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TB CARE II

DR|TB TRAINING NETWORK

Regimen Design and Dosing for Children with Drug-Resistant TB: A Case-Based Discussion

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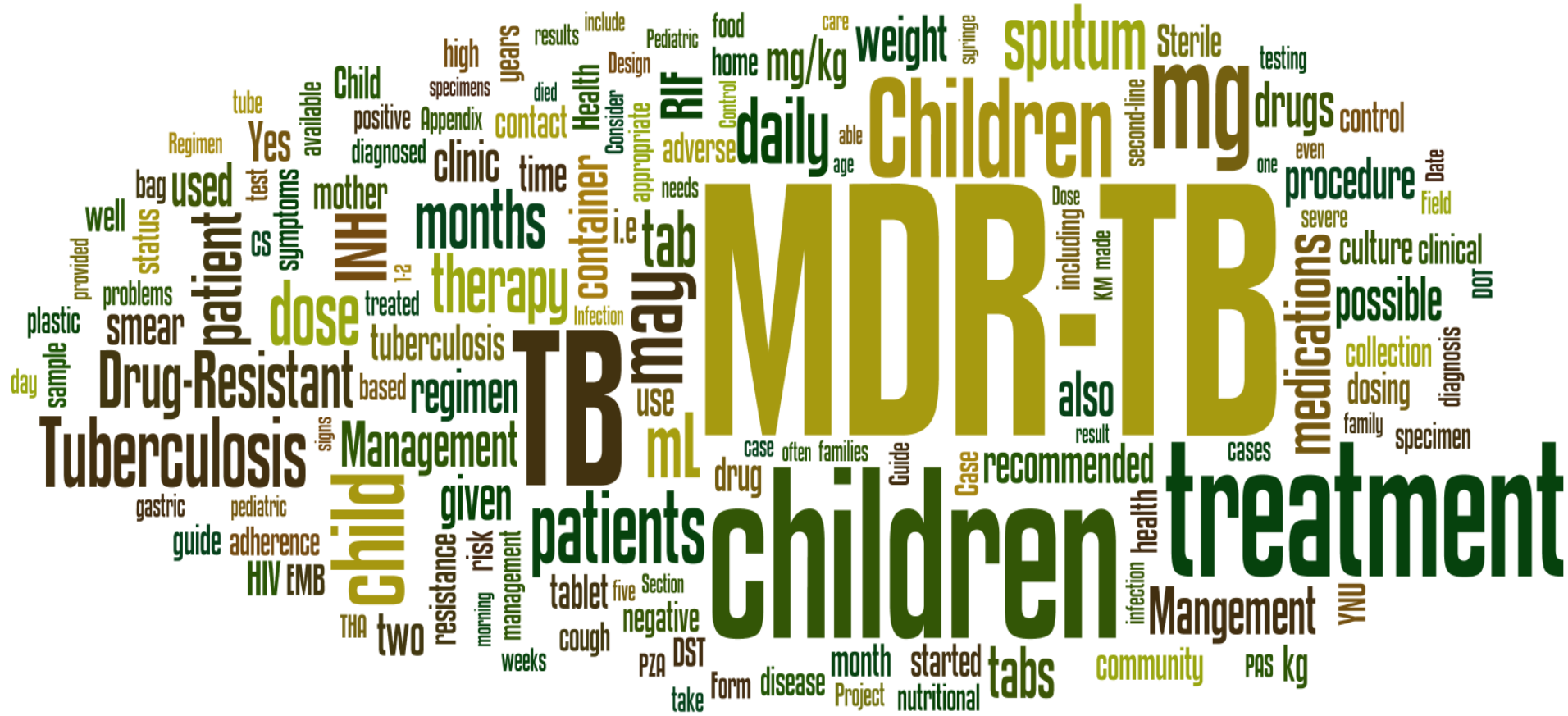
www.drtbnetwork.org

A three-year old child with fever, lethargy and difficulty walking

James Seddon

Jennifer Furin


MDR-TB
TB
Tuberculosis
Drug-Resistant
children
treatment
Children
mg
sputum
daily
weight
mg/kg
patients
patient
dose
therapy
months
INH
RIF
tab
may
mL
child
used
Yes
Management
given
two
tabs
Mangement
medications
procedure
possible
also
recommended
drugs
control
clinic
contact
container
time
mother
tuberculosis
regimen
smear
culture
clinical
collection
dosing
specimen
Sterile
testing
second-line
adverse
appropriate
Health
Consider
Design
Pediatric
food
home
care
syringe
results
include
years
high
specimens
Appendix
positive
diagnosed
available
Child
tube
Regimen
bag
well
status
test
symptoms
cs
provided
problems
plastic
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signs
gastric
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guide
adherence
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PAS
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health
infection
YNU
case
often
families
Guide
Case
drug
result
cases
family
diagnosis
DOT
Date
field
severe
even
one
needs
Dose
including
KM
made
treated
based
Infection
i.e
1-2
Control
able
age
Pediatric
syringe

Objectives

- Illustrate a pediatric case of MDR-TB
- Demonstrate when to suspect MDR-TB in a child and when to start treatment
- Understand how to construct MDR-TB treatment regimens in children
- Consider the dosage calculations of second-line TB drugs in children
- Review recent and future developments in the treatment of MDR-TB in children

Case History

- CC is a three-year-old boy who has been in the hospital for 4 weeks at the time of consultation
- He was brought to the health center by his mother nearly 6 weeks ago when she noted he was febrile, lethargic, and seemed to have little interest in playing
- At the center he was given some “antibiotics” and told to come back in one week

Case History

- The following week his mother brought him back and she reported he was no better and that he seemed to want to be carried all the time
- He was given some vitamins and sent home

Case History

- Six days later, his mother brought him to the hospital when he could no longer stand on his own and she noticed a “lump” on his back
- At that time, she also noted he was coughing and losing weight and was barely eating anything

Questions

1) What is the most likely disease to consider in the in the differential diagnosis?

2) What additional information would you want to know?

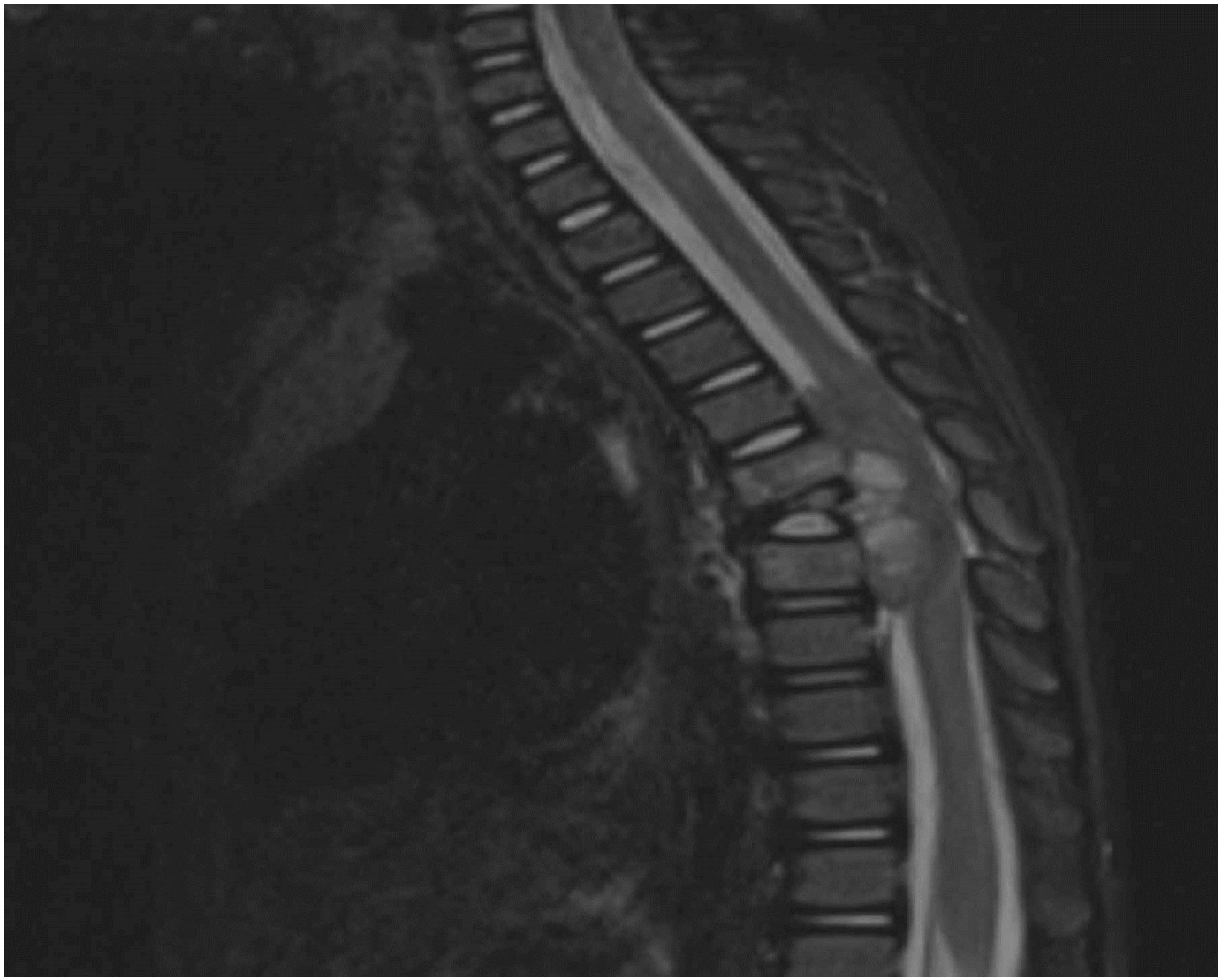
Case History

- T=39 degrees
- Weight=8.2kg length=67cm
- Pale, listless, lymphadenopathy, tachypnea, crackles and wheezes bilaterally
- Absent ankle reflexes, no spontaneous leg movement
- Fully vaccinated, HIV status unknown, uncle living in house with TB
- CXR and spine MRI shown


R

Questions

3) What is the most likely cause of this x-ray appearance?



Case History

- Admitted to the hospital and started on therapy for presumed TB with HRZE
- Gastric aspirates were obtained and shown to have AFB, but cultures were not done on the specimens (as was standard care in the NTP at the time this child presented)
- He was also started briefly on corticosteroids, but these were stopped after a week, as his physicians decided he had Potts' disease and not TB meningitis

Case History

- His condition, however, continued to deteriorate, and he eventually became bedbound, lying almost motionless in a crib with an oxygen mask over his face
- He was so malnourished, he began to develop pressure sores, including over the bridge of his nose where the oxygen mask was placed

Questions

4) What is the most likely cause of his deterioration?

5) What information would be most helpful to try and obtain?

Case History

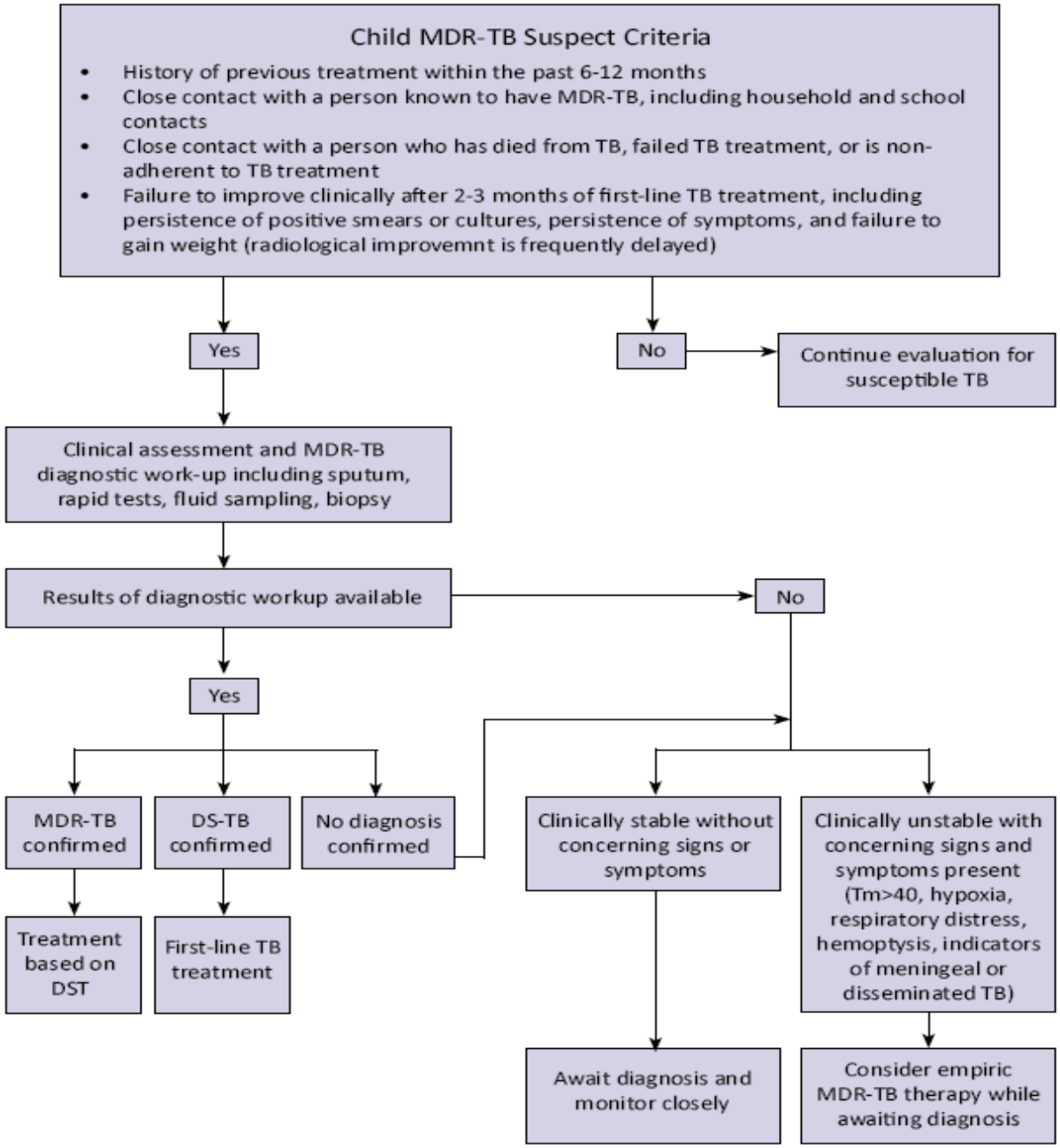
- Upon further questioning, his mother reported that the uncle who lived with them was started on treatment for a form of “strong TB”
- Uncle had MDR-TB with resistance to isoniazid, rifampin, ethambutol, and streptomycin and was on a regimen of pyrazinamide-kanamycin-levofloxacin-ethionamide-and cycloserine

Case Discussion

6) What is the most important thing to do next?

7) What drugs would you put in the treatment regimen?

When to Suspect Drug-Resistant Tuberculosis in children


Child MDR-TB Suspect Criteria
History of previous treatment within the past 6-12 months
Close contact with a person known to have MDR-TB, including household and school contacts
Close contact with a person who has died from TB, failed TB treatment, or is non-adherent to TB treatment
Failure to improve clinically after 2-3 months of first-line TB treatment, including persistence of positive smears or cultures, persistence of symptoms, and failure to gain weight (radiological improvemnt is frequently delayed)
Yes
No
Continue evaluation for susceptible TB
Clinical assessment and MDR-TB diagnostic work-up including sputum, rapid tests, fluid sampling, biopsy
Results of diagnostic workup available
No
Yes
MDR-TB confirmed
DS-TB confirmed
No diagnosis confirmed
Clinically stable without concerning signs or symptoms
Clinically unstable with concerning signs and symptoms present (Tm>40, hypoxia, respiratory distress, hemoptysis, indicators of meningeal or disseminated TB)
Treatment based on DST
First-line TB treatment
Await diagnosis and monitor closely
Consider empiric MDR-TB therapy while awaiting diagnosis

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No

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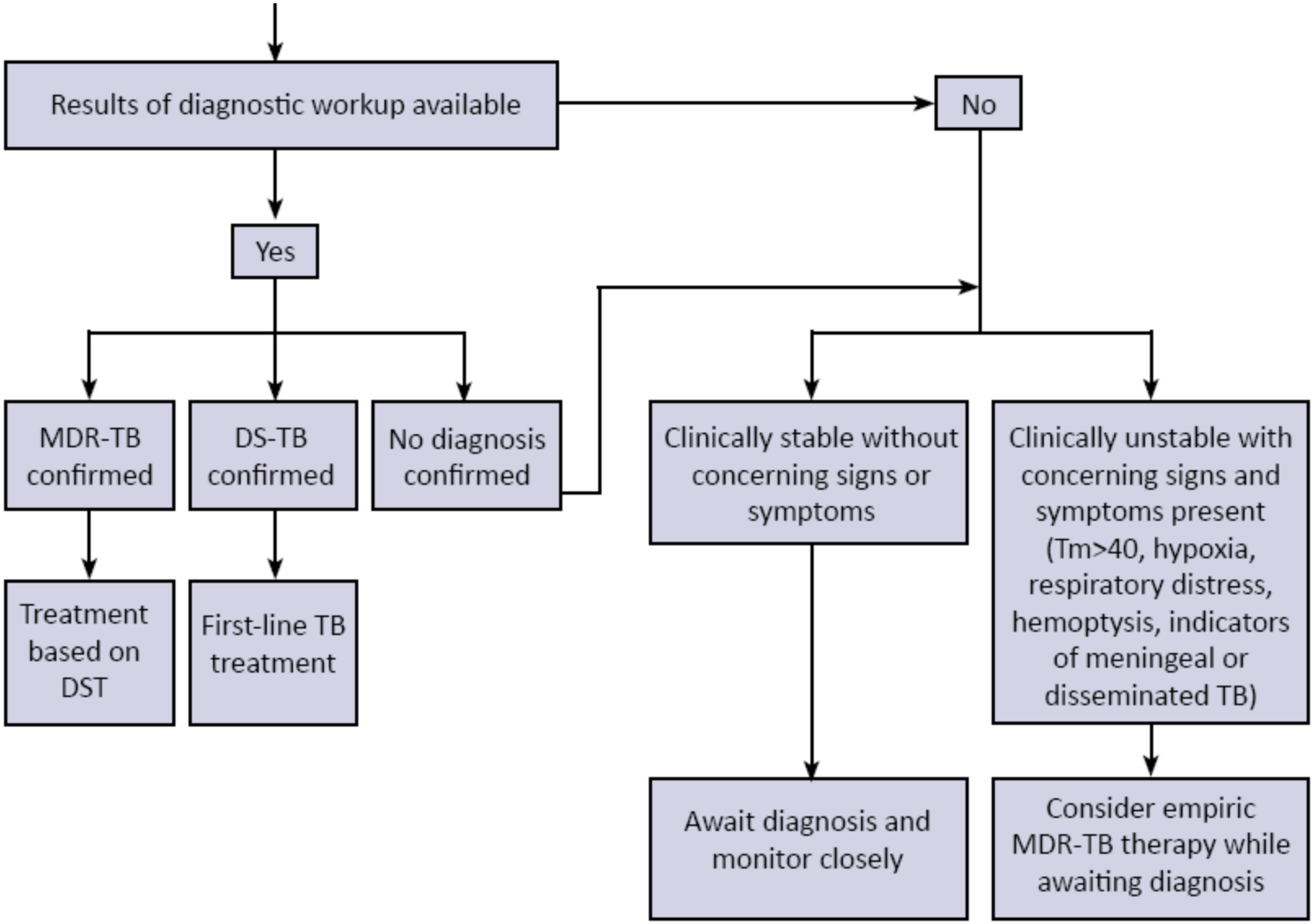
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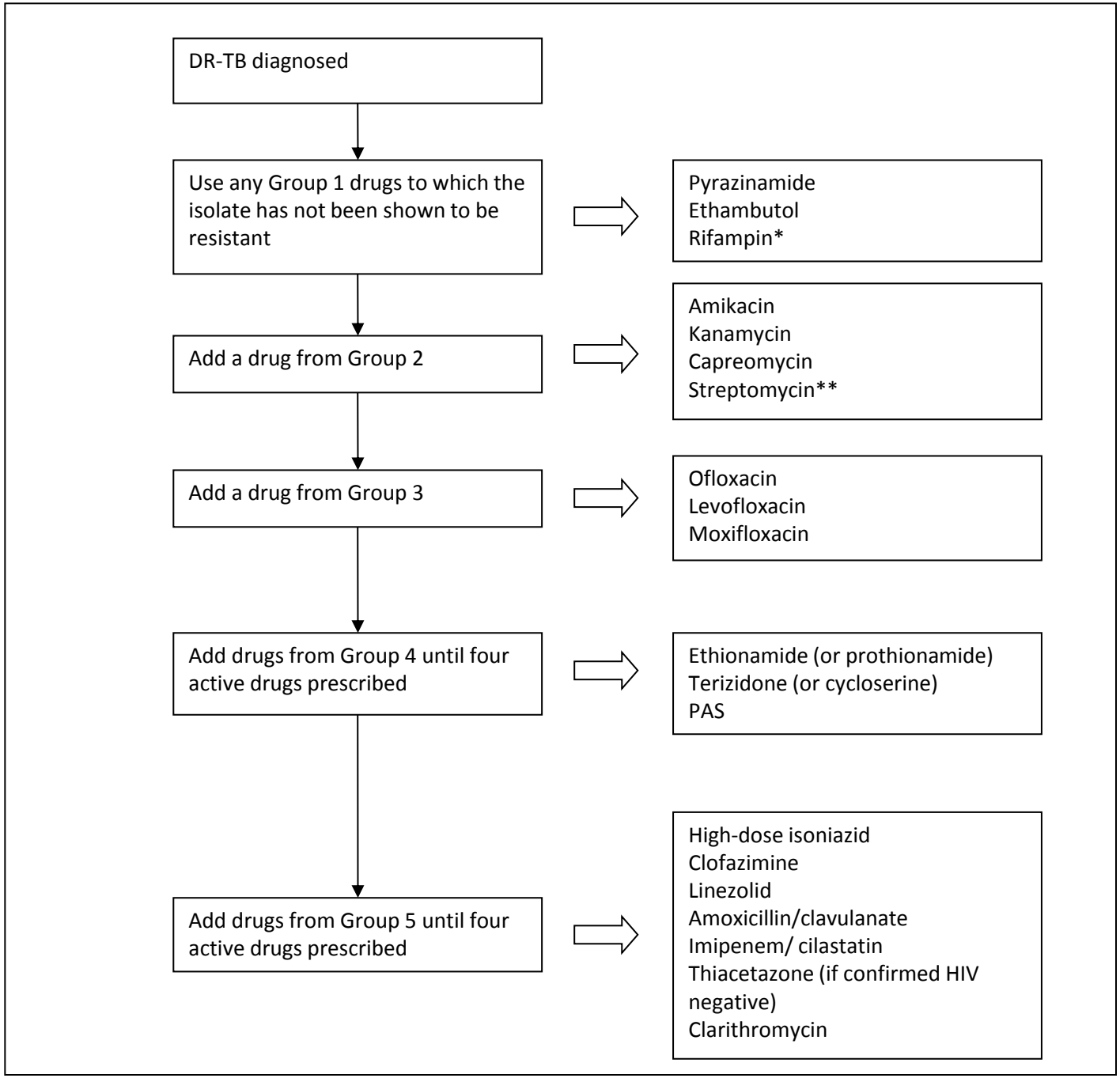
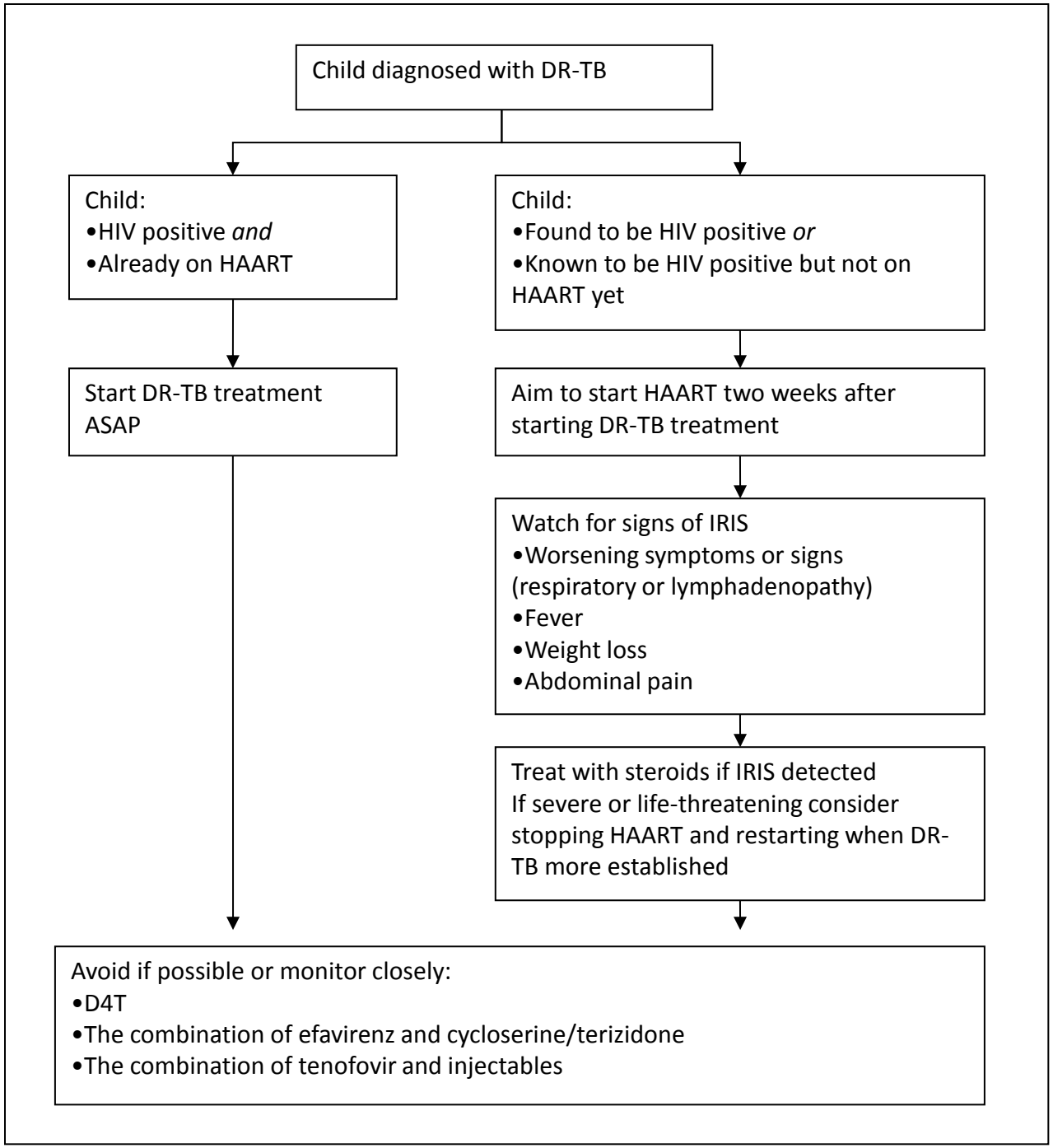
The Treatment of Children with Drug-Resistant Tuberculosis Disease


DR-TB diagnosed
Use any Group 1 drugs to which the isolate has not been shown to be resistant
Pyrazinamide
Ethambutol
Rifampin*
Add a drug from Group 2
Amikacin
Kanamycin
Capreomycin
Streptomycin**
Add a drug from Group 3
Ofloxacin
Levofloxacin
Moxifloxacin
Add drugs from Group 4 until four active drugs prescribed
Ethionamide (or prothionamide)
Terizidone (or cycloserine)
PAS
Add drugs from Group 5 until four active drugs prescribed
High-dose isoniazid
Clofazimine
Linezolid
Amoxicillin/clavulanate
Imipenem/ cilastatin
Thiacetazone (if confirmed HIV negative)
Clarithromycin

HIV Co-Infection


Child diagnosed with DR-TB
Child:
•HIV positive *and*
•Already on HAART
Start DR-TB treatment ASAP
Child:
•Found to be HIV positive *or*
•Known to be HIV positive but not on HAART yet
Aim to start HAART two weeks after starting DR-TB treatment
Watch for signs of IRIS
•Worsening symptoms or signs (respiratory or lymphadenopathy)
•Fever
•Weight loss
•Abdominal pain
Treat with steroids if IRIS detected
If severe or life-threatening consider stopping HAART and restarting when DR-TB more established
Avoid if possible or monitor closely:
•D4T
•The combination of efavirenz and cycloserine/terizidone
•The combination of tenofovir and injectables

Drug Usage, Preparation and Dosing

Drugs

	Drug	Dose
Group 1	Isoniazid	15-20mg/kg
	Pyrazinamide	30-40mg/kg
	Ethambutol	20-25mg/kg
Group 2	Amikacin	15-20mg/kg
	Capreomycin	15-30mg/kg
Group 3	Levofloxacin	15-20mg/kg
	Moxifloxacin	7.5-10mg/kg
Group 4	Ethionamide	15-20mg/kg
	Terizidone	15-20mg/kg
	PAS	150mg/kg
Group 5	Linezolid	10mg/kg bd
	Augmentin	15mg/kg tds
	Clarithromycin	7.5mg/kg bd

MDR-TB Weight-Based Dosing Chart for Children

	Group 1: Oral first-line anti-TB drugs				Group 2:	Group 3: Fluoroquinolones					Group 4: Oral bacteriostatis agents					Group 5:		
Target Dose	Ethambutol (15-25 mg/kg)		Pyrazinamide (30-40 mg/kg)		Injectable anti-TB drugs (injectable agents or parental agents)	Levofloxacin (15-20 mg/kg)		Moxifloxacin (7.5-10 mg/kg)		Ofloxacin (15-20 mg/kg)	Cycloserine/ Terizidone (15-20 mg/kg)		PAS (150-200 mg/kg)		Protionamide/ Ethionamide (15-20 mg/kg)	Anti-TB drugs with unclear efficacy or unclear role in MDR-TB treatment	Isoniazid High Dose (15-20 mg/kg)	Target Dose
Available Formulations	100 mg tablet	Suspend 400mg tab in 8 mL of water for a 50 mg/mL suspension	400 mg tablet	500 mg tablet		250 mg tablet	25 mg/mL suspension	400 mg tablet	20 mg/mL suspension	200 mg tablet	250 mg capsule	1 capsule in 10 mL water	Daily	Twice Daily	250 mg tablet		100 mg tablet	Available Formulations
Wt (kg)	Consult with a clinician experienced in pediatric MDR-TB prescribing for neonates (<28 days of age) and infants weighing <3 kg																	Wt (kg)
<3																		<3
3-3.9	1 tab	2 mL	.25 tab	.25 tab	To illustrate dose calculation, take the example of a child that weighs 6.9 kg. Both the low and high doses for the child's weight are calculated. For kanamycin: Low dose: 15 mg/kg x 6.9 kg = 103 mg High dose: 20 mg/kg x 6.9 kg = 138 mg A convenient dosing is then chosen between the two numbers. Select a dose between the two numbers and towards the higher number. In this case, choose: 125 mg per day, single dose. Calculate the number of mL to draw up in the syringe based on the mg/mL concentration of the preparation.	.25 tab	2.5 mL	not recommended	1.5 mL	.5 tab	.25 cap	2.5 mL	500 mg	250 mg	.25 tab	Group 5 drugs are not recommended by the WHO for routine use in MDR-TB treatment because their contribution to the efficacy of MDR regimens is unclear. Their role in pediatric MDR-TB treatment is even less clear. Most of these drugs are expensive, and some require intravenous administration, and/or have severe side effects. However, they can be used in cases where adequate regimens are impossible to design with the medications from Groups 1-4. They should be used in consultation with an expert in the treatment of DR-TB.	.5 tab	3-3.9
4-4.9									2 mL				1000 mg	500 mg				4-4.9
5-5.9			.5 tab	.5 tab		.5 tab	5.0 mL		2.5 mL		.5 cap	5 mL			.5 tab		1 tab	5-5.9
6-6.9													1500 mg	750 mg				6-6.9
7-7.9		4 mL																7-7.9
8-8.9	2 tabs								5 mL	1 tab								8-8.9
9-9.9			1 tab			.75 tab	7.5 mL				.75 cap	7.5 mL	2000 mg	1000 mg	.75 tab		2 tabs	9-9.9
10-10.9																		10-10.9
11-11.9																		11-11.9
12-12.9				1 tab		1 tab	10 mL				1 cap	10 mL			1 tab			12-12.9
13-13.9	3 tabs	6 mL											2500 mg	1250 mg			3 tabs	13-13.9
14-14.9																		14-14.9
15-15.9			1.5 tabs						7.5 mL	1.5 tabs								15-15.9
16-16.9	4 tabs	8 mL											3000 mg	1500 mg				16-16.9
17-17.9																		17-17.9
18-18.9						1.5 tabs	15 mL	.5 tab			1.5 caps	15 mL			1.5 tabs			18-18.9
19-19.9																		19-19.9
20-20.9									10 mL	2 tabs								20-20.9
21-21.9			2 tabs										4000 mg	2000 mg			4 tabs	21-21.9
22-22.9																		22-22.9
23-23.9																		23-23.9
24-24.9																		24-24.9
25-25.9				1.5 tabs														25-25.9
26-26.9													5000 mg	2500 mg			5 tabs	26-26.9
27-27.9	5 tabs	10 mL	2.5 tabs	2 tabs		2 tabs	20 mL				2 caps	20 mL			2 tabs			27-27.9
28-28.9									12.5 mL	2.5 tabs								28-28.9
29-29.9													6000 mg	3000 mg				29-29.9

For preventive regimens, consult with experts regarding optimal regimen construction.
The doses of isoniazid, ethambutol, and fluoroquinolones for preventive regimens are the same as in this dosing chart.

Group 2	Steptomycin	Amikacin	Kanamycin	Capreomycin
Daily Dose	20-40 mg/kg once daily	15-20 mg/kg once daily	15-20 mg/kg once daily	15-20 mg/kg once daily
Maximum Daily Dose	1000 mg	1000 mg	1000 mg	1000 mg

Group 5	Clofazimine (CFZ)	Amoxicillin-clavulanate (AMX-CLV)	Meropenem (MPN)	Linezolid (LZD)	Clarithromycin (CLR)
Daily Dose	2-3 mg/kg once daily; if the child is <25kg give 100mg every second day	80 mg/kg in two divided doses based on the amoxicillin component	20-40 mg/kg IV every 8 hours	10 mg/kg dose twice daily for children <10 years of age 300 mg daily for children >10 years of age (also give vitamin B6)	7.5 mg/kg twice daily
Maximum Daily Dose	200 mg	4000 mg amoxicillin and 500 mg clavulanate	6000 mg	600 mg	1000 mg

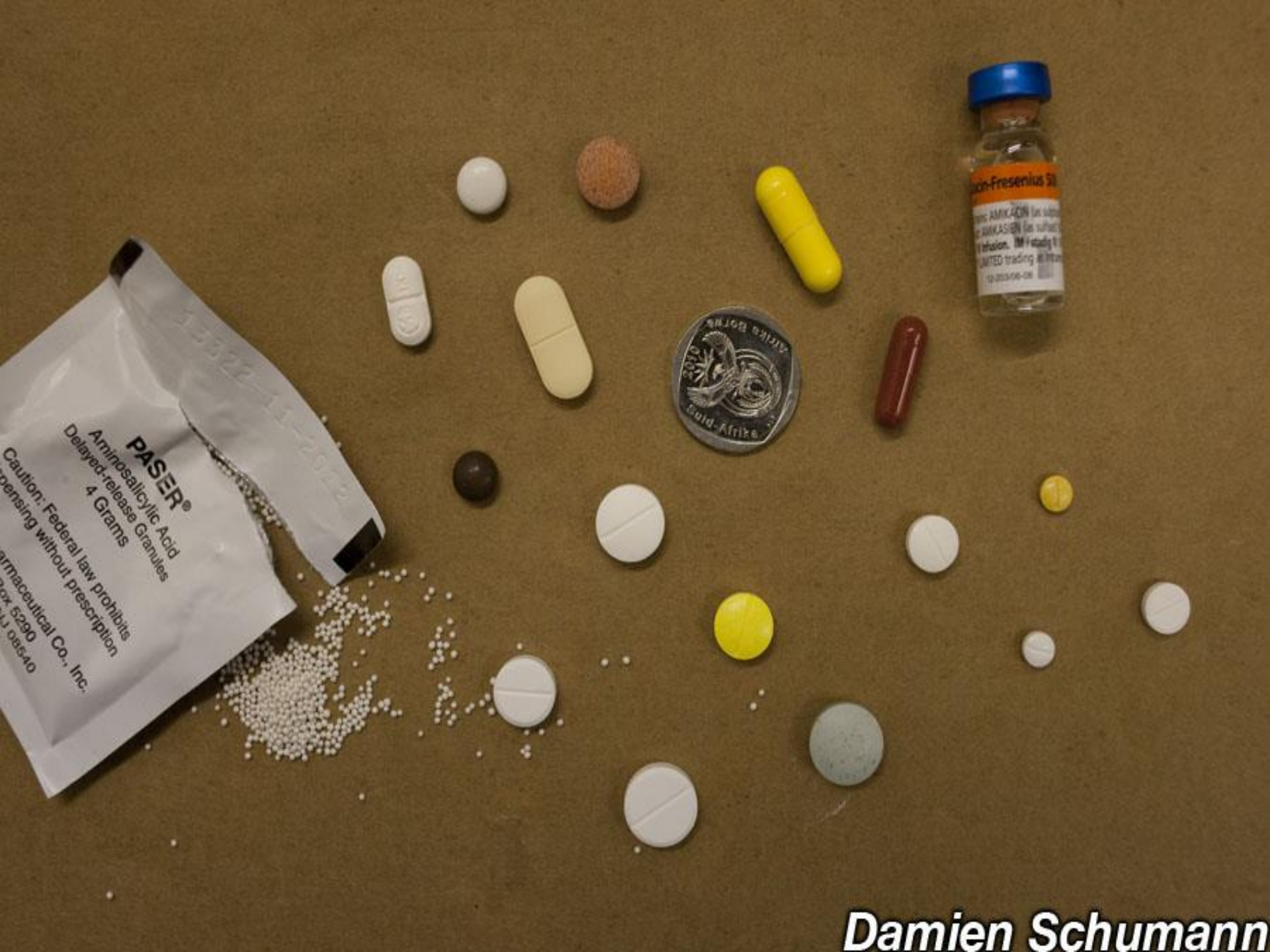
ZERO child deaths from DR-TB
Sentinel Project on pediatric drug-resistant tuberculosis

http://sentinel-project.org

v1.1

Example

- Prescribing for a 6kg child with XDR-TB:
  - Pyrazinamide (6x35=210) Tablet 500mg
  - Ethambutol (6x25=150) Tablet 400mg
  - Moxifloxacin (6x10=60) Tablet 400mg
  - Ethionamide (6x20=120) Tablet 250mg
  - Terizidone (6x20=120) Capsule 250mg
  - PAS (6x150=900) Sachet 4000mg
  - Linezolid (6x10=60) Tablet 600mg

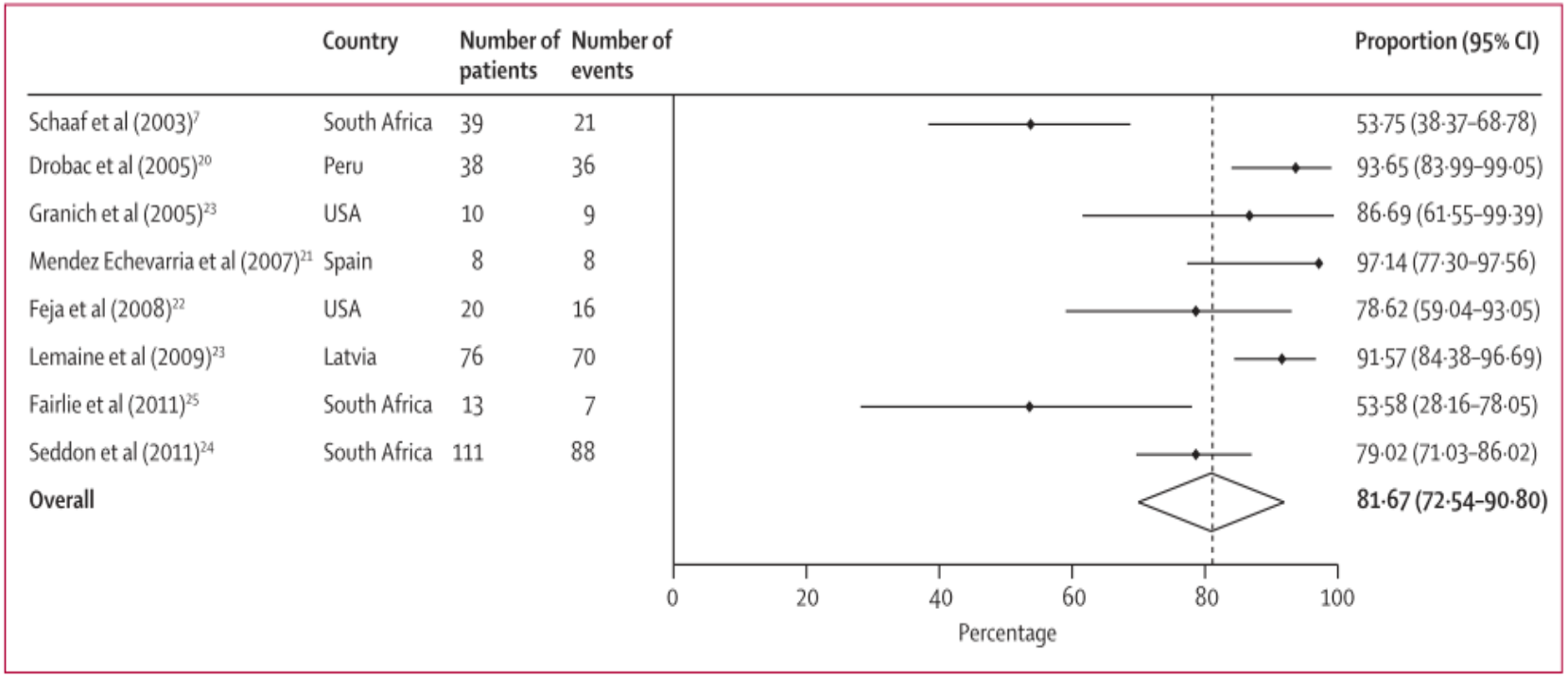

PASER®
Aminosalicylic Acid
Delayed-release Granules
4 Grams
Caution: Federal law prohibits
pensing without prescription
rmaceutical Co., Inc.
ox 5290
J 08540
Gold-Africa
Damien Schumann

Strategies for Administration of Second-Line Drugs in Children

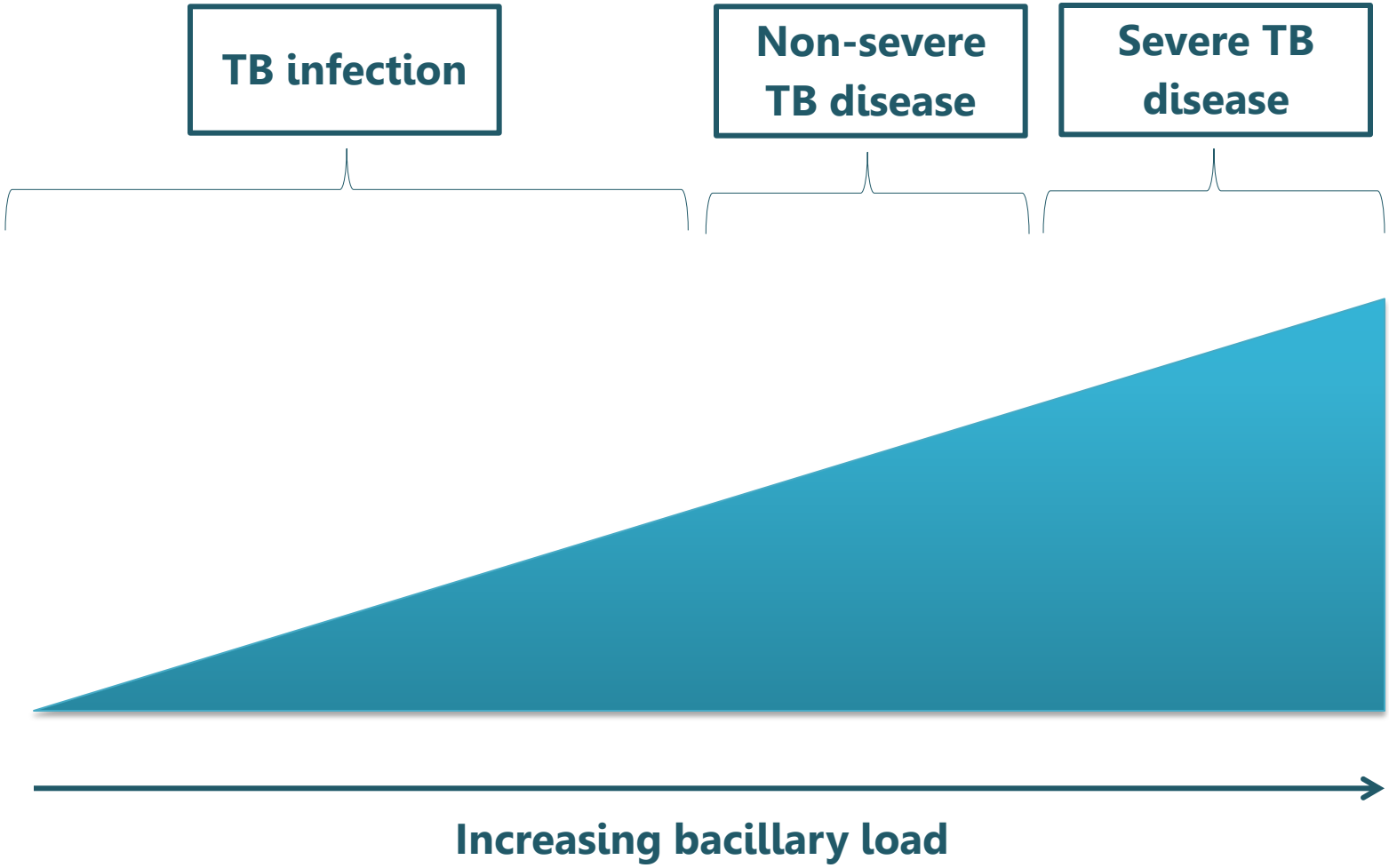
- Depend on age of child
- Injectable is painful: consider mixing with lignocaine, using hot compresses
- Pills can be difficult to swallow: consider mixing with palatable and nutritious foods and beverages
- Nasogastric tube administration may be necessary as a temporary measure
- Compounding may be needed for some drugs and ages
- Involve children and families in adherence measures and administration
- Cutting and crushing of tablets should be done by health providers wherever possible to reduce risk of errors
- If tablets cannot be crushed or cut or compounded, could try giving higher doses every other day (i.e. with CFZ)

Review of MDR-TB treatment studies in children

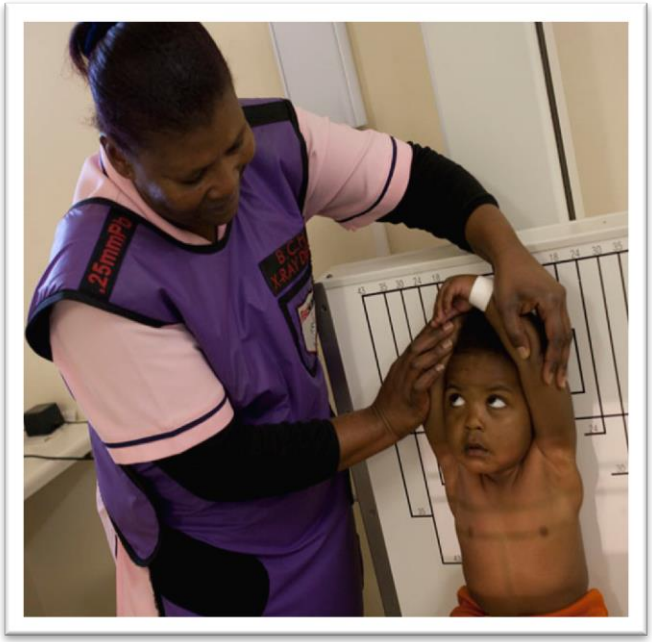
Treatment outcomes for children with multidrug-resistant tuberculosis: a systematic review and meta-analysis

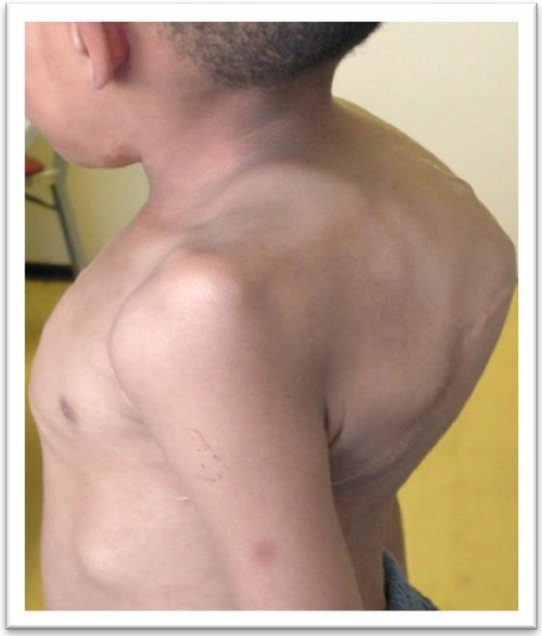


Ettehad et al. Lancet Infect Dis. 2012; 12(6): 449-456



Wiseman et al. Pediatr Infect Dis J 2012; 31(4): 347-352





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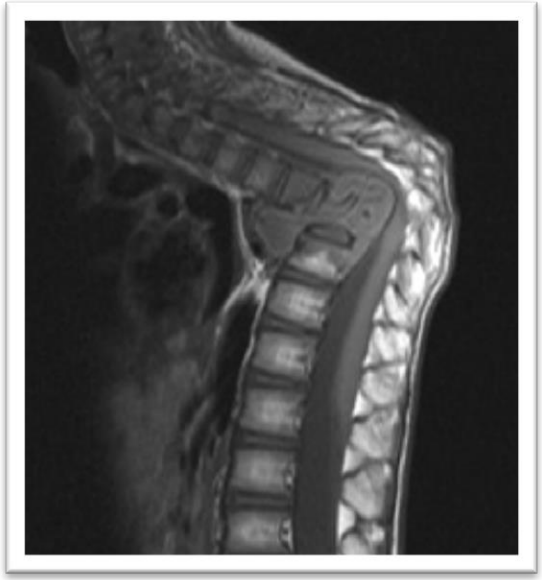
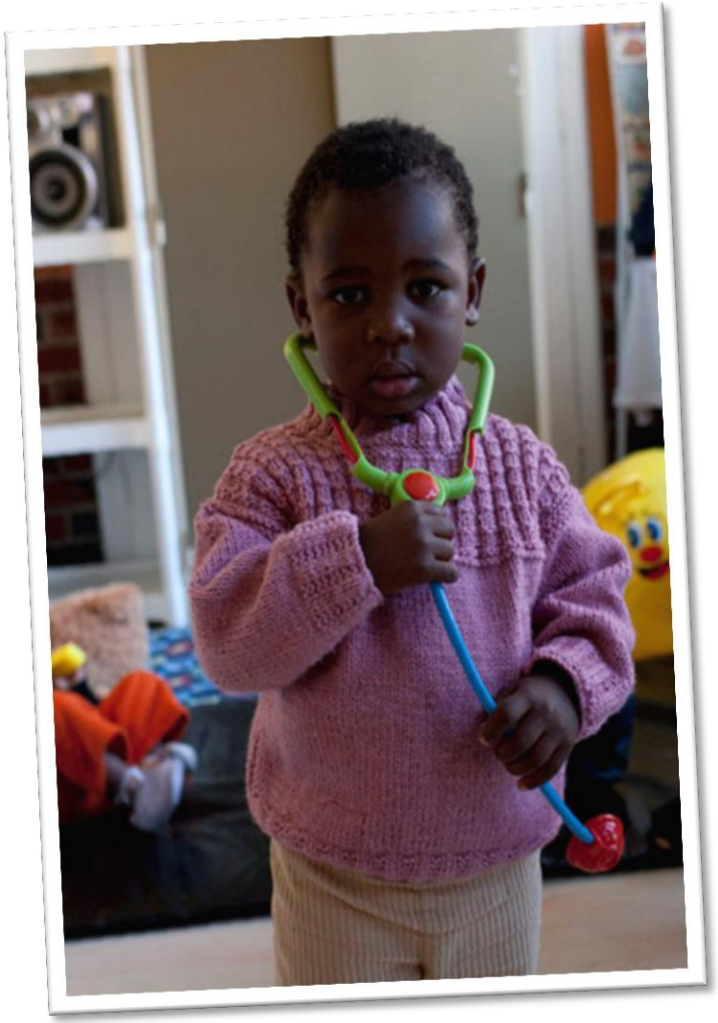


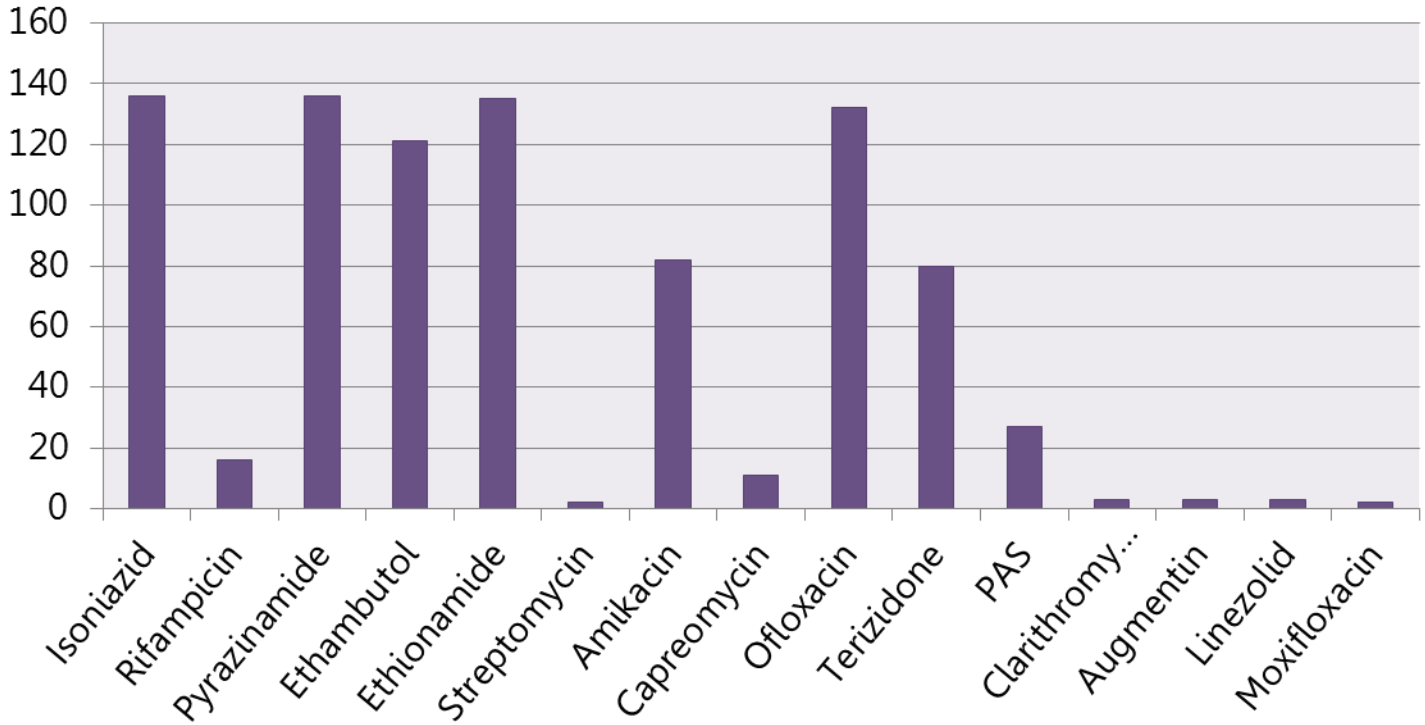
Wiseman et al. Pediatr Infect Dis J 2012; 31(4): 347-352

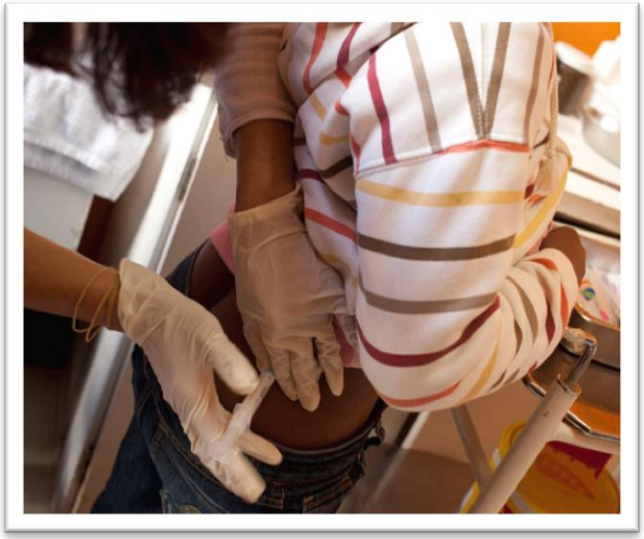
MDR-TB treatment Cape Town



- 149 children
- Median age: 36 months (IQR: 16-66)
- Male gender: 69 (46.3%)
- HIV-infected 32 of 146 tested (21.9%)

Thorax 2014; 69: 458-464





Thorax 2014; 69: 458-464

Treatment and Outcome

	Severe disease (n=45)	Non-severe disease (n=104)	OR (95% CI)	p-value
Hospital admission	42 (93.3)	61 (58.7)	9.87 (2.64-36.9)	<0.001
Injectable TB drug use	39/41 (95.1)	55/101 (54.5)	16.3 (3.27-81.3)	<0.001
Median duration of injectable drug	6 (4-6)	4 (3-5)		<0.001
Median total duration of therapy	18 (18-20)	12 (10-16)		<0.001
Mortality	3 (6.7)	0		0.008

Thorax 2014; 69: 458-464

Case Discussion

- CC was started on am empiric treatment regimen based on the DST pattern of his uncle, since he was most likely exposed to him in the home
- This regimen included PZA-Kanamycin-Levofloxacin-ethionamide-cycloserine
- Plan to treat for 24 months given extent of disease with injectable given for 6 months
- A gastric aspirate was also obtained that day and sent for culture

Case Discussion

- After 1.5 months of empiric MDR-TB treatment, the gastric aspirate done at the time of initiation of his MDR-TB treatment regimen showed that CC had resistance to HRES, KM, CM, and AMK.
- His KM was changed to CM and the rest of his regimen continued

Questions

8) If CC were being treated today, what might be some strategies for him?

The Future

- Re-tooling existing drugs
- New PK data on second-line drugs
- New drugs
- New regimens
- Host-directed therapies

Retooling existing agents

- Clofazimine
- Thioridazine
- Fluoroquinolones
- Linezolid
- Beta Lactams
- Co-trimoxazole
- Metronidazole
- Tetracyclines
- Disulfiram

Dooley et al. 2013; J Infect Dis 207(9): 1352-1358, Alsaad et al. Eur Resp J 2014; 43: 884-897

Two Pediatric Cases of Multidrug-Resistant Tuberculosis Treated With Linezolid and Moxifloxacin

Linezolid-containing regimens for the treatment of drug-resistant tuberculosis in South African children

REVIEW

Linezolid for the treatment of drug-resistant tuberculosis in children: A review and recommendations

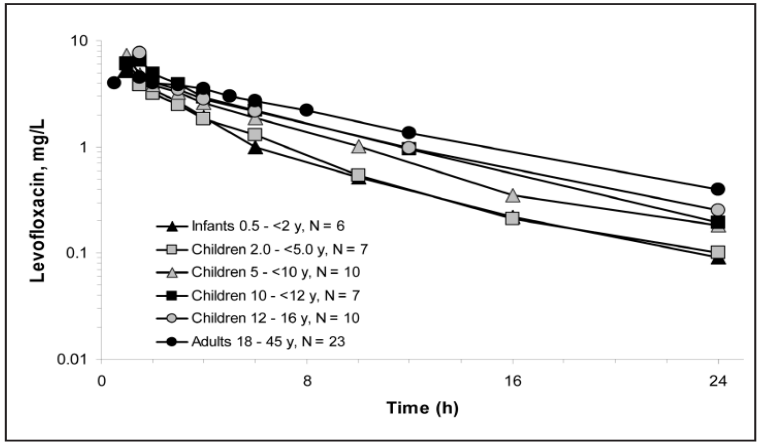
Linezolid for Treatment of Chronic Extensively Drug-Resistant Tuberculosis

MEROPENEM/CLAVULANATE AND LINEZOLID TREATMENT FOR EXTENSIVELY DRUG-RESISTANT TUBERCULOSIS

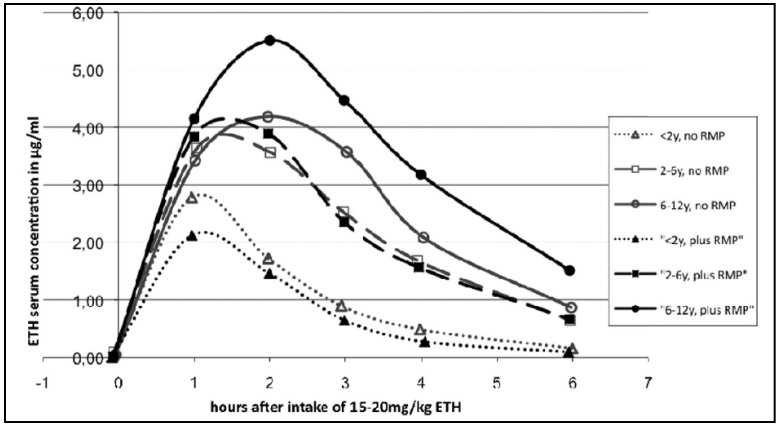
Linezolid in the Treatment of Multidrug-Resistant Tuberculosis

PK data in children

- Efficacy can be determined from adult studies
- Specific issues around
  - Toxicity and tolerability
  - Formulations
  - Pharmacokinetics

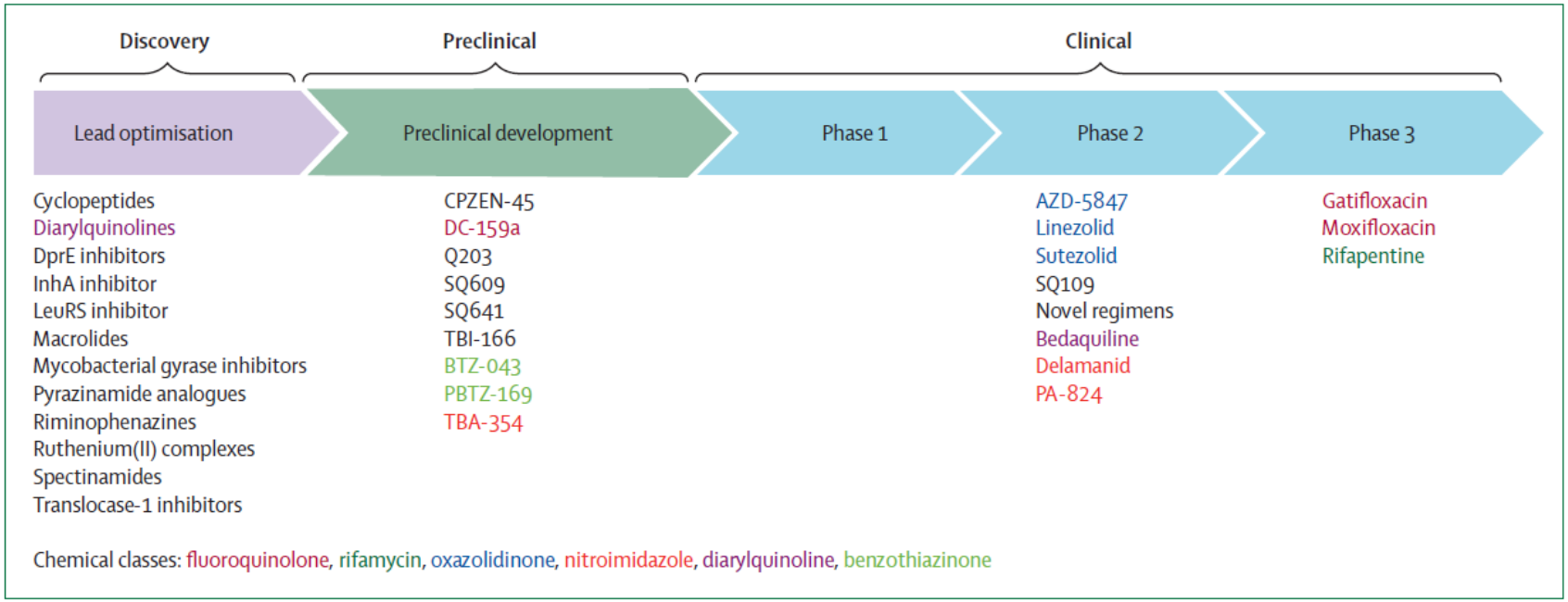


Chien et al. J Clin Pharm 2005; 45: 153-160

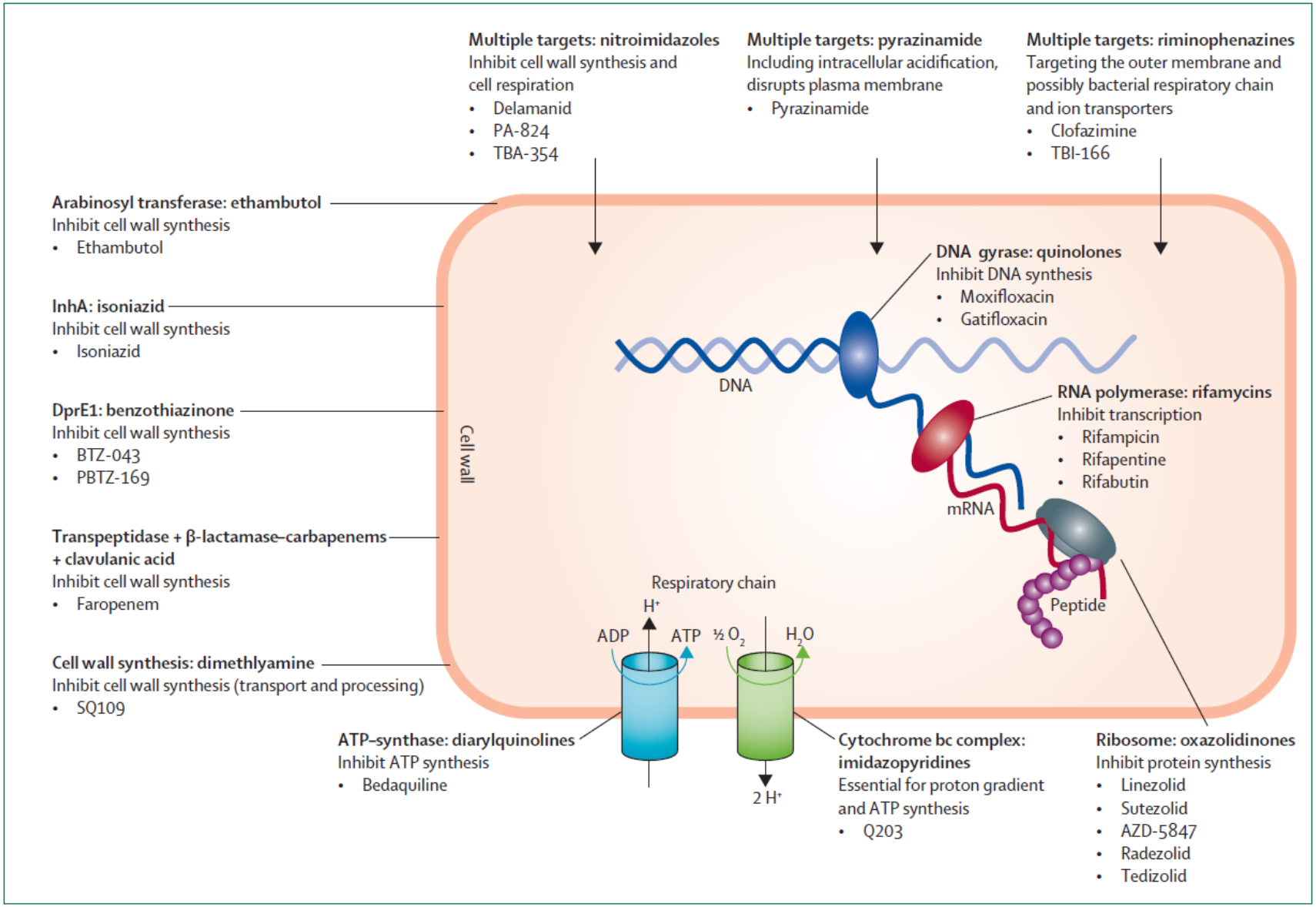


Thee et al. AAC 2011; 55: 4595-4600

New Drugs



Zumla et al. Lancet Infect Dis 2014; 14: 327-40



Zumla et al. Lancet Infect Dis 2014; 14: 327-40

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ESTABLISHED IN 1812 JUNE 4, 2009 VOL. 360 NO. 23

The Diarylquinoline TMC207 for Multidrug-Resistant Tuberculosis

The NEW ENGLAND JOURNAL of MEDICINE

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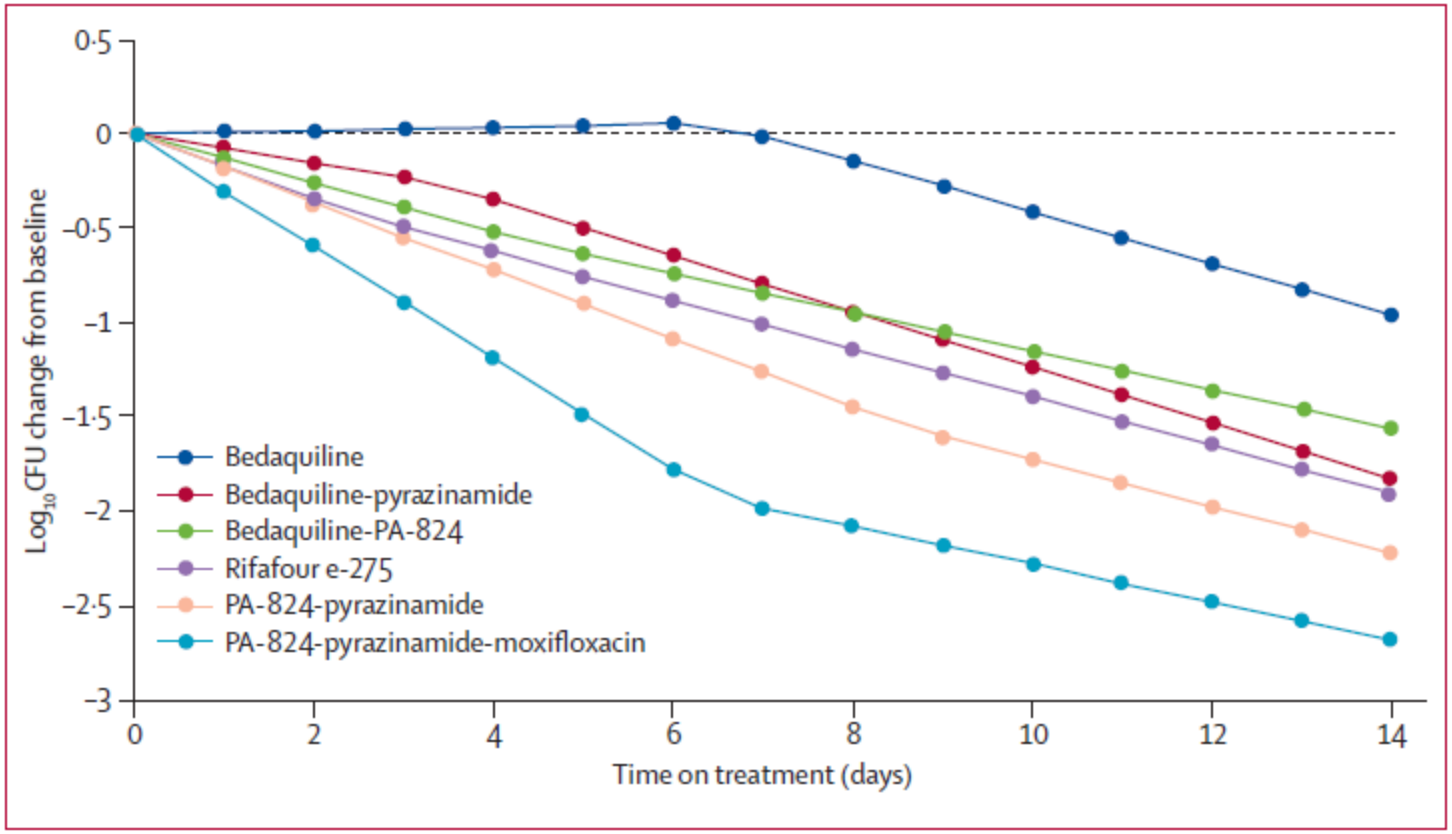
Delamanid for Multidrug-Resistant Pulmonary Tuberculosis

New Regimens

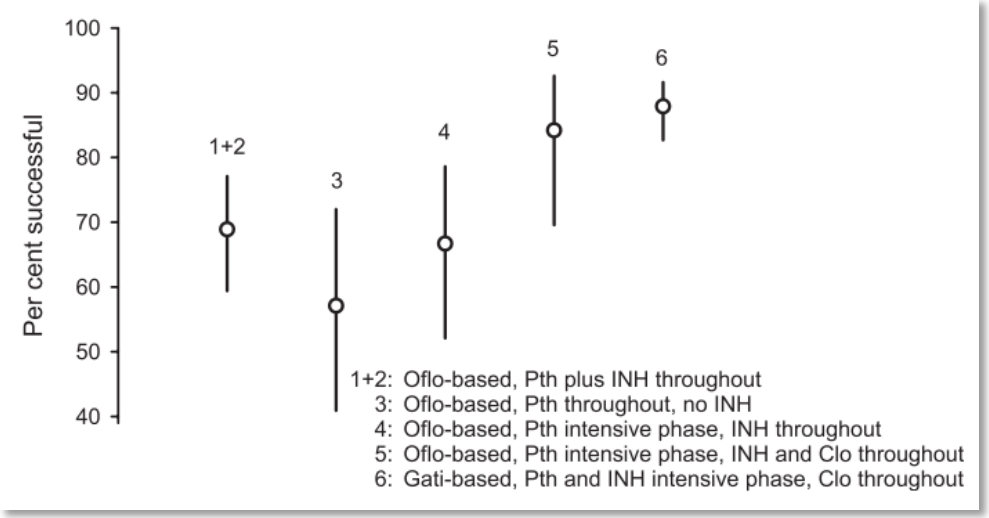


Diacon et al. Lancet 2012; 380: 986-93

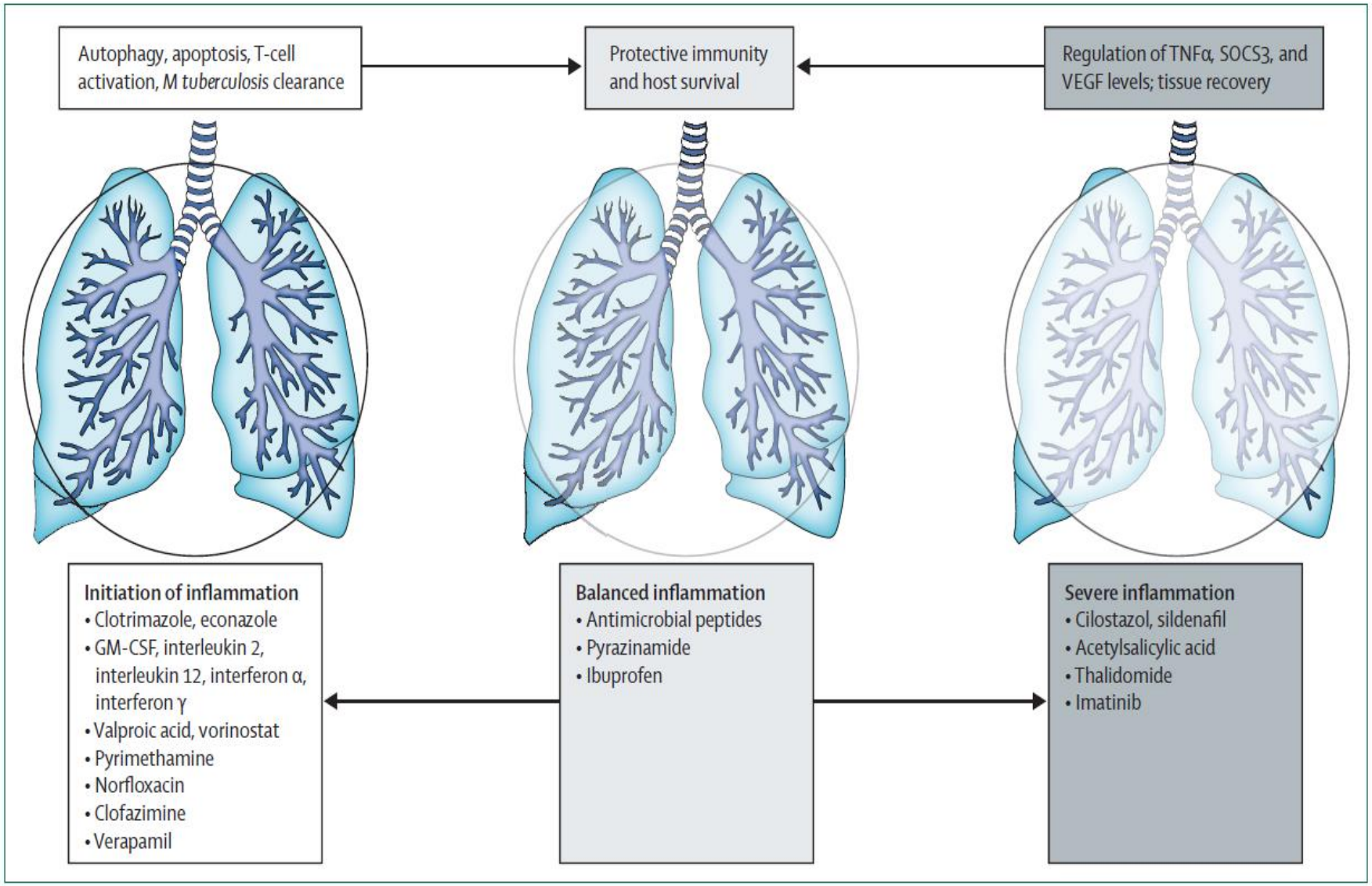
Short, Highly Effective, and Inexpensive Standardized Treatment of Multidrug-resistant Tuberculosis

Armand Van Deun[1,2], Aung Kya Jai Maug[3], Md Abdul Hamid Salim[3], Pankaj Kumar Das[3], Mihir Ranjan Sarker[3], Paul Daru[3], and Hans L. Rieder[1,4]

Regimen (sequence)	Intensive Phase	Continuation Phase 1	Continuation Phase 2	Patients Enrolled	
				Number	Col %
1	3* KCOEHZP	12 OEHZP	6 EP	59	13.8
2	3(+) KCOEHZP	12 OHEZP		44	10.3
3	3(4) KCOEZP	12 OEZP		35	8.2
4	3(+) KCOEHZP	12 OHEZ		45	10.5
5	3(+) KCOEHZP	12 OHEZC		38	8.9
6	4(+) KCGEHZP	5 GEZC		206	48.2
Total number of patients enrolled				427	100.0



Van Deun et al. AJRCCM 2010; 182(5): 684-692



Kaufmann et al. Lancet Resp Med 2014; 2: 301-320

Nutrition

Creative adherence strategies

- Mobile phones
- Alternative DOT
- Rewards/incentives

Vitamin D

cART

Helminth treatment

New formulations

- Dispersible tablets
- Sprinkles
- Melts
- Aerosol
- Nebulisers
- Depot injections

Case Resolution

- CC was eventually cured of his MDR-TB and made a full recovery
- He received a total 6 months of injectable therapy and 24 months of total drugs
- Today he is finishing secondary school and living a full and happy life
- He has had no long-term effects from his MDR-TB therapy, except his plan to become a doctor and “help other sick kids”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Summary

- Suspect MDR-TB in children if unwell with clinical TB and contact with an MDR-TB source case
- Attempt to obtain microbiological specimens for culture and susceptibility testing
- Initiate treatment (empiric if necessary) with at least four drugs felt to be effective against the likely strain
- Be aware that re-purposed drugs, new drugs and new regimens are likely to be available soon

Questions?

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