TB program

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METHODS: PROTOCOL

- Tuberculin skin test (aged ≥5), symptom screen, contact history and chest x-ray
  - If any abnormal, sputum was collected for GeneXpert
  - Children <10 received a TB-focused physical examination prior to consideration of chest x-ray
- Presumptive cases reviewed by an expert panel to confirm diagnosis
- After ruling out active TB, individuals eligible for LTBI treatment immediately commenced on short-course rifamycin-based regimen (predominantly 3HP)
  - Children aged <5 considered for latent treatment if they had a history TB exposure

Also:

- Leprosy screen for all participants
- Diabetes screen if latent or active TB

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DS: SCREENING

- Initial visit by screening teams to offer TST (80% done in homes, others at workplaces and screening sites)
- Participants transported to community sites by school bus to complete screening 48–72 hours later

At sites:

1. Registration using national hospital number
2. CHOWs, nurses, NPs delivering screening
3. Mobile XR with MD 'wet read'
4. Induced sputum collection if indicated
5. **Counsel, prescribe, dispense and directly observe first dose**

- Advance teams visited weros (traditional landholder areas) for permission and sensitization with aoleps (traditional landholders beginning one year prior to screening)
- Community kick-off event with parade, speeches and media coverage
- Children's health fair, community incentives, outreach to schools, agencies and businesses
- Awareness raising by radio, TV and newspaper throughout screening period
- Rotating teams of 15 volunteers from US NTCA provide support and supervision

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METHODS: MASS PREVENTION

- 100 new community health outreach workers (CHOWs) contracted and paid hourly minimum wage by GRMI
- One week training program
- Production line for packing and distributing 70,000+ doses
- Adult and pediatric weight bands for each regimen
  - All aged ≥2 eligible for 3HP
- Teams of DOPT workers providing patient-centered preventative treatment
- Standardized procedures and tools for documentation of DOPT and communication of potential adverse reactions to nursing and medical staff

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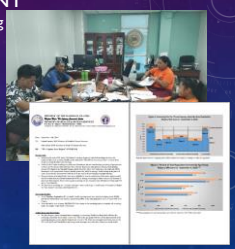
METHODS: DATA MANAGEMENT

- Clinical information derived from the screening process was collected on standardized paper forms (later data entry)
- Daily screening throughput was recorded by site supervisors and reviewed at 3x weekly hotwash meeting
- Weekly situation report provided to GRMI, stakeholders and public



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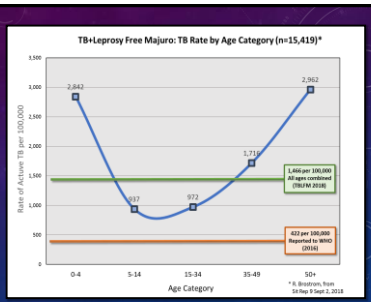
PRELIMINARY RESULTS: ACTIVE CASE FINDING

- Screening is currently ongoing
- As of September 2, 56% of the population had completed TB screening



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PRELIMINARY RESULTS: MASS LTBI TREATMENT

	Number completed screening	Latent TB diagnosis (TST ≥10mm)	Recommended for latent TB treatment	Started latent TB treatment	Leprosy (new cases)	Diabetes (all cases)	Diabetes (new cases)
Paediatric (0-14)	5361	321	469	415	12	-	-
Adult (15+)	10,058	3,491	3,132	2,976	33	753	318
Total	15,419	3,812	3,601	3,393	45	753	318
Comment		25% of those screened had TST ≥10mm	6% not medically eligible for latent TB treatment	94% of eligible patients started latent TB treatment	Leprosy rate 29.2 per 10,000	23% of those screened for diabetes had HbA1c ≥6.5	10% of those screened for diabetes had a new diagnosis

DISCUSSION: MAJURO AS A MODEL?

- Unique features
  - Island location: likely less mobile population, travel mostly to low-incidence area
  - Extensive community support and respect for local authority (traditional and official)
  - Well-funded with local funds (90% GRMI funding)
  - Availability of expert volunteers from the US National TB Controllers Association
- Transferable features
  - Focus on capacity-building for local TB program
  - GDF-sourced prevention medications
  - WHO 3b model (Systematic Screening for Active Tuberculosis)
  - Expanded paediatric diagnosis (LTBI/active) and treatment (3HP/3HR)
  - Use of clinical case conference to maximize benefit of XR-based screening

DISCUSSION: LASTING IMPACT

- How best to sustain an anticipated fall in TB rates in Majuro?
  - Culture of "see TB, treat TB" amongst clinicians
  - Scale up access to LTBI treatment in routine service delivery
  - Expand active case finding to build on community engagement
- Should mass screening and treatment be repeated after a number of years? If so, how many?

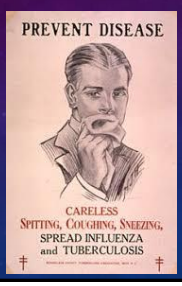
CONCLUSION

- With strong national commitment and international technical support, it is possible to bring organized mass TB-prevention activities to large active case finding campaigns in high-burden countries
- Initial data indicate a very high rate of acceptance of latent TB treatment
- The added effect of mass TB prevention to an active case finding project could be quite significant but will likely take several years to assess

ACKNOWLEDGEMENTS

- RMI MOH & GRMI
- WHO
- TB REACH
- US NTCA
- CDC
- GDF
- US DOI
- Hawaii DOH
- Zero TB Initiative
- Pacific Island TB Controllers Association
- Pacific Island Health Officers Association

TB SCREENING, BRIEF REVIEW

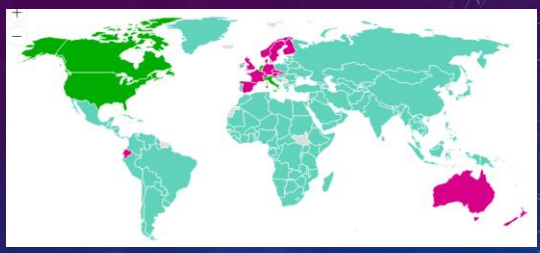


THE UN SUSTAINABLE DEVELOPMENT GOALS INCLUDE ENDING TB EPIDEMICS BY 2030

- The WHO aim is to reduce the number of TB deaths by 95% by 2035, one strategy is TB vaccination.
- BCG vaccination, at birth or as soon as possible after birth.
- The use of BCG infant vaccination could prevent over 115 000 TB deaths per birth cohort in the first 15 years of life.
- BCG vaccines are among the oldest vaccines and were first used in humans in 1921.
- BCG is a live attenuated bacterial vaccine derived from M. bovis that was originally isolated in 1902 from a tuberculous cow.
- BCG vaccines are administered by intradermal injection, usually causes a scar due to local inflammatory processes, however scar is not a marker for protection and approximately 10% of recipients do not develop a scar.
- RCTs found high protection against PTB from BCG vaccination of neonates (82% protection) , and moderate protection of school-age TST-negative children (64% protective)
- Protection after infant BCG vaccination could last for up to 15 years. No evidence of an effect of BCG revaccination in adolescents and adults after primary BCG vaccination

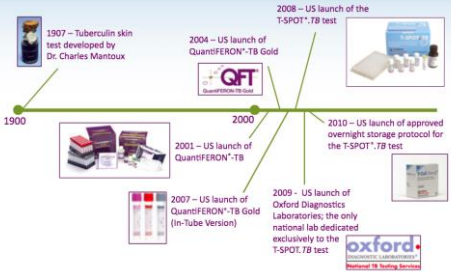
https://apps.who.int/iris/bitstream/handle/10665/260306/WER9308.pdf;jsessionid=D3F1801091611CB51B5B67FFBF75D5C3?

DATABASE OF GLOBAL BCG VACCINATION POLICIES AND PRACTICES 2017



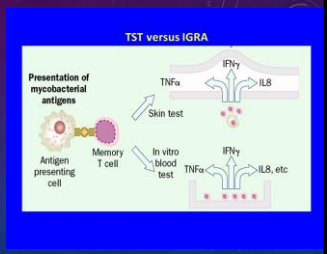
http://www.bcgatlas.org/index.php

Timeline of Advancements in TB Screening



LTBI/TB TESTING

- There is no gold standard test for LTBI
- Either tuberculin skin testing (TST) or an IFN-γ release assay (IGRA) can be used to test for LTBI
- These tests are not requirements for initiating TB preventive treatment in HIV-infected patients or in household contacts aged



https://apps.who.int/iris/bitstream/handle/10665/260306/WER9308.pdf;jsessionid=D3F1801091611CB51B5B67FFBF75D5C3?

Tuberculin Skin Test (TST) vs Interferon Gamma Release Assays (IGRAs)

Tuberculin Skin Test	IGRAs
2 visits required (minimum)	1 visit required
Method: injection into skin	Method: blood draw
Results affected by BCG	Results not affected by BCG
Results in 48–72 hours	Next-day results
Subjective results	Objective results

Tuberculin Skin Test vs IGRAs

Tuberculin Skin Test	IGRAs
2 visits required (min)	1 visit required
Method: injection into skin	Method: blood draw
Results affected by BCG	Results not affected by BCG
Results in 48-72 hours	Next day result
Subjective results	Objective results

http://www.uemedicine.com/agencies/department-of-veterans-affairs/more-accurate-tb-blood-tests-replacing-old-skin-testing-at-va/

T-CELL–BASED ASSAYS FOR THE DIAGNOSIS OF LATENT TUBERCULOSIS INFECTION: AN UPDATE

MADHUKAR PAL, MD, PHD, ALICIA ZWERLING, MSC, AND, DICK MENZES, MD, MSC

	Sensitivity*
TST	0.77 (0.71-0.82)
QFT-Gold	0.78 (0.73-0.82)
QFT-IT	0.70 (0.63-0.78)
T-SPOT	0.90 (0.86-0.93)

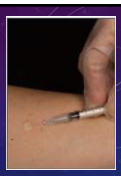
*(95%CI)

	Specificity*	
	BCG	non-BCG
TST	0.59	0.97
QFT-G & IT	0.96	0.99
T-SPOT	0.93	0.93

Ann Intern Med. 2008 August 5; 149: 177-184

TST (PPD)

- intradermal injection of purified protein derivative (PPD)
- Skin-test positivity is a marker of delayed hypersensitivity to antigens of M. tuberculosis and related mycobacteria
- Test specificity is affected by previous exposure to BCG vaccines, and environmental mycobacteria
- Test sensitivity decreases with age and impaired cellular immunity
- Interpretation of the test results depends on the epidemiological situation, and on the age and general health of the individual
- Neither IGRA nor TST accurately predicts the risk of developing active TB.



https://apps.who.int/iris/bitstream/handle/10665/260306/WER9308.pdf;jsessionid=D3F180109161 1CB5185867FFBF75D5C3?

IGRA

- IGRA is a testing based on the principle that T cells primed for M. tuberculosis antigens will respond to re-stimulation by releasing IFN-γ.
- IGRA requires fresh blood samples, and sophisticated laboratory equipment.
- IGRA has higher specificity and less cross-reactivity with the BCG vaccine than TST
- Neither IGRA nor TST predicts the risk of developing active TB. These tests are not appropriate for diagnosis of active TB

https://apps.who.int/iris/bitstream/handle/10665/260306/WER9308.pdf;jsessionid=D3F180109161 1CB5185867FFBF75D5C3?

	QFT-GIT	T-Spot
Initial Process	Process whole blood within 16 hours	Process peripheral blood mononuclear cells (PBMCs) within 8 hours, or if T-Cell Xtend® is used, within 30 hours
***M. tuberculosis* Antigen**	Single mixture of synthetic peptides representing ESAT-6, CFP-10 & TB7.7.	Separate mixtures of synthetic peptides representing ESAT-6 & CFP-10
Measurement	IFN-g concentration	Number of IFN-g producing cells (spots)
Possible Results	Positive, negative, indeterminate	Positive, negative, indeterminate, borderline

https://www.cdc.gov/tb/publications/factsheets/testing/igra.htm

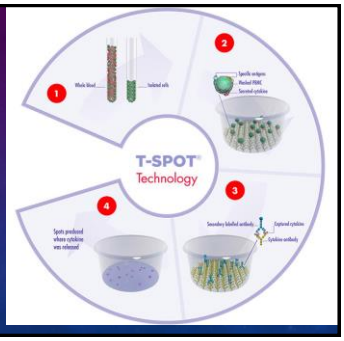
T-Spot test

1- A blood is collected from which mononuclear cells are isolated.

2- The mononuclear cells are added into plates and are stimulated with TB antigens. Cells responding to these antigens release a cytokine.

3- Cytokine antibodies are used to capture the cytokine released by the cells. A secondary labelled antibody is added and binds to the captured cytokine.

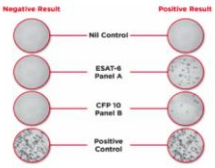
4- A detection reagent is added and reacts with the secondary labelled antibody. This reaction produces spots. Spots are then enumerated.



http://www.oxfordimmunotec.com/international/products-services/t-spot-tb-test/how-it-works/

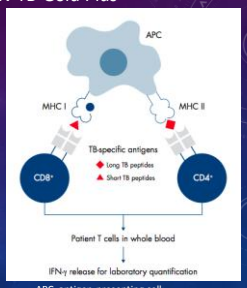
Interpreting Tuberculosis Test Results with the T-SPOT.*TB* test:

- Interferon-gamma is captured and presented as spots from T cells sensitized to TB infection
- Results are interpreted by subtracting the spot count in the negative (NIL) control from the spot count in Panels A and B
  - Positive > 8 spots
  - Negative < 4 spots
  - Borderline 5, 6, or 7 spots
  - Invalid



http://www.tspot.com/about-the-test/interpretation-t-spot-tb-results/

QuantiFERON-TB Gold Plus



APC, antigen-presenting cell;
MHC, major histocompatibility complex.

https://www.quantiferon.com/us/products/quantiferon-tb-gold-plus-us/provider-resources/why_qft-plus-providers/

QuantiFERON-TB Gold Plus

Results of the QFT-Plus assay are interpreted objectively using QuantiFERON-TB Gold Plus analysis software.

QFT-Plus Positive	• ***M. tuberculosis* infection is likely** • Nil ≤8.0; and • TB1 and/or TB2 minus Nil ≥0.35 and ≥25% of Nil
QFT-Plus Negative	• ***M. tuberculosis* infection is NOT likely** • Nil ≤8.0, Mitogen minus Nil ≥0.5; and • TB1 and TB2 minus Nil <0.35 or ≥0.35 and <25% of Nil
QFT-Plus Indeterminate	• **Likelihood of *M. tuberculosis* infection cannot be determined** • Nil >8.0 • Nil ≤8.0 and TB1 and TB2 <0.35 or ≥0.35 and <25% of Nil and Mitogen minus Nil <0.5

https://www.quantiferon.com/us/products/quantiferon-tb-gold-plus-us/provider-resources/why_qft-plus-providers/

CHOOSING BETWEEN TST AND IGRA

There are two major tests for identification of LTBI: TST and the interferon-gamma release assay (IGRA) blood test

The IGRA is especially useful for patients who are unlikely to return to have the TST read, and for patients with a history of BCG vaccination (administered in most TB-endemic countries)

The TST is an acceptable alternative to IGRA, especially in situations where IGRA is not available or is too costly (even though it is less specific than the IGRA).

For individuals with high risk of progression to active disease, either the IGRA or TST may be used; in such cases, the higher false-positive rate of the TST is acceptable. A dual testing strategy (perform one test and, if negative, perform the other) may be used, a positive result from either test would be considered positive.

Clin Infect Dis. 2017 Jan 15;64(2):111-115. doi: 10.1093/cid/ciw778.
https://www.ncbi.nlm.nih.gov/pubmed/28052967

CHOOSING BETWEEN TST AND IGRA

When an IGRA test is used to confirm a TST result, it should be drawn within three days of TST placement (ie, at the time of the TST reading).

Because prior TST may boost subsequent IGRA results; this phenomenon is not fully understood. The effect occurs in the first few days following TST and wanes after three months.

For individuals with nontuberculous m. (NTM) infection, the IGRA is preferred over TST. Exceptions include *M. kansasii*, *M. szulgai*, and *M. marinum*, which affect both the TST and IGRA.

Low-risk individuals tested before exposure, TST is recommended. if the TST is positive, then an IGRA may be useful to confirm a positive TST result to enhance specificity.

Routine dual testing with both TST and IGRA is not warranted

Clin Infect Dis. 2017 Jan 15;64(2):111-115. doi: 10.1093/cid/ciw778.
https://www.ncbi.nlm.nih.gov/pubmed/28052967

Thank you

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