Screening and preventive therapy for MDR/XDR-TB exposed/infected children (and adults)

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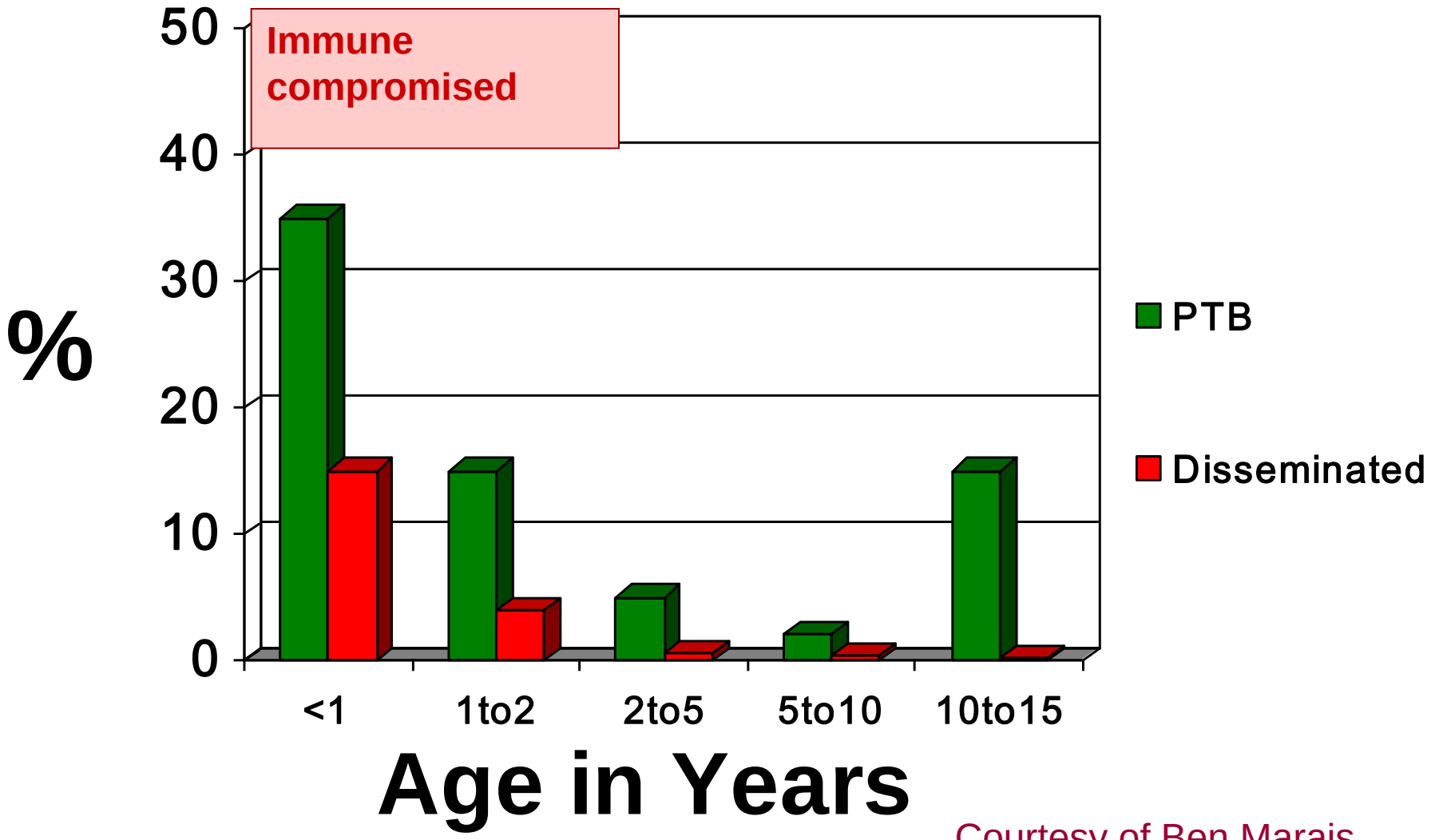
Introduction

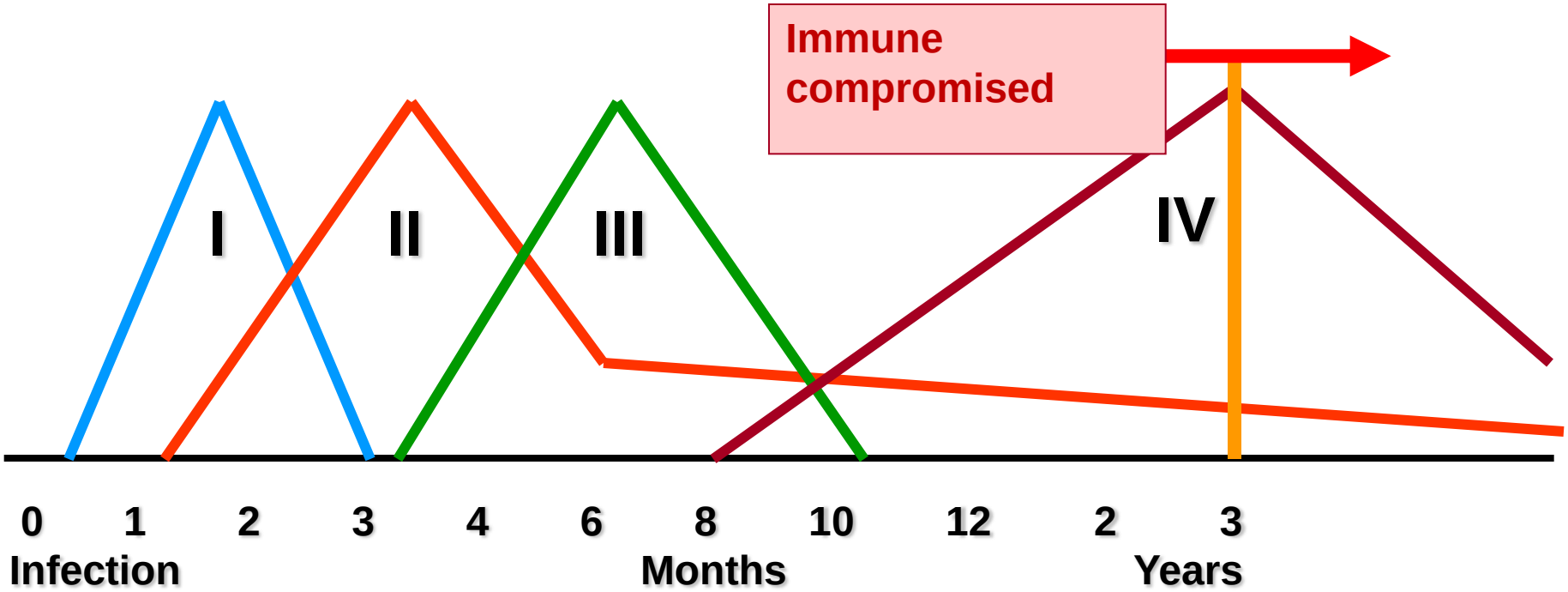
- The risk for developing TB disease after infection is high in young children (<3 yr of age) and HIV-infected individuals
- INH preventive therapy (6-9 months) for latent TB infection (LTBI) is effective in young children and HIV-infected patients with drug-susceptible TB
- In case of exposure to INH-resistant TB strains, Rx with RMP for 4 months is recommended
- No RCTs have been done to evaluate preventive therapy for MDR-TB contacts

Age-related risk



Courtesy of Ben Marais

Time-related risk



Phase of disease

I Hypersensitivity

II Miliary TB and TBM

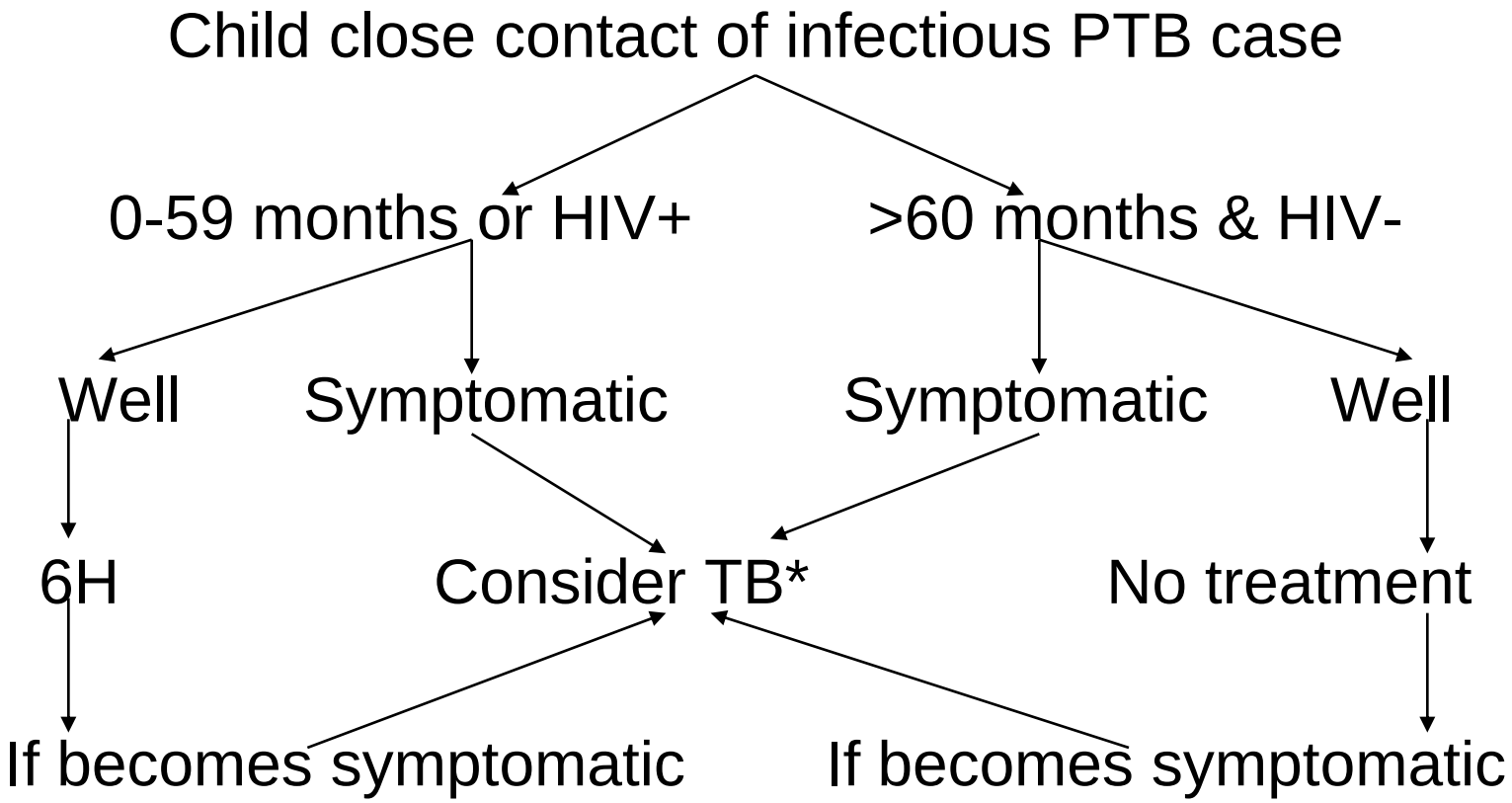
III Lymph node disease / Pleural effusion

IV Adult-type disease

HIV-infected PERSISTENT RISK OF REACTIVATION DISEASE

Courtesy of Ben Marais

Contact management algorithm



***Follow guidelines for diagnosis**

How to investigate contacts

Clinical assessment:

- History (Symptoms; closeness and duration of contact; DST of source case's isolate)
- Clinical examination

Clinical assessment alone is sufficient to decide whether contact is well or symptomatic

If available:

- TST (exposure – preventive Rx even if TST negative)
- CXR (for diagnosis of disease)

If DR-TB suspected and contact is symptomatic or has abnormal CXR – specimens for culture/DST

WHO 2008 Guidelines for Drug-Resistant TB Management - Update

Key recommendations:

- DR-TB contact investigation should be given high priority, and NTPs should consider contact investigation of XDR-TB as an emergency situation
- Close contacts of DR-TB patients should receive careful clinical follow-up

Definition of close contact:

- People living in the same household (adults & children)
- Spending many hours a day together with the patient in the same indoor living space

WHO Guidelines for Drug-Resistant TB Management - 2008 Update

- Contacts of MDR-TB patients may not be infected with the same strain; some may be infected with isoniazid-susceptible strains, particularly in high-burden areas
- Strain concordance of HH members with TB is high: In adults (50-67%) and in child contacts <5 years (75-88%)
- Close contacts of MDR-TB patients should receive careful clinical follow-up for at least two years
- If active disease is present or develops, prompt initiation of MDR-TB treatment is recommended (empiric MDR-TB regimen, even in adults, if DST and culture not available)
- WHO does not recommend the universal use of second-line drugs for preventive therapy in MDR-TB contacts

Guidance for national tuberculosis programmes on the management of tuberculosis in children

Guidelines for the programmatic management of drug-resistant tuberculosis

EMERGENCY UPDATE 2008

NHS
National Institute for Health and Clinical Excellence

Issue date: March 2011

Tuberculosis

Clinical diagnosis and management of tuberculosis, and measures for its prevention and control

This updates and replaces NICE clinical guideline 33

28th Edition

RED BOOK®

2009
Report of the Committee on Infectious Diseases

American Academy of Pediatrics
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The PIH Guide to the Medical Management of Multidrug-Resistant Tuberculosis

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Medical Management of Multidrug-Resistant Tuberculosis

International Edition

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International Edition

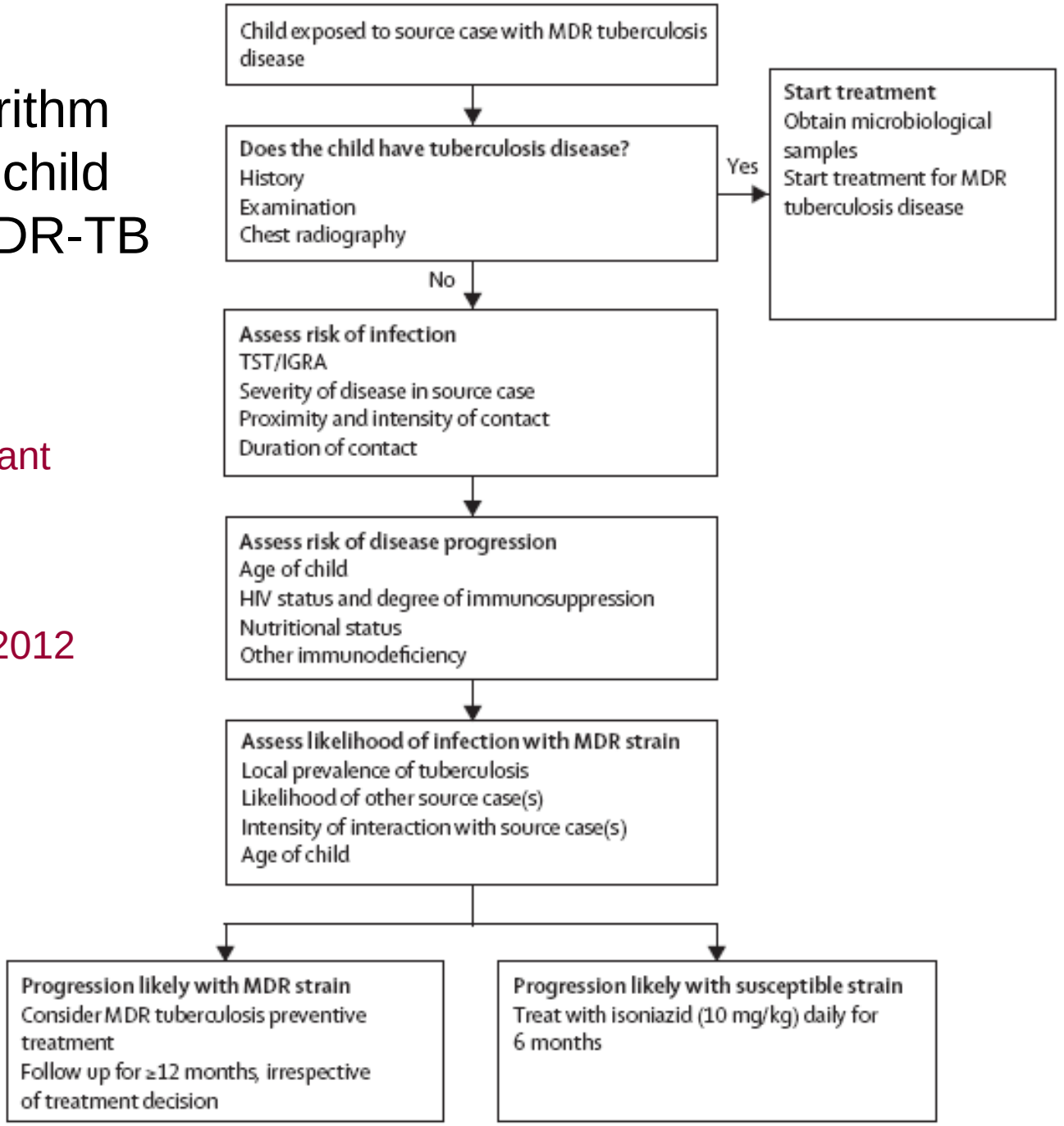
MANAGEMENT OF DRUG-RESISTANT TUBERCULOSIS

POLICY GUIDELINES

health
Department: Health
REPUBLIC OF SOUTH AFRICA

Decision algorithm for assessing child contacts of MDR-TB

Management of children exposed to multidrug-resistant *Mycobacterium tuberculosis*.
Seddon JA et al.
Lancet Infect Dis 2012



ECDC GUIDANCE

Management of contacts of MDR TB and XDR TB patients

www.ecdc.europa.eu

Executive summary

The challenge

Multidrug-resistant tuberculosis (MDR TB) and extensively drug-resistant tuberculosis (XDR TB) are posing a major public health threat as well as a big challenge for TB prevention and control in the European Union and European Economic Area (EU/EEA). As the number of people afflicted with MDR TB or XDR TB increases, so does the number of their contacts – and it is precisely these contacts that need to be identified and properly managed. The management of contacts of MDR TB and XDR TB patients is particularly challenging as the evidence base for best practises is very limited.

Public health guidance

By presenting the most recent scientific evidence and expert opinions on the topic, this document provides guidance on issues relevant to the management of contacts of MDR TB and XDR TB patients. The target audience are public health experts and policy makers in EU/EEA Member States who are developing national guidelines or recommendations on the management of MDR TB and XDR TB contacts.

Two options

In drug-susceptible TB, the provision of preventive therapy to individuals with latent TB infection (LTBI) has been shown to be effective at reducing the risk of developing TB disease among infected contacts. The concept is also valid for MDR TB and XDR TB, but limited by the current lack of availability of drugs shown to be effective against MDR TB and XDR TB infection that show an acceptable adverse-event profile in an otherwise healthy individual.

The alternative to preventive therapy is to provide information and follow-up with careful clinical observation of the identified contact considered to have LTBI. This ensures the early detection of symptoms of TB disease so that TB treatment can be initiated at the earliest possible moment if the disease should develop.

Lack of solid evidence

The evidence for preventive therapy in MDR TB and XDR TB is very scarce. Studies conducted on the benefits and adverse events of preventive therapy are not conclusive. The lack of solid evidence is a limitation when providing guidance on the topic, and the recommendations made are largely based on expert opinions. It should be stressed that, as the current evidence base does neither reject nor support provision of preventive therapy with the currently available drugs, both aforementioned options remain valid for MDR TB and XDR TB infection.

Expert opinions

The expert panel expresses support for the two different options: preventive therapy and/or careful clinical observation. 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.

Conclusion

The management of contacts of MDR TB and XDR TB patients needs to be guided by a comprehensive individual risk assessment that takes into consideration the individual risks and benefits when weighing the pros and cons of preventive therapy.

There is an urgent need for further research, specifically in two areas: studies evaluating the benefits of preventive therapy in MDR TB and XDR TB contacts, and cost-benefit analyses on implementing preventive therapy in EU/EEA Member States. We acknowledge that there are ongoing studies which appear to support the use of preventive therapy, but these results need to be confirmed in larger studies and other settings. Further, additional drugs may become available for the treatment of MDR TB, which will necessitate an update of this guidance document.

ECDC guidance: Summary (1)

- Expresses support for two different options:
  - preventive therapy and/or
  - careful clinical observation

  The central principle is that a comprehensive risk assessment should be part of the evaluation of any 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 DST pattern of the source case
  - the risk for adverse events upon initiating preventive Rx
- In case of XDR-TB, available drug regimens are limited and without proven efficacy, thus close observation is likely the only option.

ECDC Guidance: Summary (2)

- Urgent need for further research, specifically in two areas:
  - studies evaluating the benefit of preventive therapy in MDR-TB and XDR-TB contacts
  - cost-benefit analyses of implementing preventive Rx
- Acknowledge that there are on-going studies which appear to support the use of preventive therapy, but these results need to be confirmed in larger studies and other settings
- Additional drugs may become available for treatment of MDR-TB, which will necessitate an update of this guidance document

CDC - Chuuk study, Micronesia

- Contacts of 2 source cases: strain (A) resistant to HRZES; strain (B) resistant to HREth
- Evaluation of MDR-TB contacts: 15 had MDR-TB disease, 5 had DS-TB, and 119 had LTBI with positive TST.
- LTBI contacts were offered preventive Rx. 14 of the 119 cases refused, preventive Rx was initiated in 105 contacts
- A FQN-based regimen was used: FQN alone or in combination with Eth (strain A) or E (strain B)
- All therapy was DOT x 12 months
- 93 completed the MDR preventive Rx – no TB disease
- 28 contacts (15 initial screen & 11 additionally linked MDR-TB cases in persons not previously identified as contacts, and 2 out of 14 who refused preventive therapy) developed MDR-TB disease

Problems faced with child MDR-TB contacts

- High risk of infection and disease in children <3 years of age, especially breastfeeding infants
- HIV-infected children similar or higher risk
- Extensively drug-resistant (XDR)-TB contacts increasing – which drugs for prevention?
- High TB burden areas:
  - clinical follow-up challenging over long periods
  - >1 source case not uncommon
- Failure of adherent low-dose (4-6mg/kg/d) INH and combination (INH/RMP) preventive Rx common in our experience

Preventive Rx in MDR-TB contacts - systematic review

- Two observational studies met inclusion criteria.
- A prospective cohort study found individualised tailored treatment to be effective for preventing MDR-TB disease in children (OR 0.20, 95%CI 0.04–0.94) (Schaaf et al Pediartrics 2002)
- A retrospective cohort study found INH not to be effective (OR 0.46, 95%CI 0.07–2.32)

Fraser et al. IJTLD 2006

Preventive Rx for MDR-TB contacts - prospective cohort study

- TB in 2 of 41 (5%) children who received 6-month chemoprophylaxis with 2 drugs for which the adult case's strain was susceptible *vs*. 13 of 64 (20%) children who did not receive appropriate preventive Rx developed TB (p=0.05)
- Significant differences (more in prophylaxis group)
  - younger age
  - more often Mantoux TST ≥15mm induration
  - more smear-positive index cases (95% vs 67%)
  - less previous preventive Rx or treatment (HRZ)
- This implies that appropriate MDR preventive Rx could be effective in preventing MDR TB

Schaaf et al. Pediatrics 2002

Why consider high-dose INH?

- In one study, 38 of 45 INH resistant isolates were resistant at 0.1-0.2µg/mℓ but susceptible at 5.0µg/mℓ. Only 7 resistant at 5µg/mℓ or more

Schaaf et al. Eur J Clin Microbiol Infect Dis 2007

- *inhA* promoter region mutations, which make up 60% of current MDR-TB cases and 80-90% of XDR-TB cases' INH conferring mutations (WC & EC provinces) usually causes low-level INH resistance

- High-dose INH at 15-20mg/kg/day could still add value preventive therapy of child contacts of MDR/XDR-TB cases

Recent preventive Rx study WC

- 215 children, median age 31 months (IQR: 13-45) – contacts of MDR-TB or (pre)-XDR-TB cases
- 10 of 207 (4.8%) children tested for HIV were positive
- Children received:
  - 6hdHEO (n=192; 89%) if MDR-TB case's isolate was susceptible to ofloxacin or
  - 6hdH (n=23; 11%) if (pre)-XDR-TB case's isolate was resistant to ofloxacin

- Seddon & Schaaf et al – to be submitted

Recent preventive Rx study WC

Results:

- One child (0.5%), died – not TB related
- 7 (3%) developed incident TB
- 4 (2%) were lost to follow-up
- Adherence was good in 165 (77%) children
- Risk factors for poor patient outcome were:
  - HIV positivity (RR 9.87, 95%CI 0.97-55.2; p=0.05)
  - poor adherence (RR 9.66, 95%CI 1.73-97.9; p=0.006).
  - children older than 12 months had less risk of poor outcome (RR 0.16, 95%CI: 0.002-0.81; p=0.02).

Recent preventive Rx study WC

- Few children prescribed this standardized preventive therapy regimen developed TB or died if adherent to therapy
- Consideration should be given to providing preventive therapy to young children and HIV-infected children irrespective of age following exposure to MDR-TB
- HIV-infected children and infants are at particular high risk of poor outcomes (death/TB)
- RCT with a FQN + hdH vs hdH only is needed

Preventive Rx for DR-TB contacts

- No RCT available.
- Failure of INH or INH/RMP to prevent MDR-TB reported.
- INH mono-resistance: RMP x 4 mo
- RMP-monoresistance: INH x 6 mo (LPA and Xpert?)
- MDR-TB: EMB or ETH + OFX/LFX x 6-12 mo (?)
- Pre-XDR or XDR-TB – only high-dose INH (15-20mg/kg)?
- In both MDR and XDR-TB regular clinical follow-up is indicated: both ECDC and WHO recommends 2 years of follow-up (minimum is 1 year – 95% disease in 1 year). Pendulum swinging towards preventive treatment.

Our current practice

SA NTP 2011 guidelines: INH 15 mg/kg/d x 6 months

At our clinic we do the following:

- Exclude active TB disease (culture/DST if suspected)
- Long-term (12-24 months) follow-up (clinical, CXR and cultures when indicated); >90% children develop TB within 1 year of exposure/infection
- Preventive Rx: <5 year olds and HIV-infected children
- Preventive Rx (for 6 months):
  - INH at high-dose (15-20mg/kg/d)
  - A fluoroquinolone – OFX/LFX
  - Ethambutol – DST result adult case (not available!)
- Older children – Evaluate and symptomatic follow-up only

Conclusions

- Appropriate MDR preventive Rx – using 2 drugs with/without high-dose INH – could be effective in preventing MDR-TB in children
- There is an urgent need to address this issue in a randomised controlled trial(s)
- Single drug chemoprophylaxis with a fluoroquinolone (e.g. levofloxacin) or novel anti-TB agent is considered
- Until such a trial is conducted, routine clinical data collected as part of existing TB control programmes could be useful
- What about XDR-TB contact? Careful follow-up and possibly high-dose INH are probably the only options – treat as XDR-TB if TB develops

- Financial Support: SA National Research Foundation, SA MRC, USAID Treat-TB