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Global Tuberculosis
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NEW JERSEY MEDICAL SCHOOL

The Tuberculosis Taboo

Keynote Address

Pacific Islands Tuberculosis Controllers Association

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Disclosures

- Nothing relevant to declare.

Learning Objectives

- Understand the role of treating TB infection in WHO's new End TB Strategy.
- Recognize how, even though long standing global WHO policy, the act of treating TB infection is usually ignored and forgotten.
- Understand how treating TB infection before it progresses to TB disease prevents drug sensitive as well as drug resistant TB.

A Bit of Relevant Personal History -1

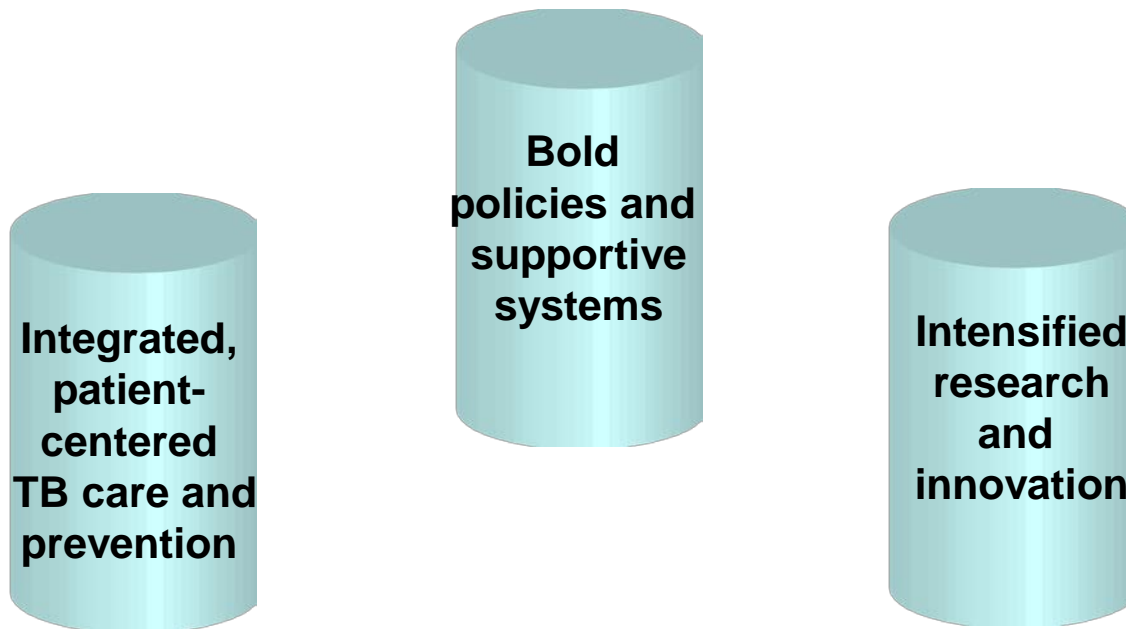
- Seminar in Infectious Diseases - Muhlenberg Hospital, NJ, March 26, 1980
- Invited panel with Donald Armstrong, Chief, Infectious Diseases, Memorial Sloan Kettering Hospital (Infectious Diseases Icon), Lee Reichman (new kid in academia), Others
- Armstrong presented case after case of disseminated tuberculosis in his patients on cancer chemotherapy
- Reichman shyly asked “If you have so many cases of TB in these obviously immunosuppressed patients, why don’t you give INH before treatment?”
- Armstrong, disdainfully and dismissingly looked at the questioner and emphatically answered: “We don’t do that”



World Health
Organization

END TB

TARGETS: 95% reduction of deaths and 90% reduction in incidence by 2035

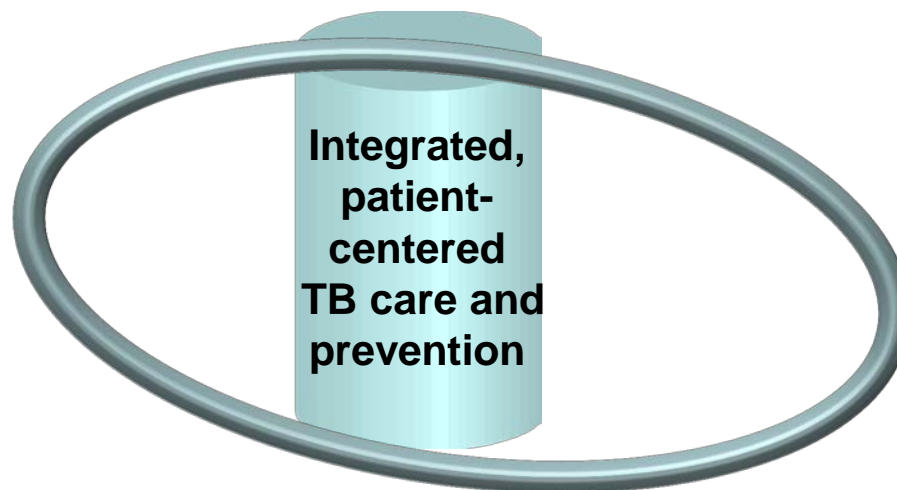




Early diagnosis of TB including universal drug-susceptibility testing, and systematic screening of contacts and high-risk groups **1**

Preventive treatment of persons at high risk and vaccination of children **4**

2 Treatment of all people with TB including drug-resistant TB, and patient support



3 Collaborative TB/HIV activities, and management of co-morbidities

- The management of LTBI among high risk groups is a key component of the World Health Organization's new End TB Strategy. It is necessary to end the global TB epidemic and eliminate TB.
- But this effective and appropriate modality is usually ignored or forgotten, rather than promoted and enhanced
- It is almost like the TB community considers it a *taboo*

Definitions - 1

Taboo

1. Proscribed by society as improper or unacceptable;
synonyms: prohibited, banned, forbidden, proscribed
2. Prohibited or excluded from use or practice

Nomenclature Modifications

- Ideal nomenclature should be simple and accurate enough to be scientifically descriptive, and easily understood by providers and patients alike
- *Treatment of latent TB infection* rather than *preventive therapy*, *chemoprophylaxis* or *IPT* promotes somewhat greater understanding of the concept
- *But, latent* is confusing and usually not understood by, or relevant to patients; certainly does not suggest immediacy or urgency

Bottom Line:

- We are **TREATING TB INFECTION** (TTI), so why not call it that

Treating TB Infection: History -1

- The first population based study, starting in 1957, was George Comstock's USPHS randomized controlled trial in household contacts in Bethel, Alaska (described in the report as an "undeveloped area") TB incidence: 578/100,000
- Resulted in a 69% reduction after one year and a community-wide 30% reduction in TB incidence

Treating TB Infection: History -2

- Marked decline in Bethel death rate (from 650 to 0 over 30 years); and incidence rate (from 1,854 to 141 over 28 years)
- The marked reduction in infection and death rates were due to: intensive case finding, hospitalization, ambulatory treatment programs, as well as the fact that much of the Bethel population received isoniazid in the TTI studies

Treating TB Infection: History -3

- The concept of a public health orientated TTI intervention faded following the 1960s
- Difficult logistical requirements and the advent and widespread promotion of DOTS made TTI only secondary
- The recent realization that TB elimination requires additional control measures, has revived the idea of a programmatic role of TTI
- ERS's *European Forum for TB Innovation* (2012) reinvigorated promotion of TTI

Treating TB Infection: History -4

- In response to the alarming occurrence of MDR-TB and XDR-TB in the WHO European Region, a *Consolidated Action Plan* was developed for all 53 Member States, recognizing that **TTI may be relevant to reduce the burden of disease**, in addition to case finding and treatment

However,

- Despite its inclusion in the *Action Plan* and country guidelines, TTI is still largely not implemented, almost like a *taboo*

Treating TB Infection: History -5

- In India, China, Russia and South Africa, TTI is a policy for children <5 and PLHIV, but is rarely implemented or reported
- NTPs often lack funding for CXR to exclude active TB, or to procure tuberculin; and fear poor adherence, side-effects, and development of resistance
- Worldwide shortages of Tuberculin, Isoniazid or other drugs may impact TTI programs

Consequently,

- Even contacts at highest risk of developing TB may not be managed adequately, TTI, thus, practically remaining a *taboo*

TB in Contacts

- Since TB is *always* spread person-to-person by the airborne route, investigating contacts is a very productive way to find new infections and cases
- An initially *paucibacillary* infection can be treated *and eliminated* far more easily when diagnosed, rather than later when it progresses to clinical TB

TB in Contacts - Risk of Active TB following infection

- 613 Australian close contacts, 2005-2013
- 67 (10.9%) active TB; 14.5% when excluding death, migration, preventive therapy
- Most risk is within *first 5 months* after infection
- Greatest risk, 56% <5 year age; 28% age 5-14
- Conclusions:
 - Risk is several fold higher than previous estimates; particularly, immediately following infection, and in children

TB in Contacts in US - 2012

- Average of 11 contacts of each TB case (21 contacts for the most contagious TB patients) are infected
- Approximately 1% of contacts already have TB disease at the time of examination

Principles of TBI treatment

- Public health approach with individual benefit which should outweigh any individual risk
- Complement to active TB case finding and treatment activities

Inducing drug resistance and ruling out active TB

- There is no significant risk of inducing drug resistance

However, to be absolutely sure:

- Always ask about symptoms of TB
- Do chest radiography
- Individuals with TB symptoms or any radiological abnormality should be investigated further for active TB and other conditions before treating for TBI

WHO new recommendations on risk groups for TTI beyond PLHIV and children

Risk population groups	Strength of recommendation
<ul style="list-style-type: none"> • People living with HIV • Adult and child PTB contacts • Patients initiating anti-TNF treatment • Patients receiving dialysis • Patients preparing for transplantation 	<p>Strong: systematic testing and treatment should be performed</p>
<ul style="list-style-type: none"> • Prisoners • Health workers • Immigrants from high burden countries • Homeless persons • Illicit drug user 	<p>Conditional: Systematic testing and treatment should be considered</p>
<ul style="list-style-type: none"> • Patients with Diabetes • People with harmful alcohol use • Tobacco smokers • Under-weight people 	<p>Conditional: systematic testing and treatment is not recommended unless they belong in the upper two groups</p>

US Preventive Services Task Force

- Supports CDC guidance to test for tuberculosis infection in populations that are at increased risk
 - People born in or who frequently travel to countries where TB disease is common
 - People who currently, or previously, live in large group settings
- CDC also recommends testing for TB infection among healthcare workers, contacts of people with confirmed or suspected TB disease, and as part of disease management for people with certain conditions, such as HIV and diabetes, or as indicated prior to the use of certain medications

September 8, 2016

Diagnosis of TBI

- Tuberculin Skin Test
- Interferon Gamma Release Assays (IGRA)

Diagnosis of TBI

- Two tests shift the investigation from the skin to the blood - *QFT Gold In Tube*[®] & *T Spot TB*[®]
- Advantages:
 - Allows for introduction of new levels of accuracy and controls
 - Allows for one visit
 - Allows for the use of antigens that cannot be injected into the skin
 - No boosting
 - Not affected by prior BCG vaccination

Diagnosis of TBI

Quality Control - TST vs. IGRA

- Next time you do or order a TST, ask yourself “when was the last time this test was quality controlled?”
- When was the last time you, yourself, or the venerable old TB nurse who has been doing TST for 40 years, or anyone else, was evaluated while doing the test?
- IGRAs move the diagnosis of TBI from the uncontrolled and unmonitored physician or nurse, to the laboratory which is quality controlled excessively

But,

There is no need to diagnose TBI unless
one is going to treat TBI

Treatment Regimens for TB Infection

Drugs	Months of Duration	Interval	Minimum Doses
INH	9	Daily	270
		2x wkly**	72
INH	6	Daily	180
		2x wkly**	58
RIF	4	Daily	120
INH-RPT	3	Weekly**	12
** Intermittent treatment			

Treatment of TB Infection – The 3HP Regimen

- 3 months Rifapentine and Isoniazid (12 weekly DOT doses) *is as good as* 9 months Isoniazid (270 daily doses) (TBTC Study 26, NEJM 2011)
- Removing required DOT does not have major effect on adherence results (TBTC Study 33)
- Potential for real impact of a 12-dose regimen to treat TBI

USPHS Study 33: Treatment completion by treatment arm: DOT v SAT v eSAT -1

	DOT	SAT	eSAT
Treatment completion % (N)	85.4 (261)	77.9 (262)	76.7 (249)

- CROI 2015, Update courtesy: Bob Belknap, Andrey Borisov, Ruth Moro, May 2016

USPHS Study 33: Treatment completion by treatment arm: DOT v SAT v eSAT -2

Compare to 9H completion rates of <50%

- NYC Health Department, 2016

Innovation is also inspiring activism in TB prevention: Priftin® Rifapentine

- Approved for TB infection (FDA, 2014)
- Listed on WHO Model List of Essential Medicines for Adults & Children (2015)
- Included in WHO LTBI Guidelines (2015)
- Listed in the Global Drug Facility catalogue (2016)
- Affordable price negotiated in US (2014)
- Subject of ongoing research (FDC and pediatric formulation development)

Rifapentine: Current status

- Currently registered for active and latent TB infection only in the United States
- Sanofi has started filing for registration to treat latent TB infection throughout Asia
- In Europe, the company's filing with EMA is complicated by the EMA's requirement for studies in the 0-2 age group
- Sanofi is developing FDCs: adults (P300 H300), dispersible for children (P150 H150) and dispersible rifapentine alone (P100) which will all have to be registered separately

Courtesy: Mike Frick, Treatment Action Group:
Personal Communication, 2016

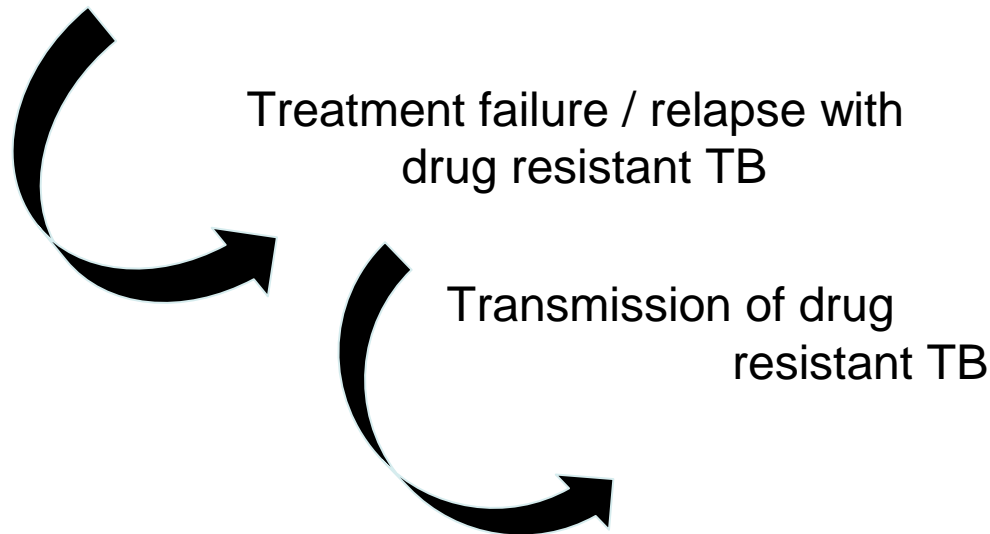
Updated: Sanofi: Personal Communication, March 2017

Now,

Lets quickly switch our attention
to contacts of MDR-TB and XDR-TB

Why Do We Have Drug Resistance?

- Inadequate treatment
 - Incorrect regimen (lack of drugs or knowledge)
 - Poor adherence



- It is far easier to prevent TB in an individual infected without disease than to treat a full blown case of TB or drug resistant TB

In other words,

- MDRTB & XDRTB do not occur in nature
- Every case of MDR & XDR TB started off as a case of drug sensitive TB that was provider mismanaged or patient (self) mismanaged
- Treating all contacts for TB infection prevents TB and downstream MDR or XDR TB

A Bit of Relevant Personal History -2

- In December 2011, I had the opportunity to visit Estonia to observe their program and meet several MDR-TB patients
- I found a severe MDR-TB problem caused by previously poor programs
- But, I also found a dedicated staff, good programs and effective implementation of the WHO Stop TB Strategy
- This paradox was explained by the fact that each of the MDR-TB patients I met had been infected by a *known MDR-TB patient* who did indeed receive appropriate treatment but *after infecting the contact with MDR-TB*

A Bit of Relevant Personal History -2 cont'd

- The tragedy is that the transmission of MDR-TB to close contacts occurs *prior to diagnosis in the source case*
- It is past time to consider the *heresy* of acting differently when the infected MDR contact has been identified, treat him/her for paucibacillary MDR-TB infection concurrently with the source patient's regimen for MDR-TB disease rather than waiting for the contact to develop more difficult to treat, transmissible MDR-TB later

MDR Contacts in Children

- Conservative estimates suggest that in high-burden regions there are at least two child contacts who are less than 5 years of age or who are infected with HIV per MDR-TB source case
- Thus, more than 1 million vulnerable contacts could be considered for TBI treatment each year
- In nearly a quarter of households with a case of MDR or XDR-TB, a contact will develop TB disease within 4 years of identification
- Prevention of progression to MDR-TB disease with TTI could be a practical and cost-effective solution both for individuals and from the public health perspective

MDR Contacts in Children - 2

- It is estimated that globally, over 67 million children are infected with TB and therefore at risk of developing disease in the future;
 - 5 million with INH resistance; 2 million with MDR; 100,000 with XDR
- Every year 25,000 children develop MDR-TB disease and 1,200 XDR-TB disease

But,

published guidelines don't yet accept TTI
of MDR-TB case contacts

ECDC Guidance (2012)

- The systematic review concludes that *it is not possible with the available evidence to support or reject preventive therapy* (for contacts of MDR-TB and XDR-TB)
- More research and particularly clinical trials are warranted before any recommendations in favor of (or against) preventive therapy can be made

ECDC Guidance: Management of contacts of MDR-TB and XDR-TB patients (2012) Emphasis mine

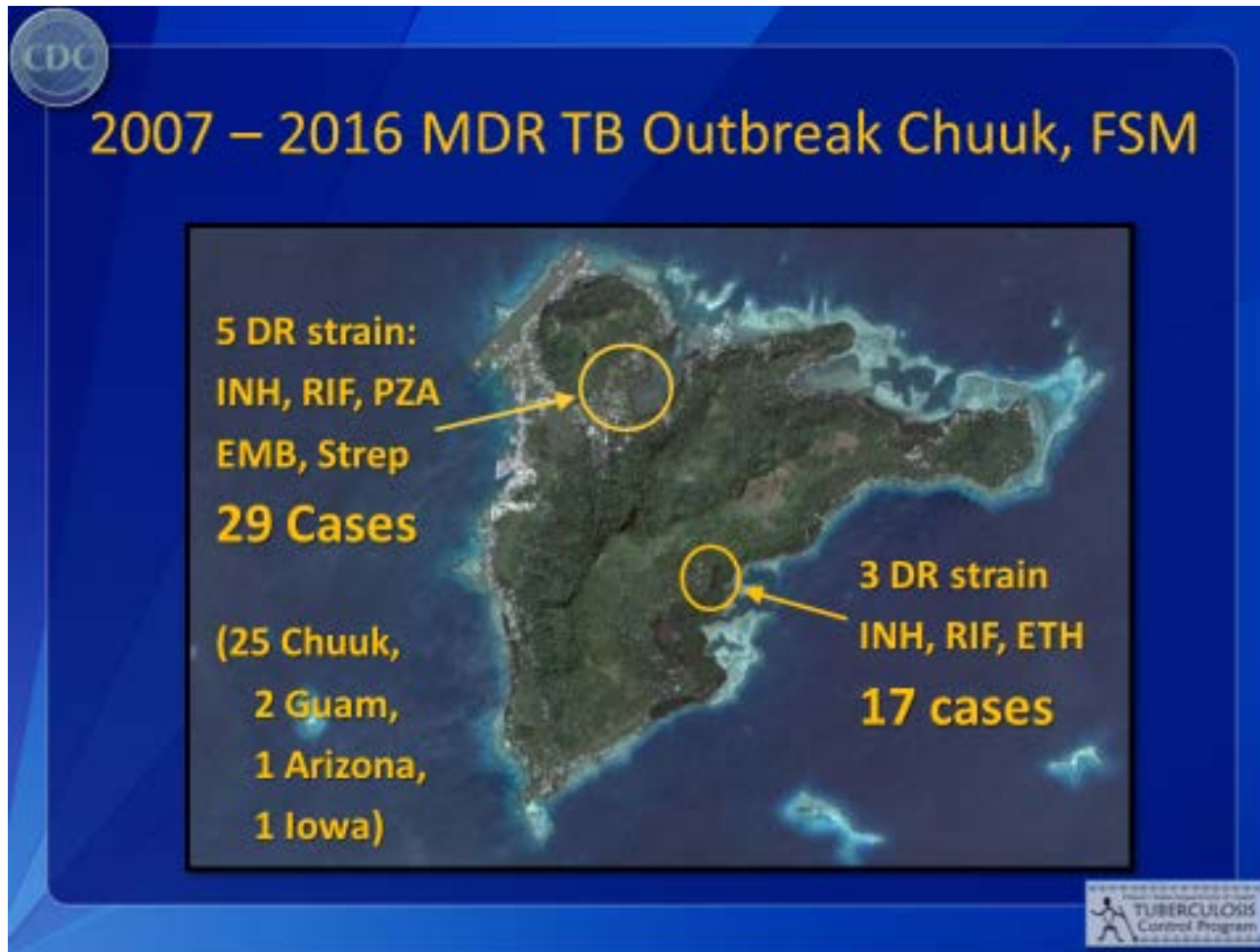
WHO: Treatment of MDR-TB contacts (2015)

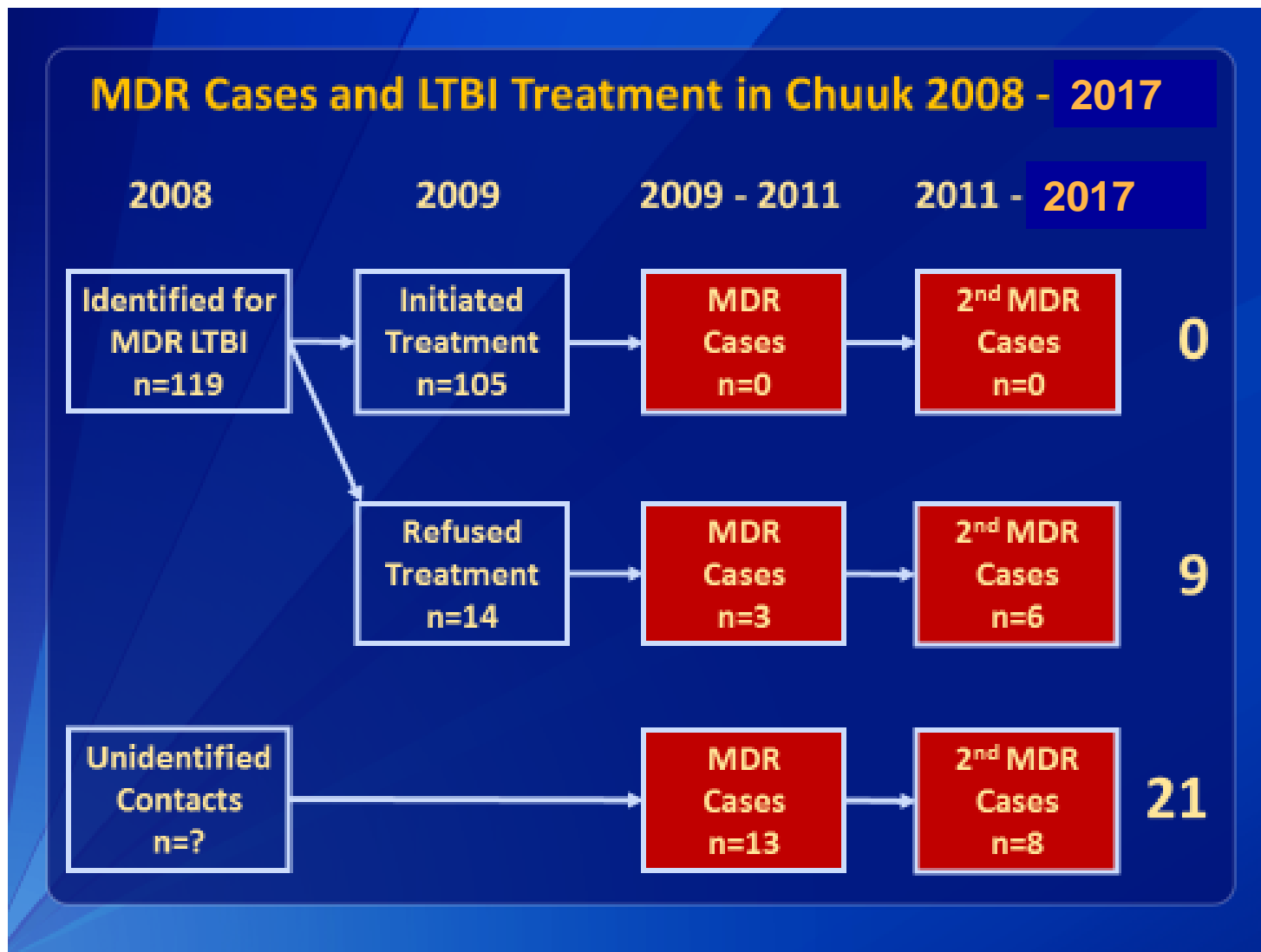
- *NO Recommendation*
- Panel agreed on strict clinical observation and “close monitoring for the development of active TB disease for at least two years is preferred over the provision of preventive treatment for contacts of MDR-TB cases”

WHO Guidelines on the Management of LTBI, 2015
Emphasis mine

I respectfully disagree...

because, even with supreme effort, including global programmatic management of drug resistant TB, the overall global MDR-TB/XDR-TB cure rate remains less than 50%; which is *no better than TB cure in the pre-drug era!*





-S Bamrah, *et al*, Treatment for LTBI in Contacts to MDRTB Patients, Federated States of Micronesia, 2009-2012
IJTL 2014, 18:912-918

Updated: Richard Brostrom, MD, July 2017

Statistical Significance

- Comparing MDRTB in identified contacts who had any treatment vs. identified contacts who refused treatment
- Difference was very highly significant $p=.0013$


- It *is* time to start identifying well defined high risk contacts of MDR-TB patients and to treat them with appropriate fluoroquinolone containing preventive therapy
- After all, MDR-TB treatment would be hard pressed to be any *less* successful


Modified from: Reichman LB, Schaaf HS, Pontali E, Migliori GB: A New Paradigm for Multi-drug Resistant Tuberculosis, *Int J Tuberc Lung Dis* (2014) 18:284


Thus, WHO needs to update its priority recommendations


FIVE PRIORITY ACTIONS TO ADDRESS THE GLOBAL MDR-TB CRISIS


Six

- 

1 Prevent the development of drug resistance through high quality treatment of drug-susceptible TB
- 

2 Expand rapid testing and detection of drug-resistant TB cases
- 

3 Provide immediate access to effective treatment and proper care
- 

4 Prevent transmission through infection control
- 

5 Increase political commitment with financing

6 - Prevent regular TB which then can't be mismanaged into **DR-TB** and treat contacts of MDR-TB with Fluroquinoline containing preventive regimen

- So there truly are compelling reasons for adopting and promoting TTI
- But how do we stop treating TB infection from being considered a taboo?

A Bit of Relevant Personal History -3

- One of the major things that I've learned in over 50 years of practice dealing with tuberculosis patients, is that in the overwhelming majority of cases, I can convince a patient to take, or not to take, a course of treatment. If I think it is important, I can usually get the patient to think it is important
- In other words, a practitioner must truly believe in a strategy, in order to promote a strategy

Bottom Line

- A case of TB prevented, is a patient who won't get sick, won't infect anyone, won't be absent from work or school and in whom *physician mismanagement or patient non-adherence cannot cause MDR-TB*
- The first pillar of WHO's new End TB Strategy includes treating TB infection in high risk infected persons
- *Appropriate treatment of TB infection in drug sensitive patients prevents active TB and consequently prevents MDR-TB and XDR-TB*
- Controlled clinical trial data regarding treatment of MDR-TB infected contacts is unfortunately still lacking, but clinical experience is accumulating rapidly; such treatment, extremely likely, prevents new drug resistant patients

Bottom Line - 2

- It is time to accept accumulating compelling data, and adopt and promote treatment of MDR-TB infected contacts; especially to prevent a disease with a less than 50% cure rate
- So obviously, treatment of TB Infection in drug sensitive as well as drug resistant contacts should no longer be considered *the Tuberculosis Taboo*

So if it is no longer considered a taboo,
what can we call it?

Bottom Line -3

- We now have, within our grasp, a new means for effectively diagnosing and treating TB infection with IGRAs and the 12-dose 3HP regimen
- Accurate one step diagnosis and 12 doses of non toxic medication with a 78-85% adherence rate to treat TB infection, thereby preventing not only TB and secondary cases, but also downstream MDR-TB, seems to me, to be the true “Holy Grail”, and certainly the polar opposite of “taboo”
- We just have to avail ourselves of it and enthusiastically promote and use it

Definitions - 2

Holy Grail

1. The bowl used by Jesus at the Last Supper allegedly brought to Britain by Joseph of Arimatheu, where it became the quest of many knights
2. A thing that is being earnestly pursued and sought after

Conclusions

- Joint use of IGRAs and 3HP are truly the Holy Grail in TB control
- The sooner these modalities are widely adopted and promoted, the sooner TB and even MDR-TB will be controlled and eliminated

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