

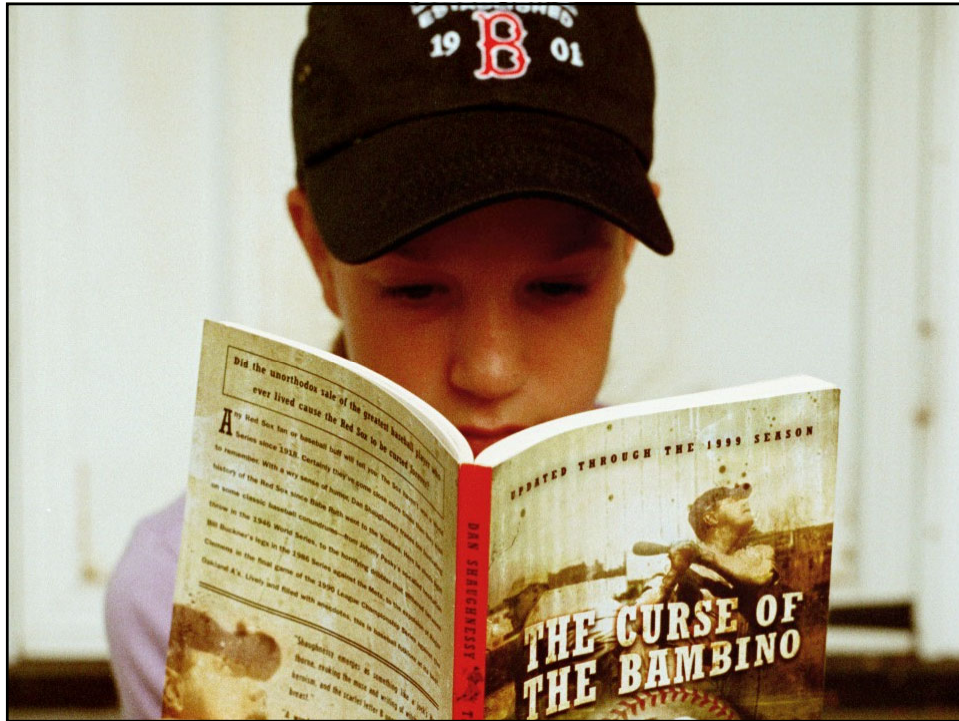
1

RUTGERS

Window Prophylaxis for Child Contacts

- What is wrong with the Red Sox?
- What is window prophylaxis? Definitions?
- Epidemiology of TB in the US with focus on age groups
- Who gets window prophylaxis?
- Why do they get it?
- Missed opportunities (Clarke, Nolan, Mehta)
- The evolution of window prophylaxis: INH & RIF
- Does it work? (Starke & Cruz)

2



3

Window Prophylaxis: Definitions and who receives it

- What is **“Window Prophylaxis”**:
 - Prophylaxis with isoniazid (INH) or rifampin (RIF) during the window period to prevent the development of TB disease

- What is the **“Window Period”**:
 - The 8-10 weeks between the initial and repeat tuberculosis test (TST or an IGRA) in a TB-exposed child

- Who gets **“Window Prophylaxis”**?
 - TB-exposed children <5 years-of-age (Our focus today)
 - Exposed contacts with impaired immunity (eg, HIV infection, chemotherapy, high dose steroids, TNF-alpha inhibitors, etc.).
 - If TBI can not be excluded after evaluation for TB disease, treatment should be continued to completion.

4

Background: Pediatric Tuberculosis in the U.S.

▪ Definition of pediatric tuberculosis (TB):

- TB disease in a person < 15 years old

▪ In 2020:

- 7,174 TB cases were reported among all age groups (2.2/100,000)
 - 317 (4.4 %) were pediatric (1.31/100,000)

Age group	N	Percent out of all age groups
0-4 years	165	2.3%
5-14 years	152	2.1%

CDC

5

RUTGERS

Transmission of *M. tuberculosis* to Children

- Children are usually infected by an adult or adolescent in the immediate household
- Casual extra-familial contact is less often the source of infection
- Children rarely infect other children or adults:
 - Tubercle bacilli are relatively sparse in secretions
 - Children with pulmonary TB rarely cough
 - Cough, when present, lacks the tussive force needed to aerosolize bacilli

6

Risk of Progression of TBI to TB Disease

- Immunocompetent adults: 5-10% lifetime risk of developing disease after infection
- Adults with TB infection and untreated HIV infection: 5-10% annual risk of developing disease
- Children and the risk of TB disease:

7

Risk of Tuberculosis Disease by Age

	Risk of disease following primary infection			Comments
	Disseminated tuberculosis/ tuberculosis meningitis	Pulmonary tuberculosis	No disease	
<1 years	10-20%	30-40%	50%	High rates of morbidity and mortality
1-2 years	2-5%	10-20%	75-80%	High rates of morbidity and mortality
2-5 years	0-5%	5%	95%	..
5-10 years	<0-5%	2%	98%	"Safe school years"
>10 years	<0-5%	10-20%	80-90%	Effusions or adult-type pulmonary disease

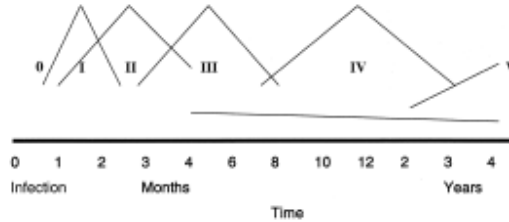
Adapted from reference 30.

Table 1: Risk of pulmonary and extrapulmonary disease in children following infection with *Mycobacterium tuberculosis*

Newton S, et al Lancet ID 2008 after Marais BJ, et al. Int J Tuberc Lung Dis 2004; Pulmonary TB in adults and children, Miller & Wallgren; T. Nelson & Sons, 1939.

8

Schematic Timeline of Primary Tuberculosis

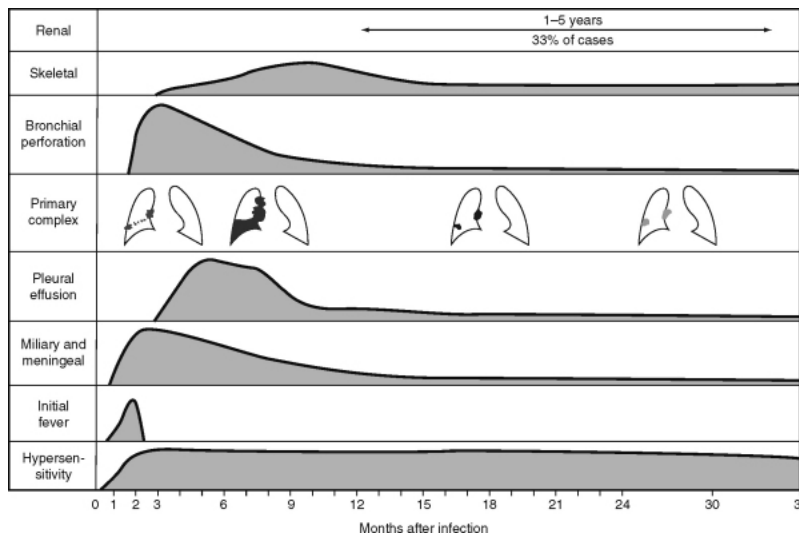


- 0 Incubation phase
- I Hypersensitivity phase
- II Phase of miliary tuberculosis and tuberculous meningitis
- III Phase of segmental lesions in children aged under 5 years and pleural effusion in those aged over 5 years
- IV Phase of osteo-articular tuberculosis in children aged under 5 years and adult-type disease in those aged over 10 years
- V Phase of late manifestations including pulmonary reactivation disease.

Adapted from Wallgren: Time-table of tuberculosis Tubercle 1948

9

Timetable of TB in Children after Wallgren

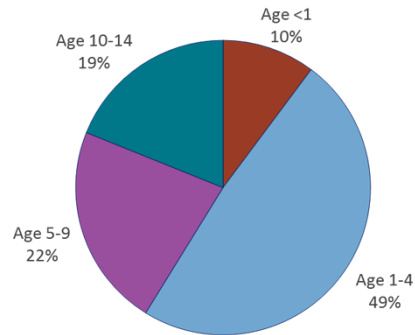


Tuberculosis. Starke JR, in Feigin, Cherry, Demmler, Kaplan, ed: Textbook of Pediatric ID 2009

10

Percentage of Pediatric TB Cases by Age Group, 1993–2016

N=21,609



11

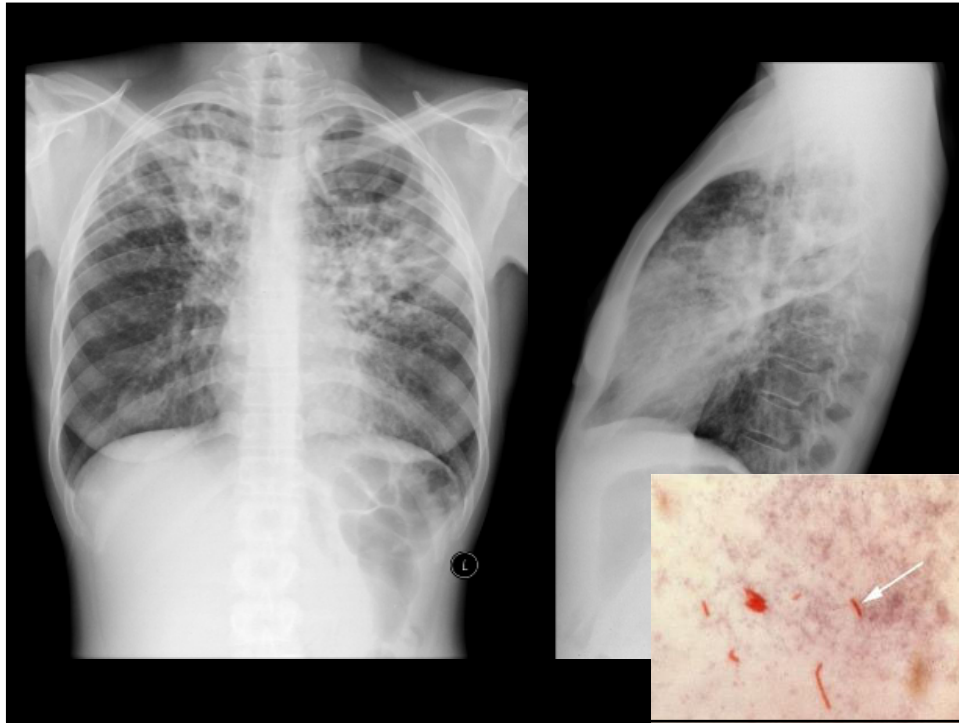
RUTGERS

Control of Tuberculosis in the United States

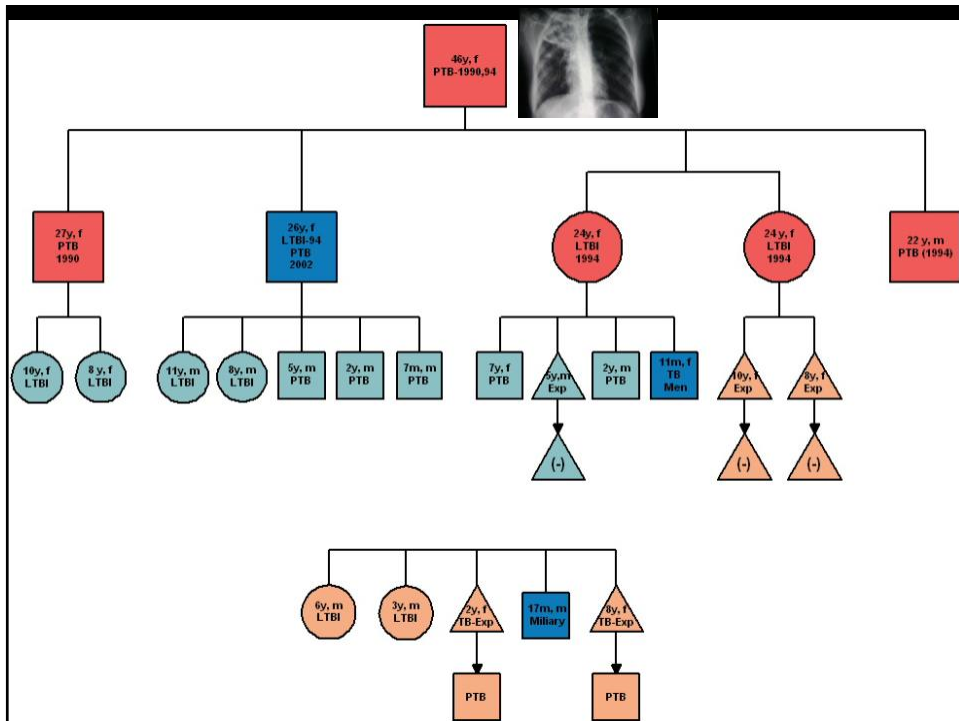
- Case finding and treatment
- **Contact investigations and the practical application of “Window Prophylaxis”**
- Targeted testing of persons with risk

Red Book 2012

12



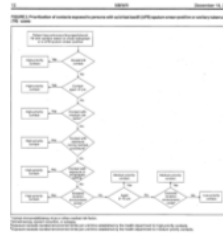
13



14

Control of TB in the United States

- Case finding + treatment -> Contact investigations
 - The most reliable TB control program is based upon aggressive and expedient contact investigations, rather than routine screening of large populations



High priority contact:

- Household
- Age <5 yrs
- Med risk condition
- Procedure
- Congregate, Time

- Can be complex and may require lots of detective work

Red Book 2009

15

Tuberculosis Exposure in Children <5 years of age and **“Window Prophylaxis”**

- History, PE, TST/IGRA, CXR are done
 - CXR is done regardless of TST/IGRA result
- IF the child is:
 - Asymptomatic and physical examination is normal
 - TST is negative (<5 mm) or IGRA negative
 - Chest X-ray is normal
- AND IF <5 years of age START: INH 10 mg/kg (max., 300 mg) PO once daily or RIF 20-30 mg/kg PO once daily



16

Tuberculosis Exposure in Children

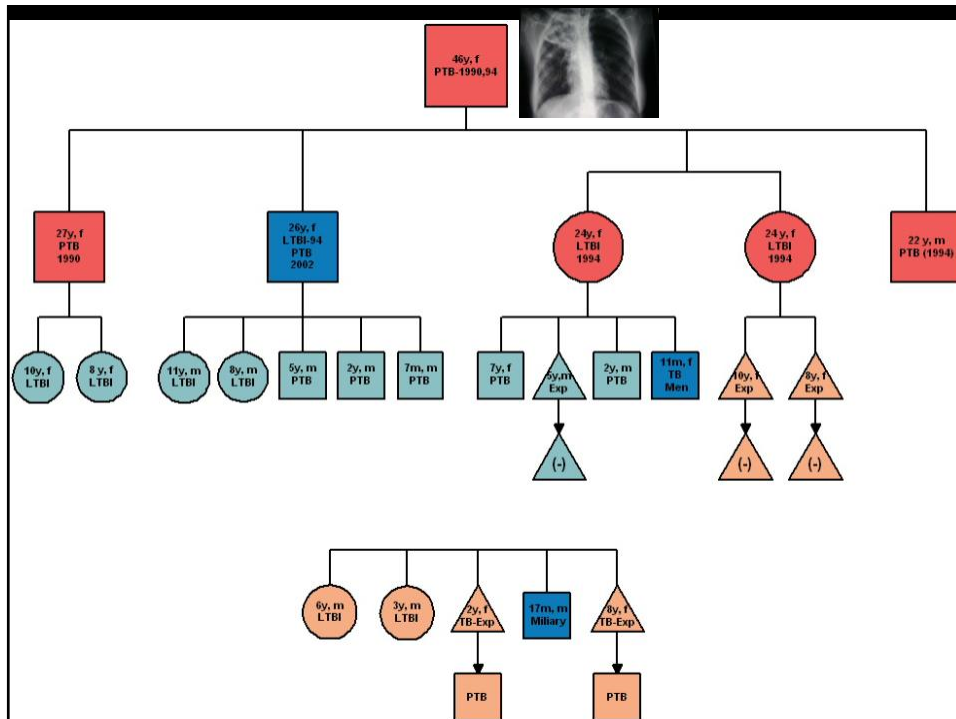
Why is INH or RIF given as **“Window Prophylaxis”** even if there is no evidence of TB infection or disease at the initial visit?

- Child may already be infected
- Infection more likely to progress to disease
- Infants and younger children are more likely to develop disseminated disease (military) or meningitis

TST/IGRA repeated 8-10 weeks after contact broken with infectious adult:

- If TST/IGRA (-), discontinue prophylaxis
- If TST/IGRA (+), re-evaluate child and treat accordingly

17

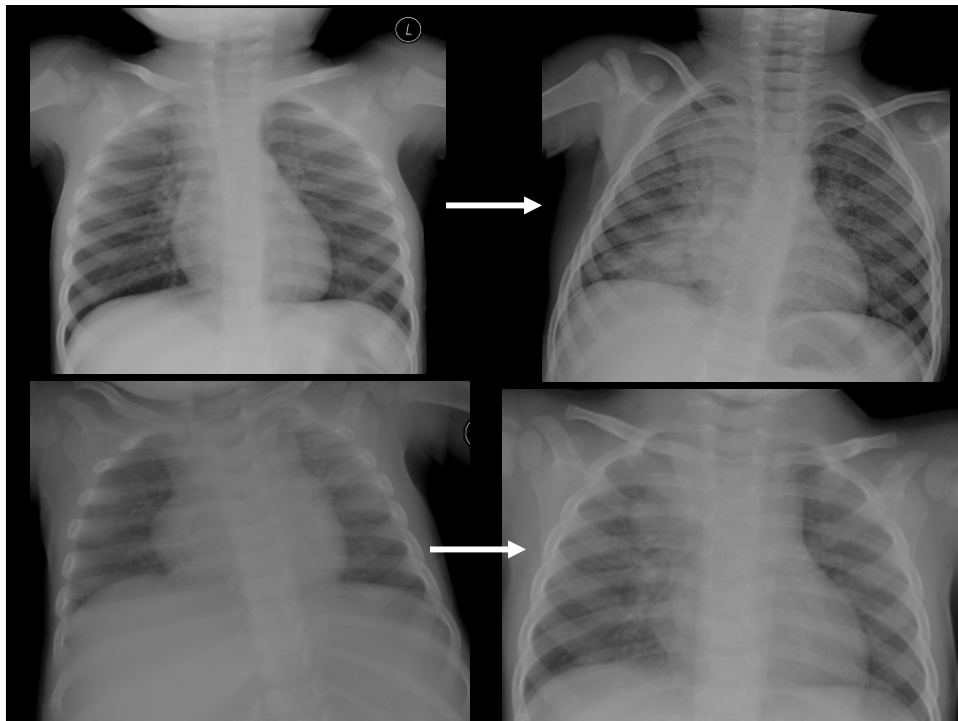


18

Potential Missed Opportunities in TB Control

- Initially, 5/18 children are diagnosed as TB-exposed with no evidence of TBI or TB disease
 - Two (Ages 6 & 28 months) identified in the contact investigation have 0.0 mm TSTs and normal CXRS at the health department
 - Mother says at the health department that she would like to them to be seen by their private pediatrician
 - No PE done
 - No INH “window prophylaxis” given

19



20

Potential Missed Opportunities in TB Control

- Two other children from the same family who have TBI are referred to the same pediatrician for evaluation and management at mother's request:
 - Receive prescriptions for INH plus 8 refills
 - No follow-up appointments are given
 - Social history: Homeless, 5 children, mother with her own serious health problems, holding down a full-time job
 - Set-up for another missed opportunity? Strong probability
 - Will therapy for TBI be completed?
 - Was it? Yes, why? DOT of infection (DOTI)

21

Prevention of Tuberculosis in Children: Missed Opportunities

- Failure to find and appropriately manage adult source cases (Case finding)
- Delay in reporting the initial diagnosis of TB
- Contact investigation interview failure
- Delay in evaluation of exposed children
- Failure to completely evaluate exposed children
- **Failure to prescribe prophylaxis INH (WP)**
- Failure to maintain a contact under surveillance
- LTI diagnosed; treatment not prescribed
- Failure to complete treatment for LTI (Adherence)

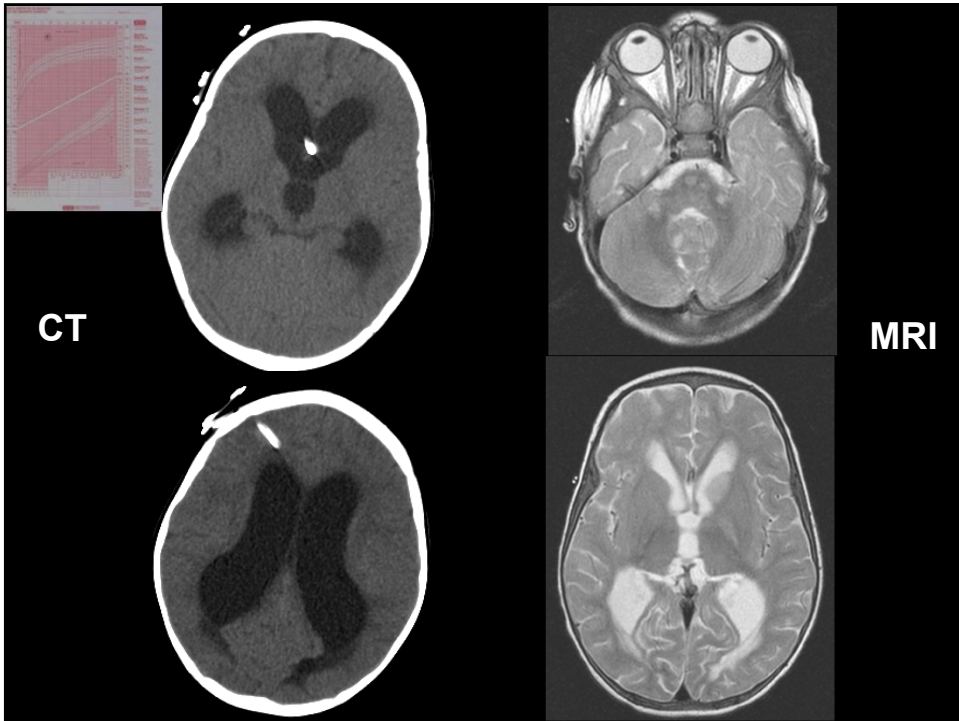
Nolan RJ. AJPH 1986

Mehta J, Bentley S. Am J Prev Med 1992

22



23



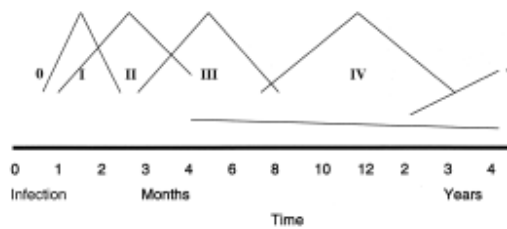
24

Does INH Window Prophylaxis Work?

- By 1947, TB was treated with streptomycin and para-aminosalicylic acid (PAS) for 2 years
 - While effective, it was not unusual for young children with primary TB, doing well on these 2 drugs to suddenly develop TB meningitis
 - In 1952, INH became available and clinical investigators soon noted that clinical meningitis did not develop in children receiving INH for their TB
 - This was substantiated among 2750 children in the TB Meningitis Prophylaxis Study (INH (2) vs. placebo (31) in TBI)
 - The USPHS randomized study of INH in 16,298 TB exposed house-hold contacts <20 years of age: Placebo: 16 developed disease vs. 5 in the INH group
 - Then scientist-clinicians began to think about the other group of children that were prone to develop TB meningitis and military or disseminated TB:

25

Schematic Timeline of Primary Tuberculosis



- 0 Incubation phase
- I Hypersensitivity phase
- II Phase of miliary tuberculosis and tuberculous meningitis
- III Phase of segmental lesions in children aged under 5 years and pleural effusion in those aged over 5 years
- IV Phase of osteo-articular tuberculosis in children aged under 5 years and adult-type disease in those aged over 10 years
- V Phase of late manifestations including pulmonary reactivation disease.

Adapted from Wallgren: Time-table of tuberculosis Tubercle 1948

26

Window Prophylaxis: Does it work?

- Until 2019 evidence was inferential, though all models and theories supported it; safety and efficacy had never been assessed
- A study from Houston authored by Andrea Cruz and Jeff Starke retrospectively studied the safety of INH in 752 TB-exposed children <5 years of age.
 - Median age: 2.4 years
 - 41.4% resided in the home of the index patient
 - Index pt. Microbiology:
 - AFB smear positive: 68.2%
 - AFB culture positive: 90.4%
 - Index pt. drug susceptibilities:
 - INH and rifampin susceptible: 93.4%
 - INH resistance: 4.7%
 - INH and rifampin resistance: 1.9%

Cruz AT, Starke, JR. Emerg Infect Dis 2019

27

Window Prophylaxis: Does it work?

- Outcomes:
 - Window Prophylaxis:
 - INH: 97% (DOPT BIW)
 - RIF: 2.7% (DOPT daily)
 - Safety: (AE:7/752): Median time to AE: 5 weeks
 - No hepatotoxicity
 - Vomiting: 2 children
 - Angioedema: 1
 - Weakness: 1
 - Diarrhea: 1
 - Rash: 2
 - Conversion of TST: 37 children (4.9%)
 - No difference in conversion rate: <2 years of age and >2 years of age
 - Median TST induration 12 mm

Cruz AT, Starke, JR. Emerg Infect Dis 2019

28

Window Prophylaxis: Does it work? YES

- Accepted by families
- Safe, well-tolerated
- No association between TST conversion (Cruz & Starke)
 - Sputum smear status
 - Cohabitation
 - If TST or IGRA convert at the 8-10 week mark: Re-eval (S/S, PE, CXR)
 - Completion of treatment: 9-months of INH b
 - Changing to full shorter regimen to complete reasonable
 - No data on treating with shortened 4R or 3HP added to the INH window prophylaxis regimens when pt. started on INH in study.
- 4R is used in many areas for “window prophylaxis.”
 - Some experts use standard 10-20 mg/kg/day
 - Higher dose 20-30 mg/kg/day can also be used
- Conclusion: Window prophylaxis was safe and effective.

29



30