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18th Annual Conference of the Union-North America Region:

Multi Drug Resistant TB:
Management of LTBI Caused by MDR/XDR Isolates:
THE CONS OF SUSCEPTIBITY DRIVEN TREATMENT

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Background

- Latent TB Infection Treatment for contacts of drug susceptible tuberculosis (TB) patients is highly effective in both non human immunodeficiency virus (HIV) infected and HIV-infected children and persons.
- The evidence for this is mainly for isoniazid (INH) preventive treatment in drug-susceptible TB.
  - Based on multiple well designed trials over the last 50 years including Cochrane Systematic reviews that confirmed the benefits[1-3]

[1] Smieja et. al Cochrane Database of Systematic Reviews 2000 (2):CD001363
[2]. Gray et al Cochrane Database of Systematic Reviews 2009(1):CD006418
[3]. Akolo et al Cochrane Database of Systematic Reviews 2010 (1):CD000171

Background

- Full implementation of LTBI treatment could potentially reduce the burden of TB disease in a community by 31% to 59%.[1]
- Treatment of LTBI may reduce morbidity and mortality in high-risk populations, including people with HIV and children.[2]
- It is included in many guidelines for TB control (eg the Centers for Disease Control and Prevention (CDC)/American Thoracic Society (ATS), and the UK's National Institute for Health and Clinical Excellence (NICE) and European Centers for Disease Control)

[1]Toman K. Questions and answers. WHO 2004.
[2] Mohle-Boetani et al JAMA 2002; 287:1040-1042

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Background

- The WHO reports in 2012, an estimated 450,000 people developed MDR-TB and there were an estimated 170,000 deaths from MDR-TB
  - 3.6% of newly diagnosed and 20% of previously treated patients are MDR
  - 9.6% of MDR-TB cases are XDR-TB
  - Only 48% of 2010 cohort of MDR-TB was successfully treated

WHO Global TB Report 2013

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Background

- Prevention may be especially important for MDR-TB contacts, given the challenges associated with diagnosis, treatment and complications associated with MDR-TB disease[1]

1 Padayatchi et al Pediatr Infect Dis J 2006;23:147-50

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Background

- Data from TB contact investigations in the United States indicate that on average 5–15 relatives, friends and/or associates (including children and people with HIV) are evaluated for each TB patient, of whom 20–30% are infected with TB[1-4]
- Three studies in South Africa found that 5–12% of child contacts of patients with MDR-TB had TB disease and 51–53% had LTBI.[5-7]
- Another study in Peru followed 945 close contacts of MDR-TB for 5 years and found 72 (8%) cases.[8]

[1] CDC Guidelines for investigation of contacts of TB ptsMMWR;54:1-47
[2] Jereb et al 1999 IJTLD 2003;7(Supp 3):S384-90
[3] Sprinson et al IJTLD 2003;7 (Supp3):S363-368
[4] Webb et al IJTLD 2003;7 (Supp3):S353-357
[5] Schaaf et al Pediatrics 2002;109:765-771
[6] Schaaf et al Ped Inf Dis J 2000;19:695-699
[7] Schaaf et al Ped Inf Dis J 1999;18:494-500
[8] Bayona et al IJTLD 2003;7 (Supp3):S501-509

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Contact Investigations for MDR

- In contrast to the United States, where contact tracing and LTBI testing and treatment are an important priority for TB control programs, and where substantial resources are invested in contact tracing, 5–15 contacts are typically evaluated per case.
- Recent study by Cain et al found in a survey of Global TB programs, only 0.6 contacts per MDR case was being identified, which they felt suggested limited priority is given to MDR-TB prevention strategy.[1]

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[1]Cain et al IJTLD 14(3):269-274

Contact Investigations for MDR

- The reason most commonly cited for not treating contacts of MDR-TB for LTBI in their study was lack of policy or guidelines, and lack of evidence to support such guidelines, along with the low likelihood that treatment with standard drugs for LTBI would be effective

Evidence for MDR LTBI Treatment

- Fraser et al in 2006[1] published a systematic review of treatment of LTBI in persons at risk for MDR-TB
- Screened 907 potential references through 2004 of which 32 were full text publications of which only 2 met inclusion criteria of having included patients at risk for MDR, and was a comparative study in which LTBI treatment was provided

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Fraser et al IJTLD 10(1):19-23

Fraser et al 2006

- Found no randomized controlled trials addressing the effectiveness of chemoprophylaxis in close contacts of MDR-TB cases.
- Only two observational studies, one prospective and one retrospective cohort, addressed the subject.
- Thus evidence is extremely limited in both quantity and quality.

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Evidence for MDR LTBI Treatment

Article 1

- Schaaf et al.[1] conducted a prospective cohort study of childhood contacts of MDR-TB cases.
- Of 105 contacts without active disease at baseline who were followed up for 30 months, 41 received appropriate chemoprophylaxis, i.e., ***tailored to the susceptibility profile of the index case***.
  - Of the 64 contacts who were not treated for LTBI, 33 (52%) were infected (TST≥15mm) at baseline, as were 28 of the 41 (68%) contacts who were treated.
  - Active disease developed in two of the 41 contacts (INH and an ***individualized regimen*** that usually contained PZA, ETA, Oflox or EMB) who received chemoprophylaxis and in 13 of 64 contacts who did not (OR 0.20, 95%CI 0.04–0.94).

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[1] Schaaf et al Pediatrics 2002; 109:765-771

Diagnostics and Drug Susceptibility Availability

- There was a 42% increase in detected MDR-TB, due in part to the use of molecular diagnostics
- Globally only 5% of new culture confirmed TB cases and 9% of previously treated TB cases were tested for MDR
- Only 23% of confirmed MDR cases were reported to have been tested for fluroquinolone and second line injectables susceptibility
- Worldwide and in most countries with highest burden of MDR-TB less than one third of cases detected

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WHO Global TB Report 2013

Evidence for MDR LTBI Treatment

Article 2

- Kritski et al.[1] conducted a retrospective cohort study of household contacts of drug-resistant TB cases.
- Total of 218 patients participated who were exposed to 64 index cases, 59 had MDR-TB.
- Among TST positive contacts (TST≥10 mm), active disease developed in two of 45 treated contacts compared with 13 of 145 who did not receive **INH** (OR 0.46, 95%CI 0.07–2.32).
- The two contacts who developed TB despite treatment for LTBI had isolates resistant to INH and RMP, as did their index cases.

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[1] Kritski et al AJRCCM 1996;153:331-335

WHY INH?

- Most of contacts were started on INH (as per guidelines) either due to lack of availability of DST (1996 study) or prior to availability of DST

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WHY INH?

Concordance of MDR pts and Contacts

- Of the six contact-MDR-TB index case pairs studied in South Africa, five had matching genotyping results (the other contact had MDR-TB but a different genotype).[1]
- In Peru, among 42 contacts of MDR-TB who were subsequently diagnosed with TB, 35 (83%) also had MDR-TB while seven (17%) did not.[2]
- A study in South Africa reported a 68% concordance between DST results in the source case and the child contact.[3]

[1]Schaaf et al Ped Inf Dis J 2000;19:695-699
[2] Bayona et al IJTLD 2003;7(Supp 3):S501-509
[3]Schaaf et al Arch Dis Child 2003;88:1106-1111

Discordance of MDR pts and Contacts

- Discordance could be due to imperfect reproducibility of DST results for EMB, streptomycin, PZA and second-line anti-tuberculosis drugs; selection for a resistant subpopulation in the index case after infecting the contact or infection with a different strain.[1]
- The significance is that just because you were exposed to an MDR strain does not mean you are infected with that patient's strain (esp in high burden countries) which means the regimen used to treat LTBI must be widely effective

[1]Cain et al IJTLD 14(3):269-274

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62nd World Health Assembly

- In 2009 the WHO adopted resolution WHA62.15 (2009) on the prevention and control of MDRTB and extensively drug-resistant TB (XDR-TB). The resolution urges Member States to take action on multiple fronts towards achieving universal access to diagnosis and treatment of M/XDR-TB by 2015.
- Although much attention was given to M/XDR-TB control, preventive treatment for contacts of MDR-TB patients is not mentioned in the World Health Assembly resolution.

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Global Policies and Practices for managing Persons exposed to MDR-TB

- Cain (CDC) et al surveyed National TB Program directors and MDR-TB program managers about current practices for managing MDR-TB contacts in countries with an MDR-TB prevalence>2% in new patients and those with programs managing MDR-TB [1]
- 25 of 35 (71%) of countries that met the criteria responded
  - 24 of 25 had guidelines for managing TB contacts
    - 19 of 24 (76%) usually or always evaluated contacts and treated LTBI (68% with TST and 63% CXR)

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[1]Cain et al IJTLD 2010 14(3):269-274

Global Policies and Practices for managing Persons exposed to MDR-TB

- In contrast, 10 (40%) of these 25 countries had guidelines for managing **MDR-TB** contacts
- 11 (44%) of these 25 countries usually or always evaluated MDR-TB contacts
- 9 (36%) of these 25 countries treated LTBI
  - Only 2 (8%) used a regimen that has activity against MDR-TB (FQ or EMB/PZA other 7 INH only)
- Lack of evidence or guidelines was the main reason for not treating MDR-TB contacts
  - Authors concluded that ***"There is an urgent need to generate evidence to guide policy"***

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[1]Cain et al IJTLD 2010 14(3):269-274

2012 Systemic Review

- Given increased attention for MDR/XDR and need for evidence, van der Werf et al published another systemic review to try to support policy development for management of contacts of multidrug-resistant TB patients-(Update of 2006 Systemic Review)
- Of 1195 references assessed in the update, only one additional study could be included (Thus 3 studies reviewed, including 2 studies previously reviewed by Fraser et al)

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2012 Systemic Review

- Attamna et al. described the incidence of MDR-TB disease in people who were in close contact with pulmonary MDR-TB patients, and compared the incidence in persons who were offered prophylaxis with those who were not.[1]
- The study was performed between 1998 and 2006 in Israel, where there were no guidelines for prophylaxis in close contacts of MDR-TB patients.
- The decision was at the discretion of the treating physician. The duration of follow-up was at least 3 years, with a maximum of 6 years.

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[1]Attamina et al Thorax 2009;64:271

2012 Systemic Review

- A total number of 476 close contacts of 78 index patients were identified
- There were no TB events in the treated or the untreated group

[1]Attamina et al Thorax 2009;64:271

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2012 Systemic Review

- Conclusions: *"Evidence about how best to treat contacts of MDR-TB is lacking; this lack of evidence was the most commonly cited reason not to treat contacts of MDR-TB among respondents who believed that such treatment should not be offered. We believe there is an urgent need for evidence to guide the development of policy in this area."*

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Treatment of MDR-TB Contacts

- Whether preventive therapy is favorable depends both on the effectiveness and the adverse events of the drugs used

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Adverse Effects of MDR-TB LTBI Rx

- In 1992, the CDC suggested that PZA plus either EMB or a fluoroqinolone may be useful regimens for treating LTBI in contacts of MDR-TB.
- However, subsequent reports suggested that these regimens are poorly tolerated, with over 50% of individuals discontinuing LTBI treatment, most commonly due to hepatotoxicity.[1-3]

[1] Horn et al NEJM 1994;24:1264-65
[2] Ridzon et al Clin Inf Dis 1997;24:1264-65
[3] Younossian et al Eur Respir J 2005;26:462-464

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Adverse Effects of MDR-TB LTBI Rx

- Langendam et al performed a systematic review to assess adverse events in healthy individuals and MDR-TB contacts treated with anti-tuberculosis drugs potentially effective for preventing development of MDR-TB.[1]
- 20 studies of 6901 assessed eligible
  - 16 studies in healthy volunteers taking either levofloxacin, moxifloxacin, Oflox or rifabutin mainly for 1 week
    - Serious adverse effects <1% and treatment discontinuation <5% considered rare but mild adverse events occurred frequently
  - 4 studies describing preventive therapy of MDR-TB contacts
    - Therapy stopped 58-100% of the included persons because of mild (eg N/V) to serious

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Langendam et al PLoS 2013; 8(1):e53599

Adverse Effects of MDR-TB LTBI Rx

- The quality of the evidence was considered very low
- The available evidence suggests that shortly after starting treatment the occurrence of serious adverse events is rare
- Mild adverse events occur more frequently and may be of importance because these may provoke treatment interruption.

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Management of LTBI Caused by MDR/XDR Isolates: THE CONS OF SUSCEPTIBITY DRIVEN TREATMENT *(At least for now)*

- Not enough evidenced based proof that any regimen is effective in MDR/XDR contacts
- Most countries with the highest burden of MDR/XDR do not have the ability to do second-line testing esp against FQs
- Not all contacts of an MDR/XDR patient will be infected with that patient's strain (so MDR regimen may not be effective)
- Many MDR regimens with high termination rates (*"not effective if not taken"*)
- Waiting for DST will prolong initiation of therapy of vulnerable contacts
- Most programs do not have policies in place to evaluate for LTBI among MDR Contacts

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Guidelines

- Guidelines of the American Thoracic Society (ATS) and the US Centers for Disease Control and Prevention (CDC) recommend the prescription of preventive therapy for MDR TB contacts[1]
- World Health Organization (WHO)[2] and National Collaboration for Chronic Conditions and Center for Clinical Practice (NICE)[3] does not recommend the prescription of preventive therapy and instead recommends careful clinical follow-up for a period of at least two years
- The International Standards for TB Care (ISTC) and European Union Standards for TB Care (ESTC) [4] indicate that strict clinical monitoring but do not suggest preventive therapy for LTBI if the source case is an MDR TB patient.

[1] CDC/ATS AJRCCM 2000;161 (4 Pt 2):S221-S247
[2] WHO 2008 WHO/HTM/TB/2008:402
[3] NICE 2011Clinical Guideline 117
[4] Miglori et al Eur Resp J 2012;39(4):807-819

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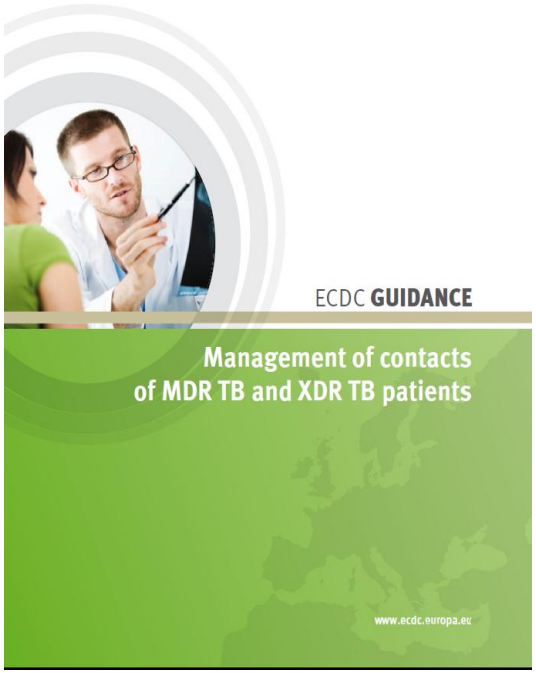
European CDC



- Published March 2012-provides guidance through review of scientific evidence and expert opinion
- 2 option approach:
  - Treatment approach is limited by current lack of availability of drugs shown to be effective against MDR/XDR infection that show an acceptable adverse-event profile (neither reject or support therapy)
  - Provide information and follow up with careful clinical observation of the contact which ensures early detection of disease and prompt diagnosis/treatment

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European CDC Guidelines

- The central principle that the expert panel follows in their opinions is that a comprehensive risk assessment should be part of the evaluation of the MDR TB or XDR TB contact.
  - The individual risk assessment should take into consideration the following: the MDR TB contact's risk for progression to TB disease; the drug susceptibility pattern of the source case of infection; and the contact's risk for adverse drug events if initiating preventive therapy.
- In case of XDR TB, the available possible drug regimens are very limited and without proven efficacy, thus close observation is likely the only option

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NEEDS

- Quicker and wider availability of second-line DST
- Cost-benefit analyses on implementing MDR/XDR preventive therapy strategies
- Better drugs for preventive therapy
- Guidelines for implementing MDR/XDR preventive therapy strategies including improved contact investigations and “buy-in” from high burden, resource challenged programs
- Most importantly, urgent need of well designed studies evaluating the benefits of preventive therapy for MDR/XDR contacts

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NEEDS

- The ECDC acknowledged that there are ongoing studies (Federated States of Micronesia) which appear to support the use of preventive therapy, but these results need to be confirmed in larger studies and other settings

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THANK YOU!!

TB Consultation Hotline

1-800-4TB-INFO

Southeast National TB Center/FL DOH TB HOTLINE

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Fraser 2006

- They recommended the need for a randomized treatment trial that was estimated to require a sample size of at least 800 contacts assuming that 8% of untreated contacts develop active disease and a 60% reduction in the risk of active TB in treated contacts, a trial with 80% power and 5% chance of a type I error.
  - Randomization by household would increase the required sample size.

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Treatment and Management of MDR TB Contacts

Why All the Controversy?

- Few evidence based recommendations for the treatment of MDR TB contacts from CDC, ATS, and other groups
- Risk of treating vs. not treating
- Tolerance of meds/toxicities – “above all, do no harm”
- Length of treatment?

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Reasons to Treat Contacts to MDR-TB Cases

- Decrease likelihood of progression to active TB
- Severe consequences of clinically active MDR TB for patient and community
- Treat MDR TB when the bacterial burden is low

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Principles of Treatment in MDR TB Contacts

- Always exclude active TB disease before considering LTBI treatment
  - *Evaluate all exposed contacts to identify all active cases and prevent further transmission*
- Estimate likelihood of infection with an MDR TB strain
- Consider the risk of progression to active TB disease
  - HIV testing and counseling

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Principles of Treatment in MDR TB Contacts

- Tailor LTBI treatment to individual case
  - Regimen should contain 1 to 2 drugs to which source case isolate is susceptible
  - Immunosuppressed individuals should not be treated with monotherapy
- Remember:
  - Efficacy of the regimen largely dependent on adherence and completion of therapy
  - Education of patients is important – adverse effects and importance of adherence

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service

Reprinted from
MORBIDITY AND MORTALITY WEEKLY REPORT
Recommendations and Reports
June 19, 1992 / Vol. 41 / No. RR-11

CDC
CENTERS FOR DISEASE CONTROL

Management of Persons Exposed to Multidrug-Resistant Tuberculosis

MDR LTBI Treatment Options

- Treatment with ≥ 2 drugs to which source case isolate is sensitive
- Monotherapy with a fluoroquinolone
- INH alone
  - Utilize in patients likely to be exposed to DS-TB before DR-TB
- Clinical monitoring for 2 years without medication
  - Must clinically evaluate patient regularly

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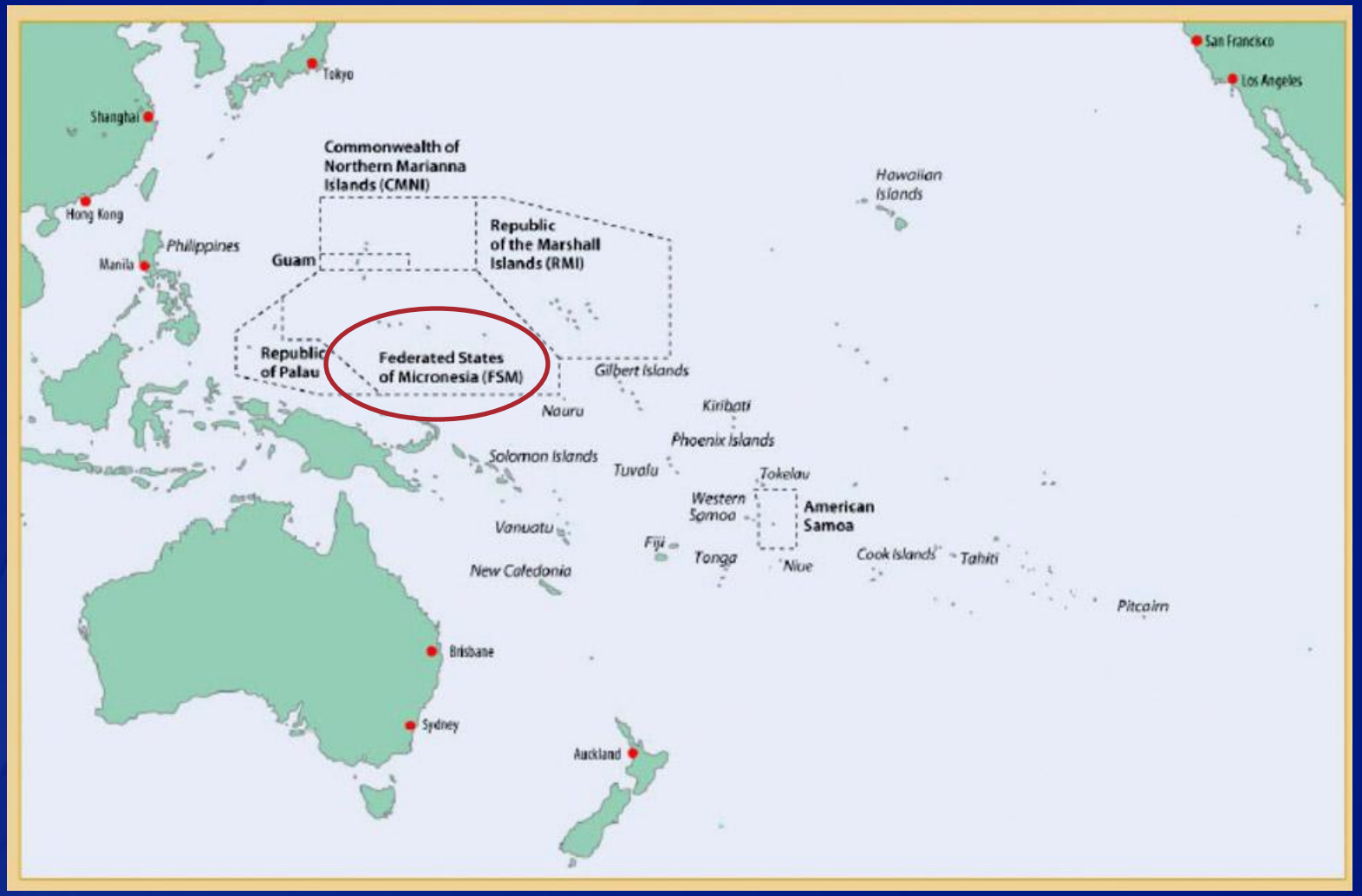
Treatment of MDR LTBI in Contacts of Two Multidrug-resistant Tuberculosis Outbreaks — Federated States of Micronesia, 2008–2013

National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Division of TB Elimination

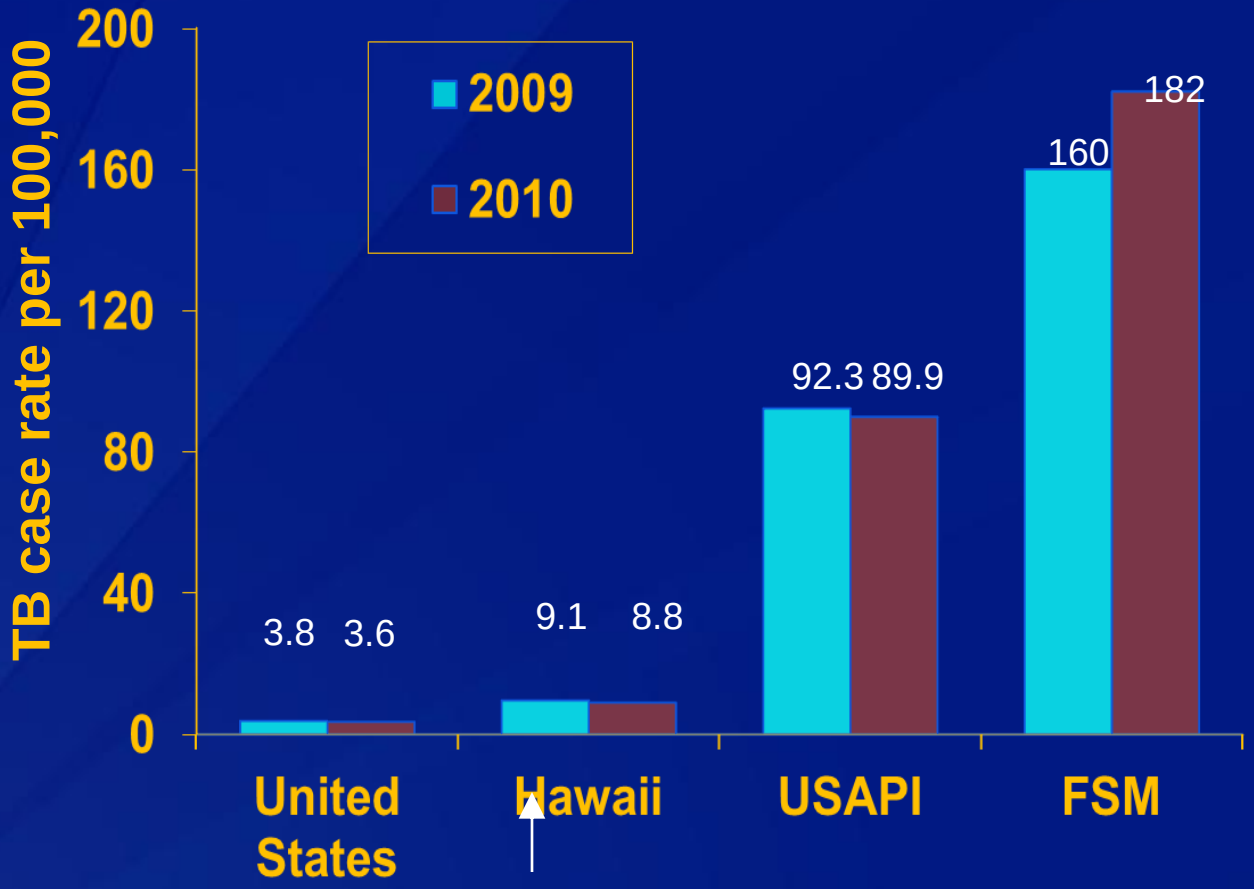
Background

U.S. Affiliated Pacific Islands (USAPI)



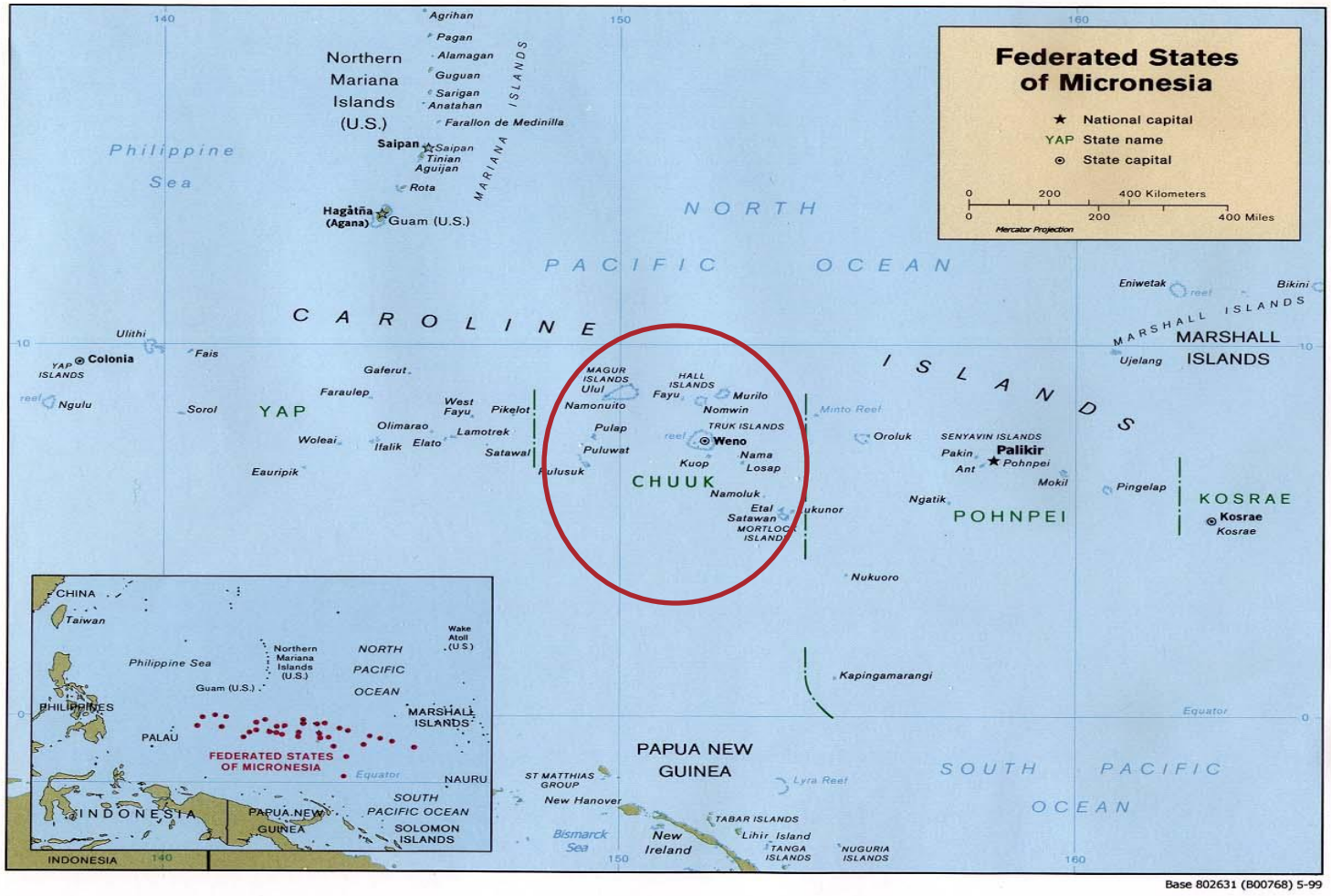
http://www.pacificcancer.org/site-media/uspi-map-big.jpg

TB Case Rates per 100,000



Source: CDC. Reported tuberculosis in the United States, 2011.

The 4 States of FSM: Yap, Chuuk, Pohnpei, & Kosrae



MDR TB in Chuuk, FSM

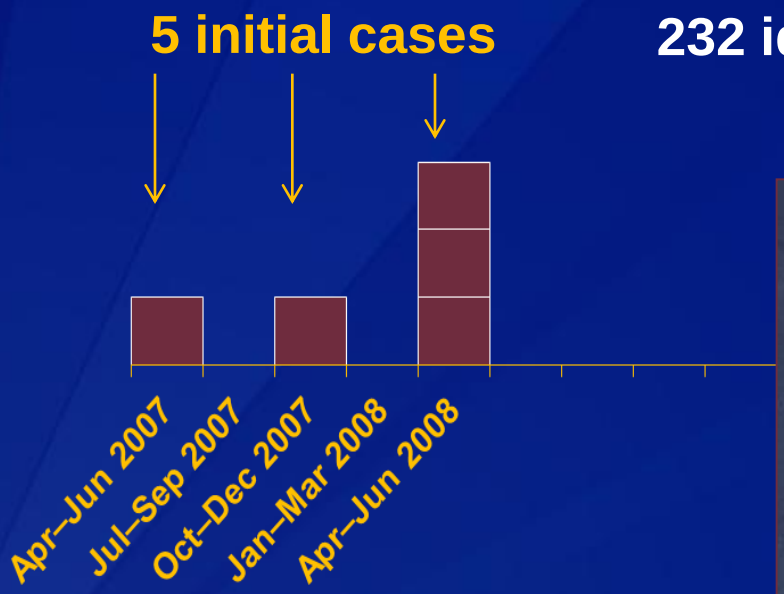
- During April 2007–June 2008, four cases of laboratory-confirmed MDR TB were reported in Chuuk
- Three (75%) of 4 patients had died
- 2-year-old child and mother with MDR TB → evidence of recent transmission
- No 2nd line medications available as of June 2008

Emergence of MDR TB in Chuuk State

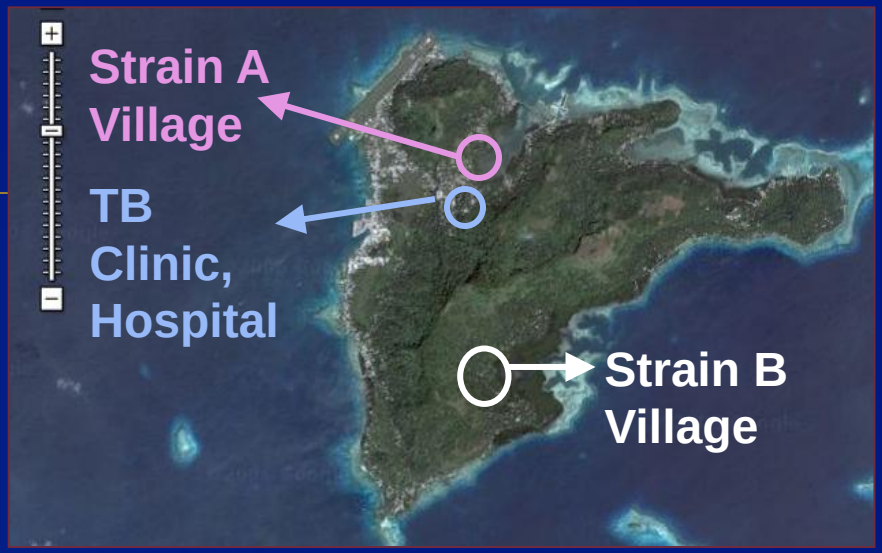
- **Strain A resistant to INH, RIF, PZA, EMB, & streptomycin**
  - Primary resistance
  - Likely imported
- **Strain B resistant to INH, RIF, & ethionamide**
  - Secondary resistance
  - Circulating strain resistant to INH & ethionamide acquired RIF resistance

Summary Results of Chuuk Investigation, July 2008

- Two distinct, simultaneous MDR TB outbreaks on Weno Island



232 identified and evaluated contacts



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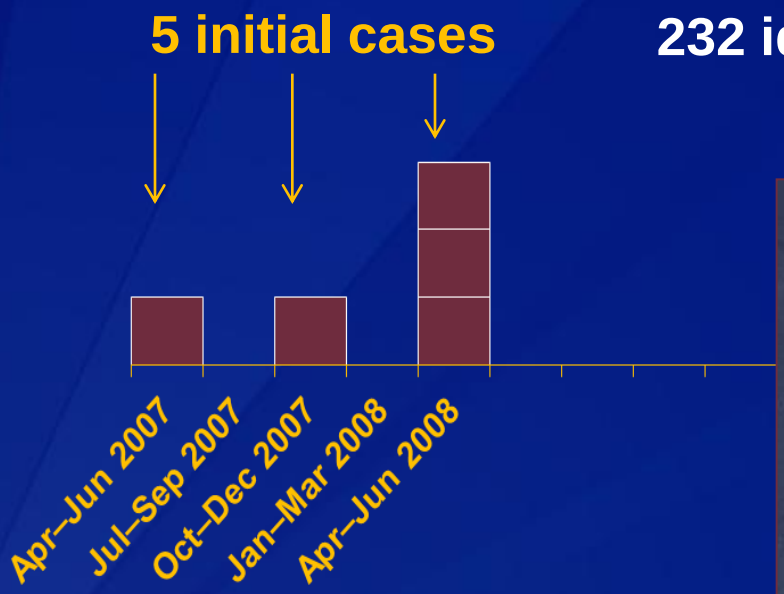

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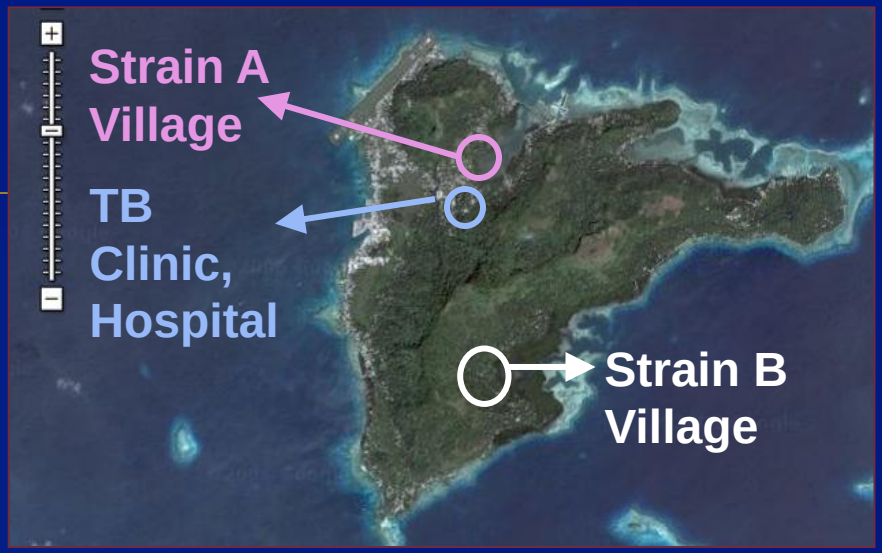


LTBI Treatment of MDR TB Contacts in Chuuk — Objectives

- Determine feasibility of implementing MDR LTBI treatment and follow-up in a resource-limited setting
- Study tolerability of MDR LTBI regimens
- Potentially, study efficacy of MDR LTBI regimens

Chuuk MDR LTBI Methods

- **MDR LTBI treatment by DOT for 1 year**
- **FQ-based regimens**
  - **Children received FQ +/- ethambutol or ethionamide**
- **Monthly questionnaires by field workers**
  - Symptom screen and missed doses
- **Quarterly visit by healthcare provider**
- **Biannual chest radiograph and clinical evaluation**
- **Contacts followed for 2 years after completion**

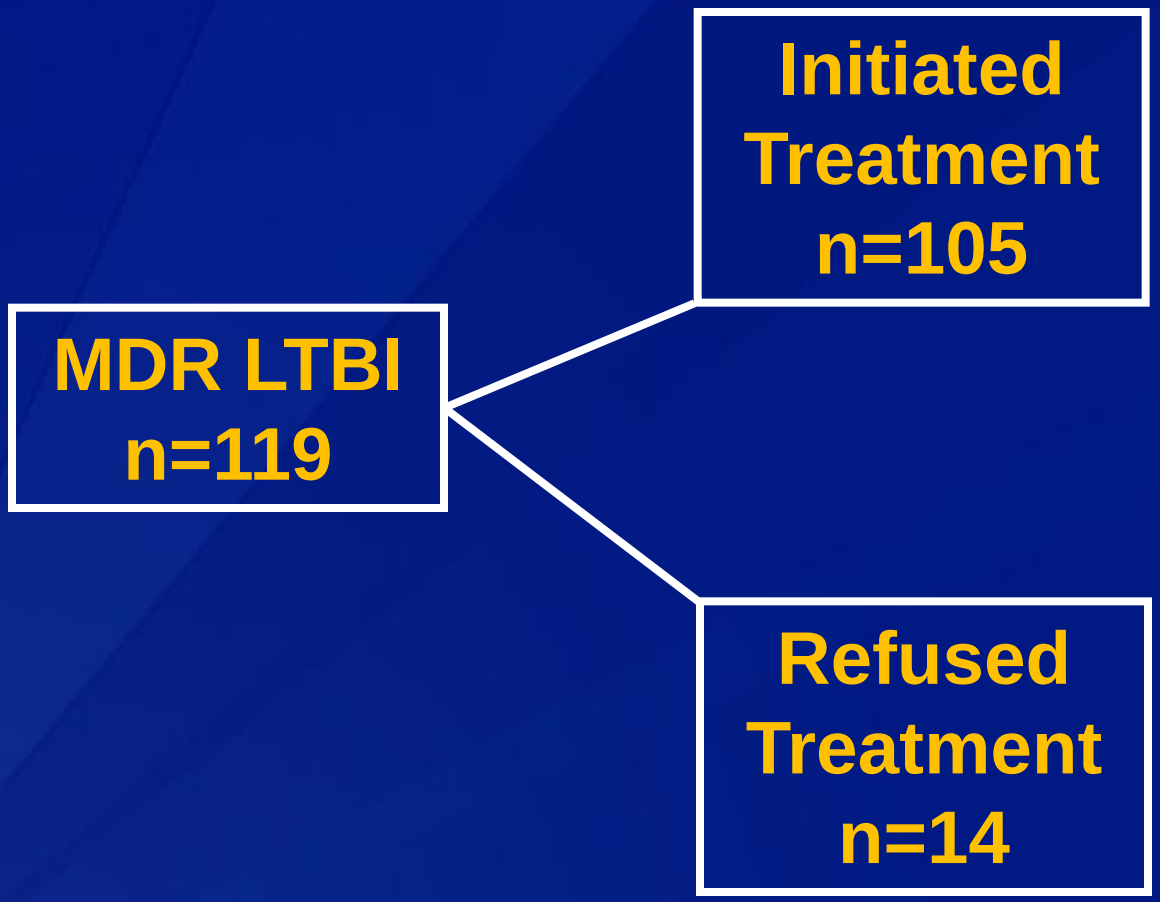
MDR TB Contact Evaluation

- **Among the 232 identified contacts, 6% attack rate during July 2008–Jan 2009**
  - 5 patients diagnosed with MDR TB
  - 9 additional patients developed MDR TB while awaiting LTBI treatment
- **Two contacts who had not been identified during contact investigations also found to have MDR TB**
- **119 other TST (+) with no evidence of active disease**

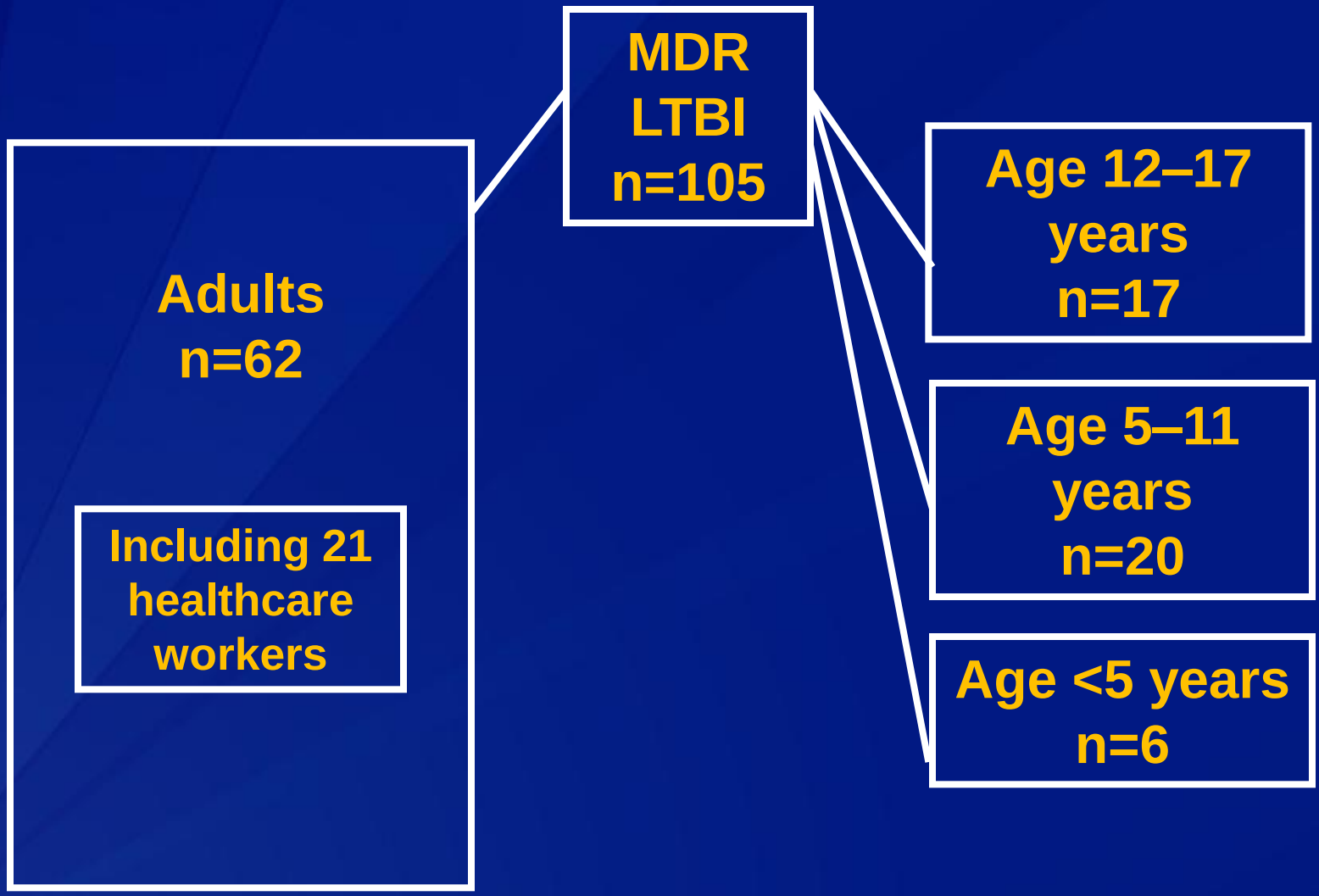
Treatment of MDR TB Contacts in FSM

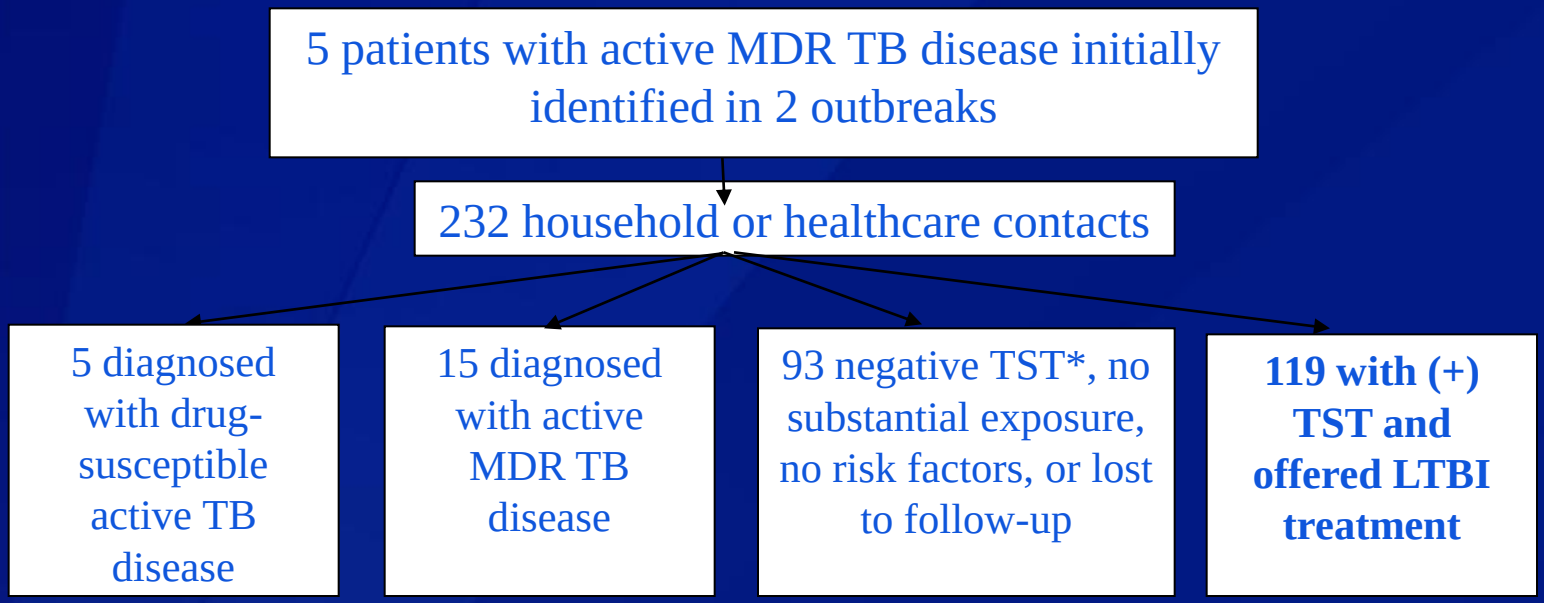
STUDY RESULTS

MDR LTBI Treatment

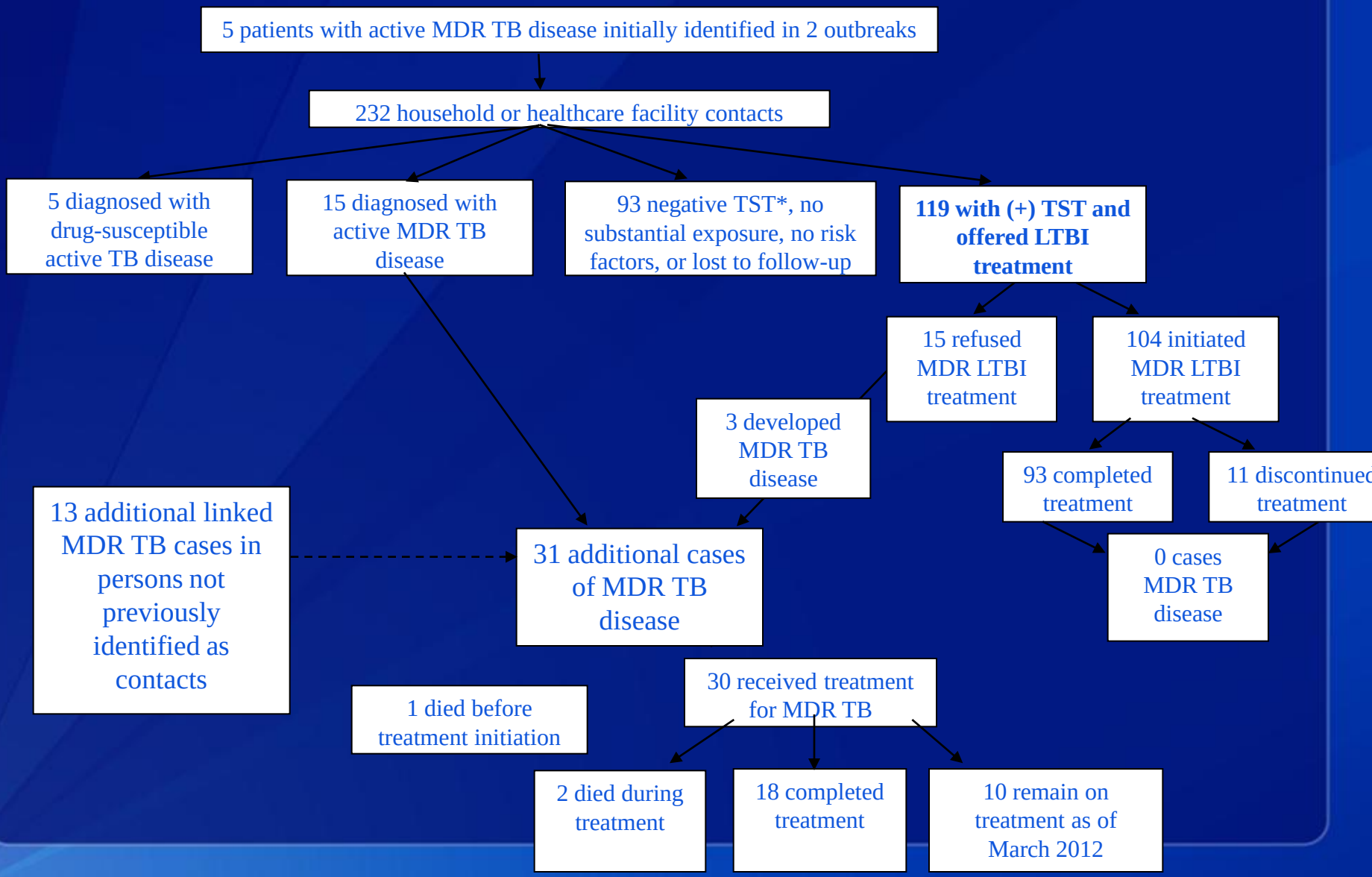


Contacts with LTBI, by Age




5 patients with active MDR TB disease initially identified in 2 outbreaks
232 household or healthcare contacts
5 diagnosed with drug-susceptible active TB disease
15 diagnosed with active MDR TB disease
93 negative TST*, no substantial exposure, no risk factors, or lost to follow-up
119 with (+) TST and offered LTBI treatment


5 patients with active MDR TB disease initially identified in 2 outbreaks
232 household or healthcare facility contacts
5 diagnosed with drug-susceptible active TB disease
15 diagnosed with active MDR TB disease
93 negative TST*, no substantial exposure, no risk factors, or lost to follow-up
119 with (+) TST and offered LTBI treatment
15 refused MDR LTBI treatment
104 initiated MDR LTBI treatment
3 developed MDR TB disease
93 completed treatment
11 discontinued treatment
0 cases MDR TB disease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15 refused MDR LTBI treatment
104 initiated MDR LTBI treatment
3 developed MDR TB disease
93 completed treatment
11 discontinued treatment
13 additional linked MDR TB cases in persons not previously identified as contacts
31 additional cases of MDR TB disease
0 cases MDR TB disease
30 received treatment for MDR TB
1 died before treatment initiation
2 died during treatment
18 completed treatment
10 remain on treatment as of March 2012

Chuuk Experience — Adherence

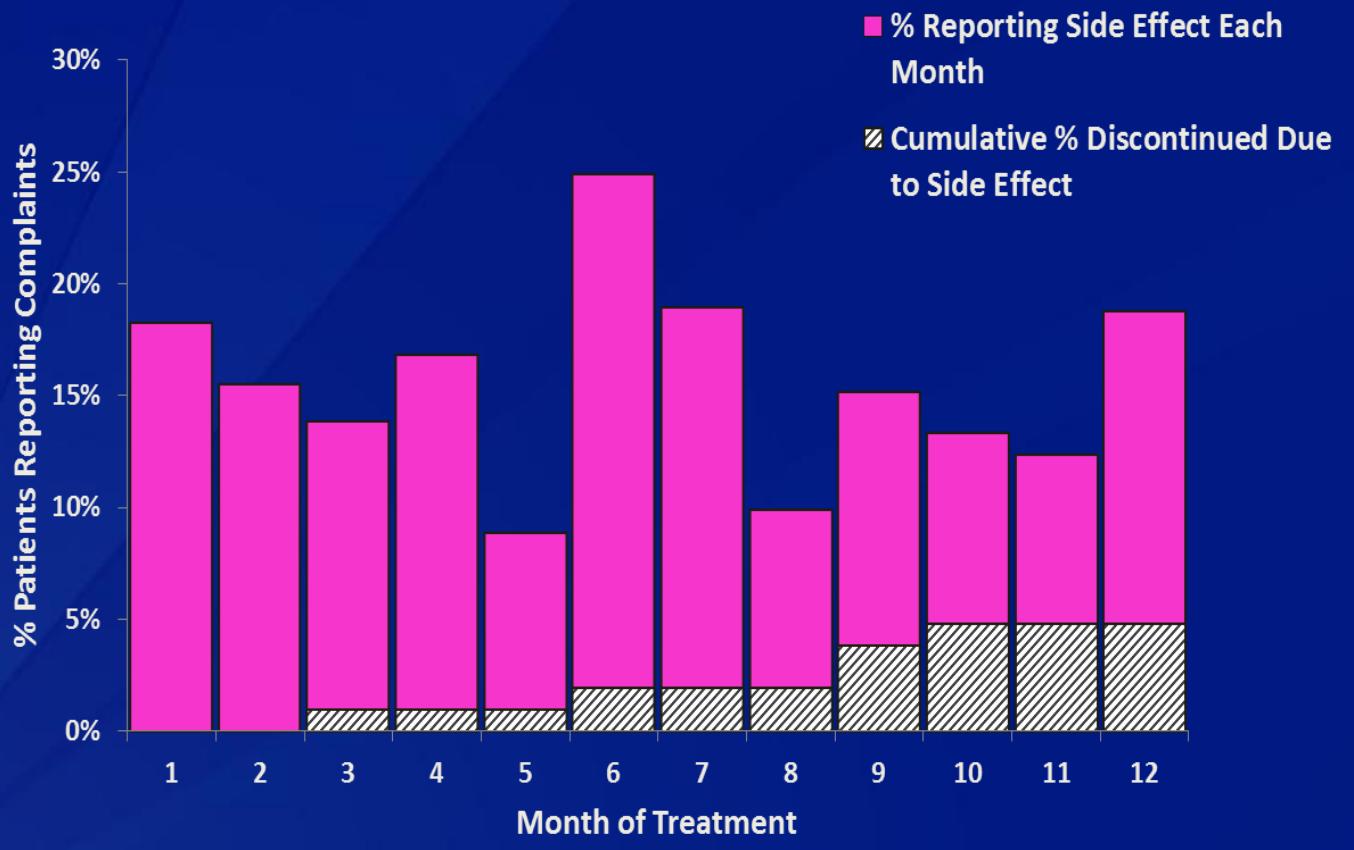
Patients	Number	Percent
Treatment completion, all (N=105)	**93**	**89**
Healthcare personnel (n=21)	**14**	**70**
Child <12 yrs (n=26)	**25**	**96**

Chuuk Experience — Side Effects

- **52 patients reported side effects but completed treatment**
  - Patients reported side effects at**159 (15%)** of **1,038** monthly visits

Symptom	Number	Percent
Total reported	**253**	
Nausea	**112**	**44**
Headache or dizziness	**72**	**28**
Fatigue	**22**	**4**
Tendon / joint pain	**21**	**4**

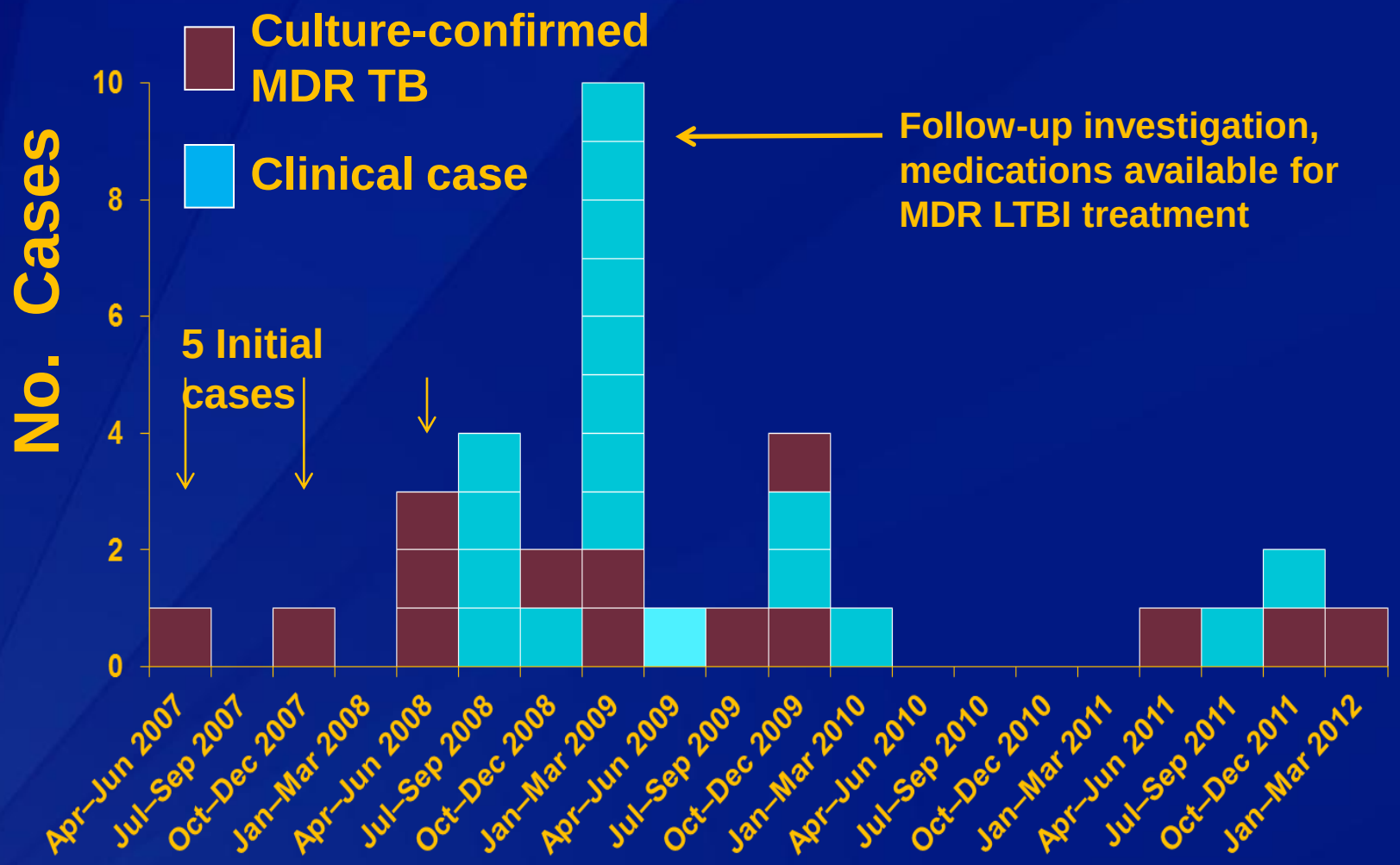
Chuuk Experience — Timing of Side Effect Onset during MDR LTBI Treatment



Chuuk Experience — Efficacy

- **15 contacts refused MDR LTBI treatment**
  - 3 developed MDR TB disease
- **Other patients who developed TB disease**
  - 13 contacts not offered LTBI treatment
    - 11 previously not identified
    - 2 lost to follow-up after initial evaluation
- 15 develeoped MDR TB disease prior to FQ availablility
- **No contacts treated for MDR LTBI developed TB disease**

MDR TB Cases — Chuuk, 2007–2012* (n=33)



* as of January 31, 2012

Chuuk Experience — Conclusions

- **Treatment effectiveness**
  - No randomized trials to show efficacy
  - Efficacy difficult to demonstrate with low numbers

- **Important outcomes**
  - High completion rate
  - Regimens were safe and tolerable
  - LTBI treatment by DOT is doable
  - No patients treated for MDR LTBI developed TB disease

In Press…..

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