Early experiences with new TB drugs in adolescents and children

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Médecins Sans Frontières (MSF)

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MEDECINS SANS FRONTIERES

OVERVIEW

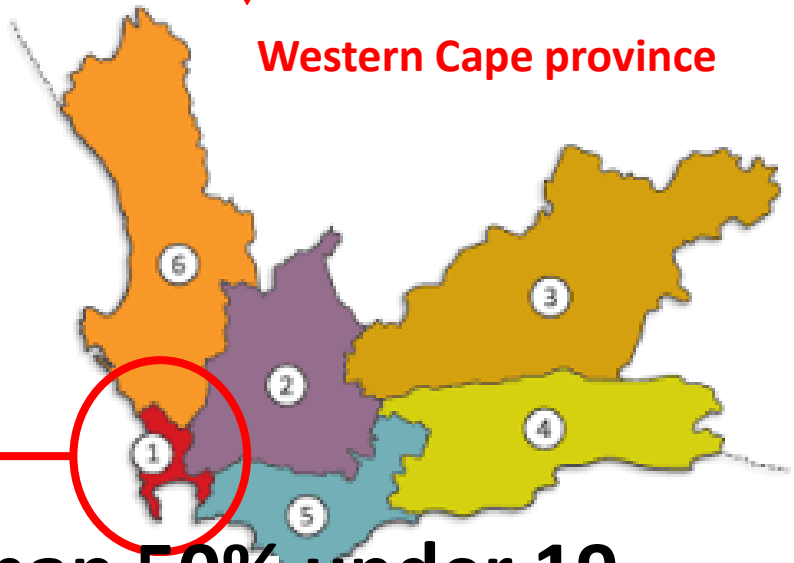
- Context: Khayelitsha
- Summary of the current use of new drugs in Khayelitsha in children and adolescents
- Case studies

Context

KHAYELITSHA RR-TB PROGRAM

South Africa

Western Cape province

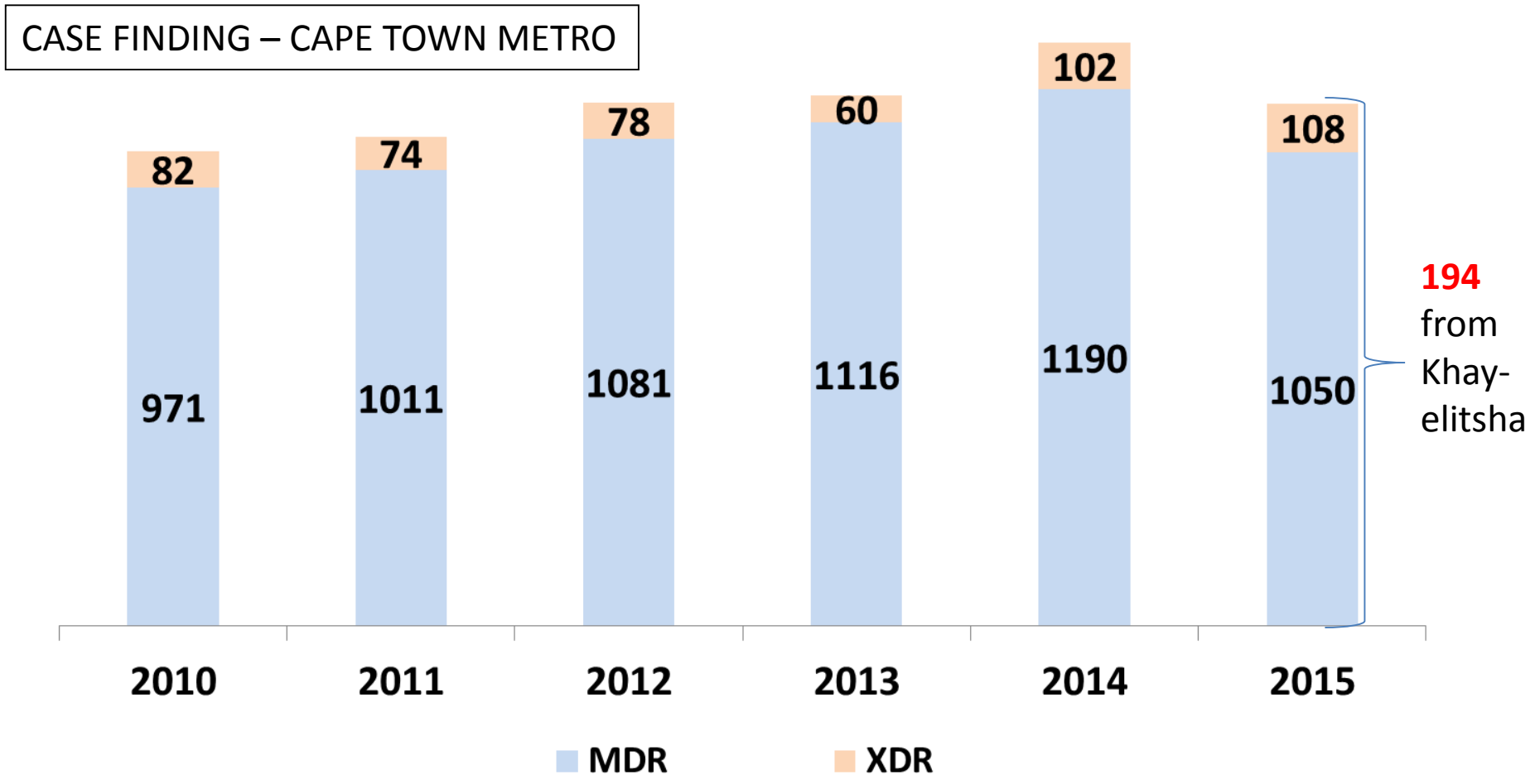


Cape Metro

Peri-urban slum

2.4 million people, more than 50% under 19

MDR and XDR-TB case finding in the Cape Town Metro in Western Cape, SA



Courtesy of Judy Caldwell (CoCT)

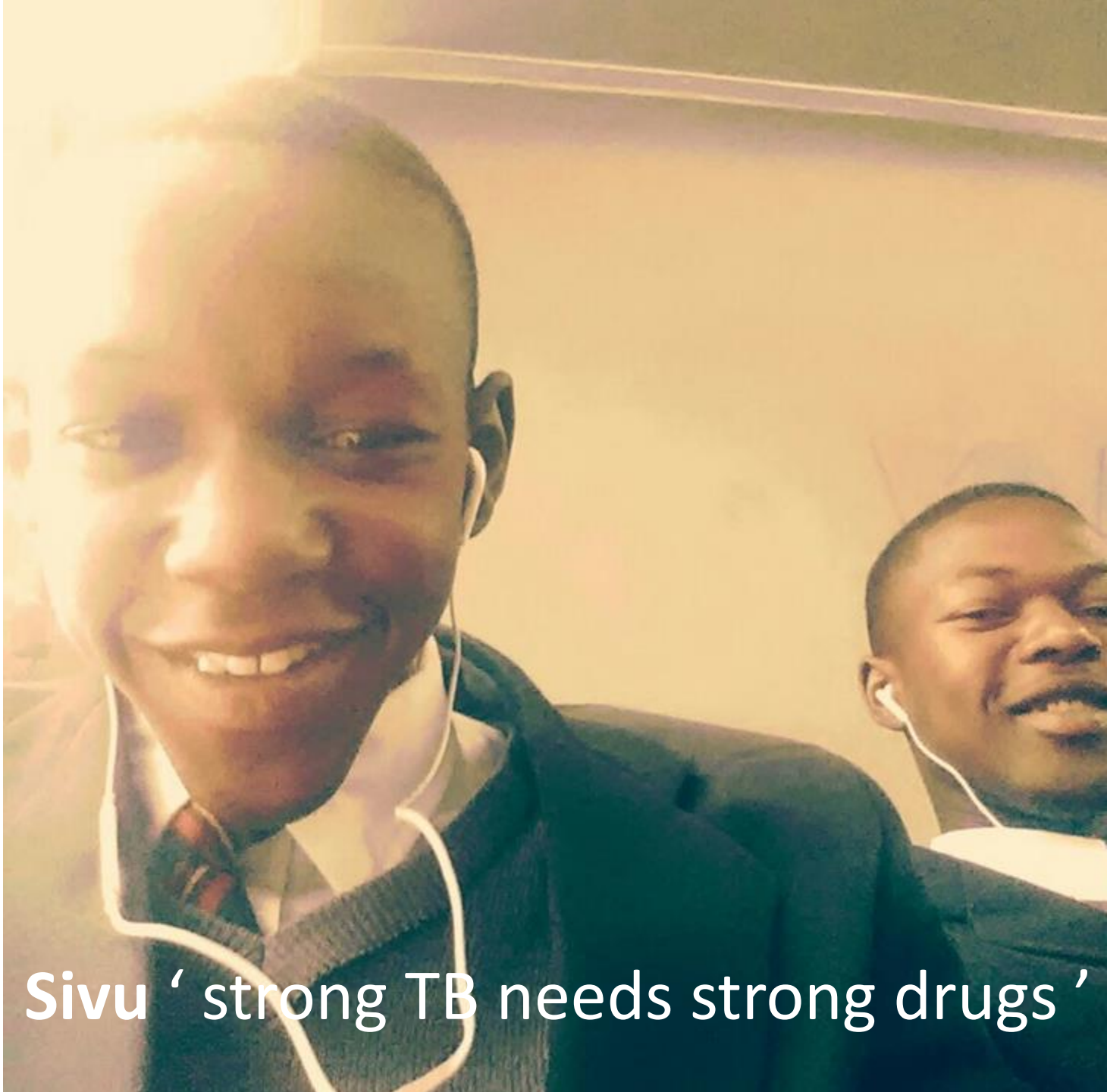
Access to new drugs in children

YEAR Rx started	Age Group	SR Meds Taken	Grand Total
2016	<5	No SR	10
	6 -12	No SR	3
	13-18	No SR	2
		BDQ	4
		BDQ & LZD	1
		BDQ & LZD & DLM	2
		DLM	3
2017	<5	No SR	3
	6-12	No SR	1
		DLM	1
	13-18	No SR	1
		DLM	2

Out of a total of 33 children with DRTB, 13 received a new drug, most above 12

Khayelitsha RR-TB Programme

- Child services in Khayelitsha
  - 10 primary care facilities
  - Local district hospital (KDH)
  - Most adolescents are managed in PHC with a focus of allowing them to return to school as soon as possible
  - Children are mostly managed in TB hospital by DRTB paediatric expert



Case 1 : **Sivu** ‘ strong TB needs strong drugs ’

Case 1

- 14 year old boy
- No TB contacts, mom noticed some coughing and loss of weight
- Presented to clinic with haemoptosys – required life saving surgery at private hospital

Case 1: Post surgery back at CHC

Current Regimen:

What is your treatment approach now?

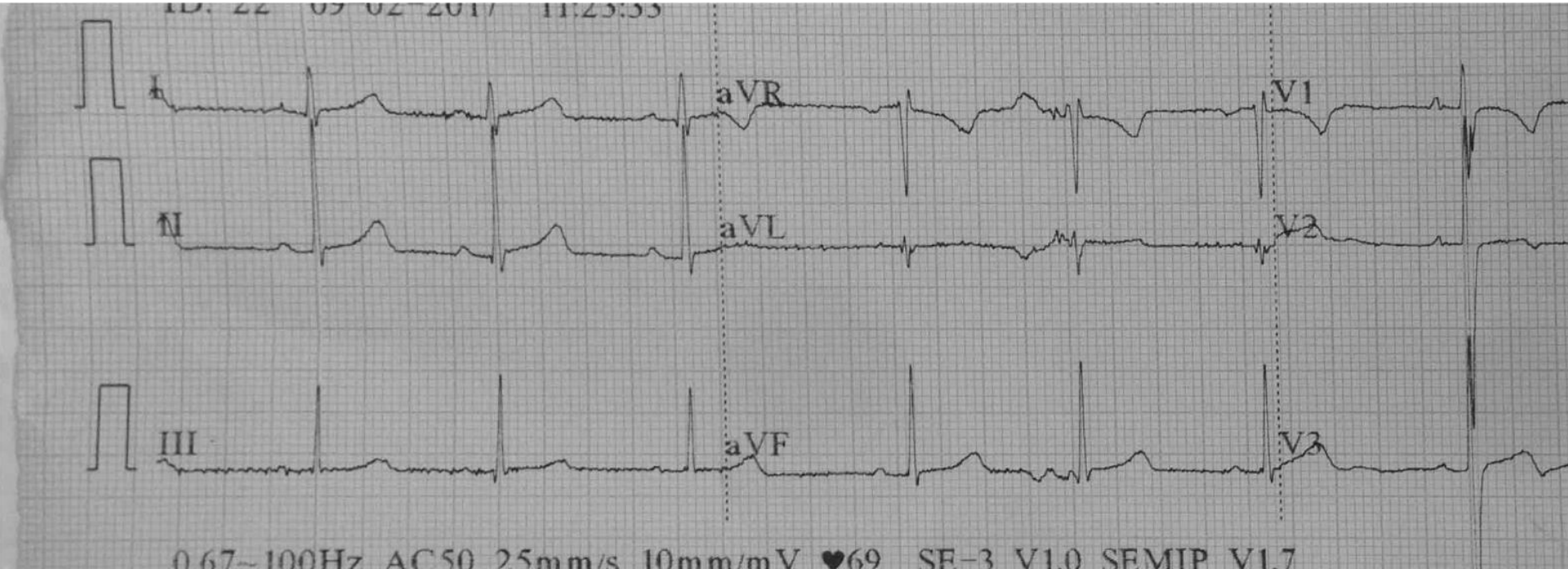
What other information would you like?

Albumin - 44

Sample date	GXP RIF	Smr	Culture	LPA Rif	LPA INH	inhA	KatG	LPA Ami	PhenCm	LPA Ofx	Phen Mfx
26/12/2015	Res	Pos	Pos	Res	Res			Sens		Res	

Case 1: Constructing a regimen

- Parents and Sive are very worried about him missing school
- Horrible experience thus far the daily injectable – both parents and Sive horrified that it can cause hearing loss and needs to be monitored if used. Also how will he go back to school if daily injection at clinic is needed?
- Have read about new drugs – DLM and BDQ on Google. But are worried about what they have read ‘’not recommended for children’’ ‘’ not recommended in combination’’



Consideration

- Adult type disease
- FQN resistance
- Surgery probably removed part of diseased lung, but still TB lung changes visible on CXR post –surgery
- Valid concerns about kanamycin
- Consider reasonable pill burden

WHO considers that currently only the medicines shown in this Table have a role in the composition of MDRTB regimens under programmatic conditions

Table 6. Medicines recommended for the treatment of rifampicin-resistant and multidrug-resistant TB[1]

~~A. Fluoroquinolones~~[2]		Levofloxacin Moxifloxacin Gatifloxacin	Lfx Mfx Gfx
B. ~~Second-line injectable agents~~		Amikacin Capreomycin Kanamycin (Streptomycin)[3]	Am Cm Km (S)
C. Other core second-line agents[2]		~~Ethionamide / Prothionamide~~ Cycloserine / Terizidone Linezolid Clofazimine	Eto / Pto Cs / Trd Lzd Cfz
D. Add-on agents (not part of the core MDR-TB regimen)	**D1**	Pyrazinamide Ethambutol High-dose isoniazid	Z E H^h
	D2	Bedaquiline Delamanid	Bdq Dlm
	D3	*p*-aminosalicylic acid Imipenem-cilastatin[4] Meropenem[4] Amoxicillin-clavulanate[4] (Thioacetazone)[5]	PAS Ipm Mpm Amx-Clv (T)

[1] This regrouping is intended to guide the design of conventional regimens; for shorter regimens lasting 9-12 months the composition is usually standardised (See Section A)

[2] Medicines in Groups A and C are shown by decreasing order of usual preference for use (subject to other considerations; see text)

Patient/ Hospital number: 36553998

Diagnosis : Pre-XDR TB <18 years old

The National DR-TB Clinical Advisory Sub-Committee has approved your application for access to treatment with Bedaquiline. The recommended DR-TB regimen is:

Proposed DR-TB Treatment Regimen:		Weight: 53 kg	
Drug	**Dosage**	**Frequency**	**Duration**
BEDAQUILINE	400mg, then 200mg	daily three times per week	2 weeks 22 weeks
DELAMANID (if approved)	100mg	twice daily	24 weeks
LINEZOLID	600mg	daily	As per guideline
CLOFAZIMINE	100mg	daily	
PARA-AMINOSALCYCLIC ACID (PAS)	4g	twice daily	
TERIZIDONE	750mg	daily	
PYRAZINAMIDE (PZA)	2g	daily	
ETHIONAMIDE (ETO)	750mg	daily	
KANAMYCIN	1g IMI	daily	
LEVOFLOXACIN	1g	daily	

Additional Medication: Pyridoxine 150mg daily

Additional comments: Can include Kana if no adverse events have occurred.

Kind regards


Pill burden

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~~ETHIONAMIDE (ETO)~~	~~750mg~~	~~daily~~	
~~KANAMYCIN~~	~~1g IMI~~	~~daily~~	
~~LEVOFLOXACIN~~	~~1g~~	~~daily~~	

Additional Medication: Pyridoxine 150mg daily

Additional comments: Can include if any adverse event have occurred.

Regimen started: 22/02/2017

Kind regards


Sputums: still positive

Approach taken

- Reassured and counseled on acne rash, unlikely to be drug related

- Benzyl peroxidase for acne

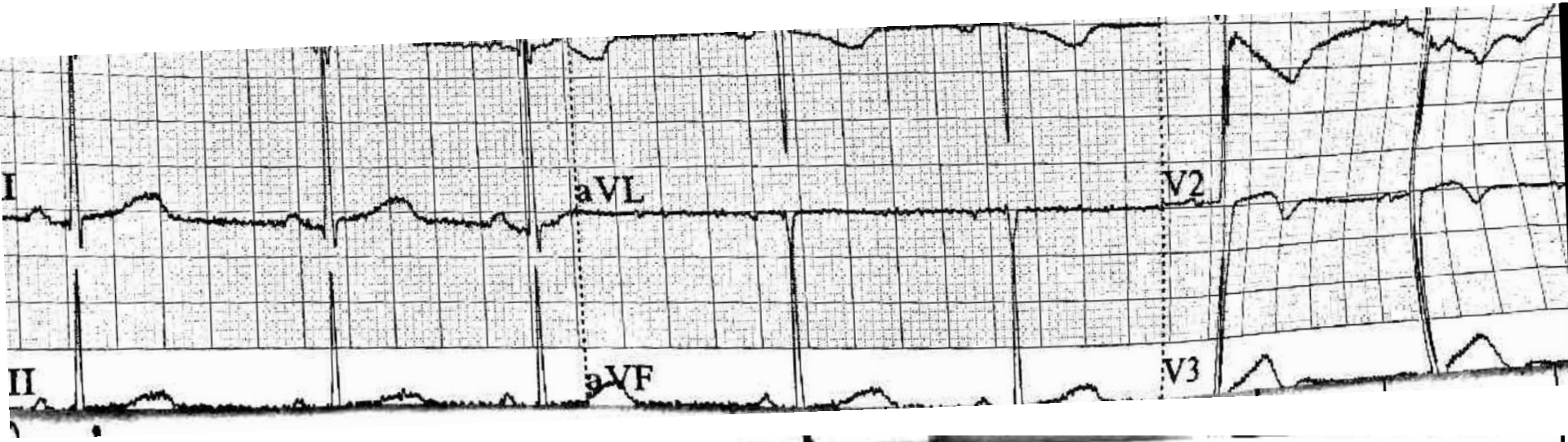
Current regimen: Z/hdINH/TZD/PAS/DLM/BDQ/LZD/Clof

Follow up

6 weeks:

- Clinic staff very concerned. On routine ECG follow up (done two weekly for first two months and then two monthly) machine noted ’sinus arrhythmia’.

Current regimen: Z/hdINH/TZD/PAS/DLM/BDQ/LZD/Clof



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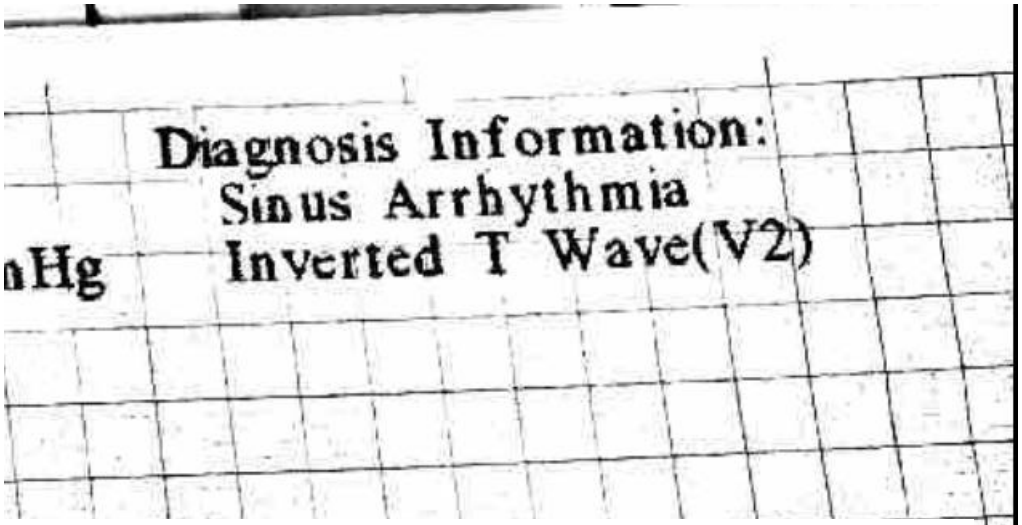


Should BDQ or DLM or both be stopped?

Follow up

- **Month 2** – rash much improved. But feels tired and dizzy. P = 96. HB 8.2.

Now what to do with the Linezolid?

Follow up

- May (Month 3 on treatment) – two times negative sputum's!!!!
- Able to go back to school!
- HB has improved to 9.5.
- Linezolid restarted at 300mg

Follow up

- June (Month 4 on treatment): complaining of severe burning pain in the feet – difficulty walking to school. HB 10.4.

- **What now?**

Current regimen: Z/hdINH/TZD/PAS/DLM/BDQ/LZD/Clof

.

Follow up

Month 6: End of intensive phase. PNP has resolved completed Sputums negative doing well, good CXR resolution. DLM extended for a further 6 months BDQ stopped after 6 months.

Continuation phase:

Z/TZD/hdINH/DLM/PAS/Clof

Follow up

- Coping at school – still gets tired since running since operation
- Gained 5 kgs
- Sputums have been negative, managing well with treatment

7. Bacteriological Rsults

Sample Date	Lab number	Smear	Culture	GEN Xpert Pos / Neg	GENXP Resit / Susept	PCR R	PCR INH	PCR Ofx	PCR Ami	INH Mutation	R	RIF Mutation	Ami	Cm	Ofx	Ter
26/12/2016	ST00955764	ND	ND	Pos	R											
26/12/2016	ST00956730	3+	Pos			R	R	R	S				ND		ND	
28/12/2016	ST00958540	2+	Pos													
10/02/2017	XD01039928	Neg	Pos			R	R	R	S	inhA			ND		ND	
17/03/2017	XG00258546	Neg	Neg													
25/04/2017	XD01187447	ND	Neg													
24/05/2017	XD01243364	Neg	Neg													
23/06/2017	XD01300794	Neg	Neg													
25/07/2017	XD01366915	Neg	Neg													
04/09/2017	XD01447274	Neg	Neg													
06/10/2017	XD01515870	Neg	To follow													

ECG QT interval
446
418
438
427
446
437
361
402
337

Discussion

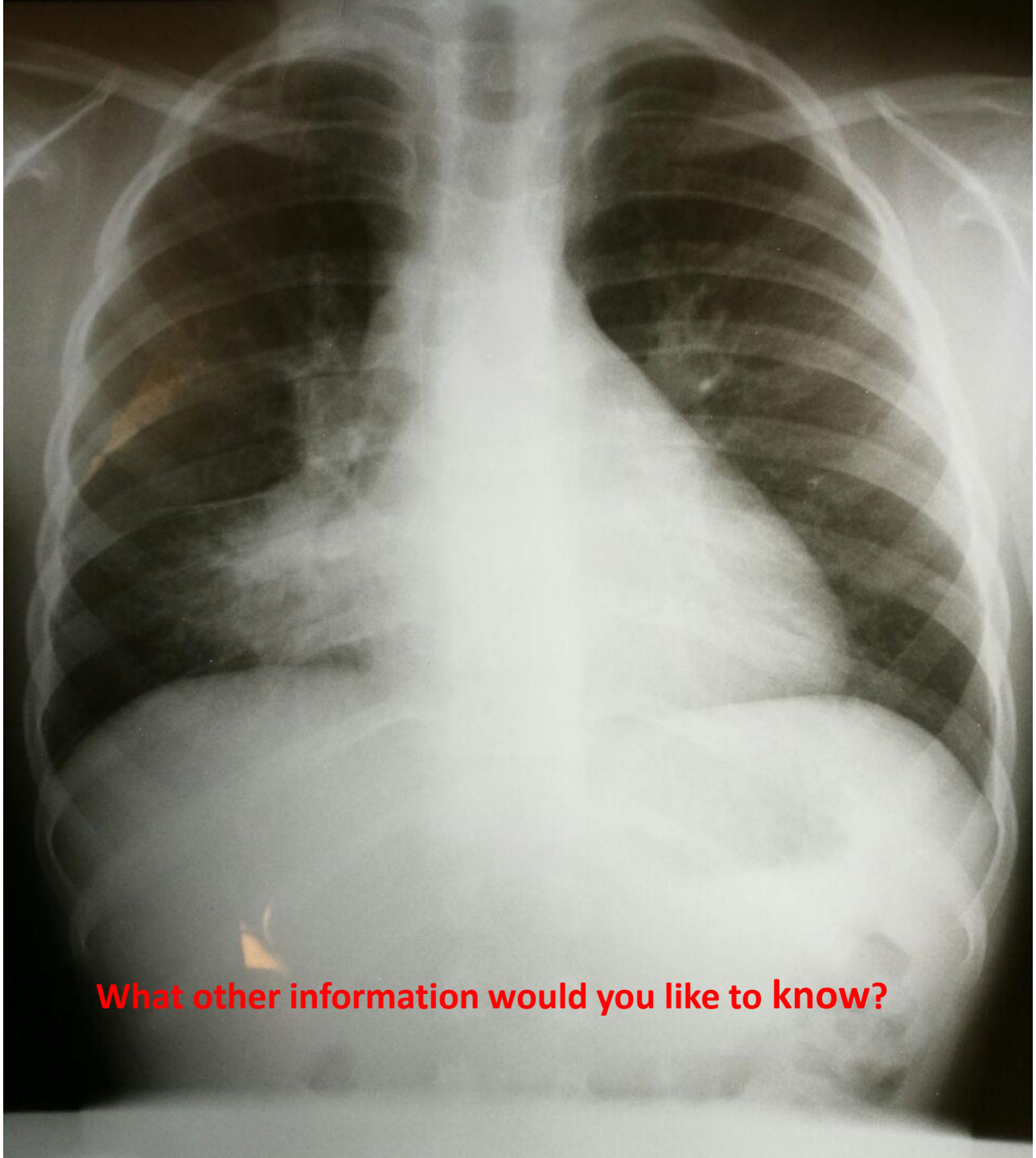
- Important to provide reassurance as needed and involve family in decisions around new drugs
- New drugs provide effective and tolerable treatment options
- There is a tend to “’fear’’ what we do not have experience in (BDQ/DLM combo) – important to use caution but also consider we are dealing with a dangerous disease and need strong guns (especially in adolescents)

Case 3: Owe

‘the time has come’

Case 2: OWE

- 10 year old, lives with mom and mom's boyfriend.
- Mom brought her to clinic with coughing and not playing normally in March 2017
- Weight 33 kgs – dropped 1 kg of weight over past month


What other information would you like to know?

Follow up:

- Sputum 31/03/2017 Showed Gene Xpert positive, inconclusive.
- No symptom screen done on mom
- DSTB treatment started at the end of March

Follow up:

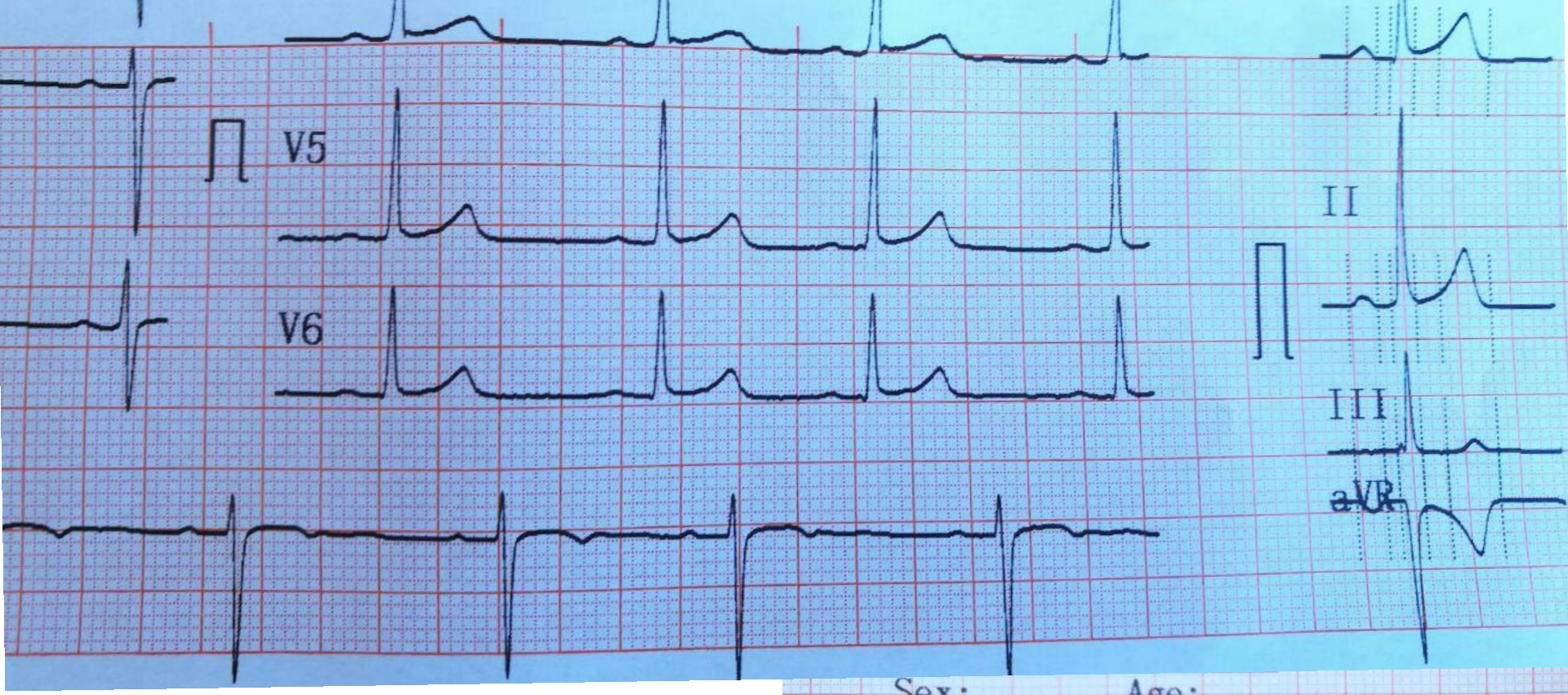
- **2 weeks later**
- Still coughing – no improvement on DSTB
- Sputum results from 05/04/2017 show **MDR TB with inha mutation, sensitive to FQN and injectable on LPA**
- On more extensive symptom screen: mom is also coughing and had a sputum done a month ago at the clinic – sputum results MDR TB

- On inquiry: mom is HIV positive and so is Owe (perinatal transmission – both stopped ART in 2014 from treatment fatigue)

RESULTS AT THIS STAGE:

DATE	K^+	Creat	GFR	Mg^{2+}	Ca^{2+}	WCC	Hb	Plts	ALT	T.Bilirubin
11/05/2017	hamolysed	34			2.28		11.7	365	13	6

Sample date	GXP RIF	Smear	Culture	LPA Rif	LPA INH	inhA	Gen Inj	Gen Ofx	Pheno Ofx	Pheno Mfx	Pheno Am	Pheno Cm
05/04/2017	Neg		Pos	R	R	Mut present	S	s				



Sex: _____ Age: _____
Height: _____ cm Weight: _____ kg
SYS: _____ mmHg
DIA: _____ mmHg 12/05/17

HR	[bpm]	:73
PR Interval	[ms]	:160
P Duration	[ms]	:110
QRS Duration	[ms]	:92
T Duration	[ms]	:190
QT/QTc	[ms]	:375/415
P/QRS/T Axis	[deg]	:15.8/54.4/34.4
R(V5)/S(V1)	[mV]	:2.44/1.80

THE LANCET
Respiratory Medicine

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Comment

The time has come: sparing injectables in paediatric MDR-TB

Ethel D Weld, Anthony J Garcia-Prats, Jennifer J Furin, Theodore C Bailey, Anneke C Hesseling, Kelly E Dooley

Published: 23 March 2017

DOI: http://dx.doi.org/10.1016/S2213-2600(17)30078-4

Article Info

Summary Full Text Tables and Figures References

Proponents of critical thinking recount this fable: a daughter asks, “Mother, why do you cut the end

17/5/17	DLM approved + provided by MSF:	
	DELAMANID 50mg BD 6/12 — from	
	LEVOFLOXACIN 500mg OD	
	PYRAZINAMIDE 1000mg OD	
	ETHAMBUTOL 600mg OD	MPO
	TERIZIDONE 500mg OD	
	ISONIAZID 500mg OD	

Follow up

- Admitted to TB hospital (mom's preference)

- At TB hospital Clofazamine (and PAS) added to allow for short course regimen.
- In TB hospital 4 months.

Follow up

- Discharged to clinic month 4: Owe doing well, growing. Good sputum response – planned for 1 year of treatment.
- Well established on ABC/3TC/EFV

7. Bacteriological Rsults

Sample Date	Lab number	Smear	Culture	GEN Xpert Pos / Neg	GENXP Resit / Susept	PCR R	PCR INH	PCR Ofx	PCR Ami	INH Mutation	R	RIF Mutation	Ami	Cm	Ofx	Ter
05/04/2017	XD01147846	ND	Pos	Neg		R	R	S	S	inhA			ND		ND	
25/05/2017	XD01243023	Scanty	Neg													
08/06/2017	XD01271373	Neg	Neg													
21/06/2017	XD01295021	Neg	Neg													
21/07/2017	XD01356702	Neg	Neg													
21/08/2017	XD01418119	Neg	Neg													
18/10/2017	XD01536460	Neg	To follow													

Follow up

Abs CD4	HIVVL
157	12346
148	14786
180	118

ECG QT interval	
	446
	418
	438
	427
	446
	437
	361
	402
	337

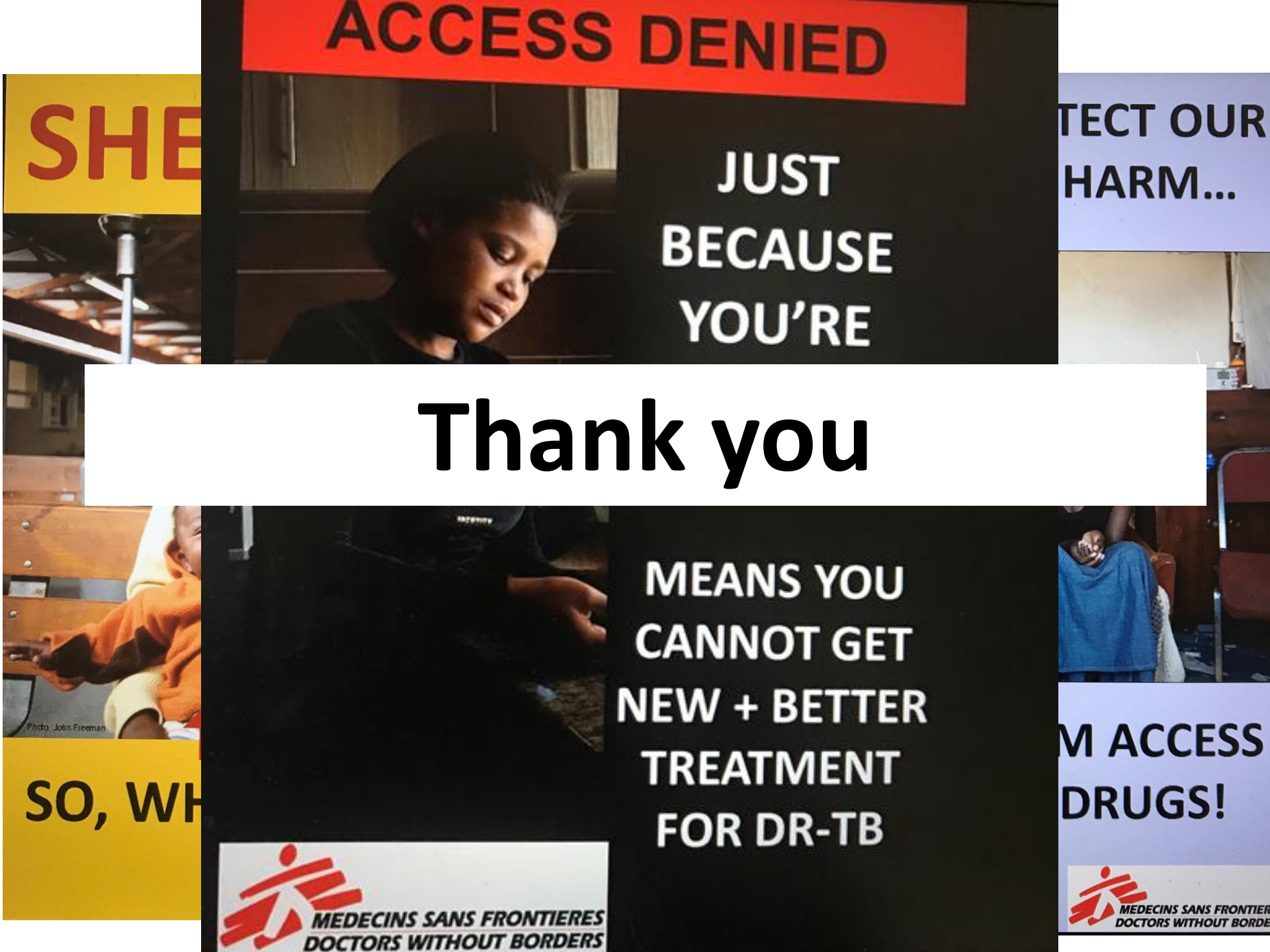
Follow up

- **Sadly:** mom passed away from MDR TB (TB intracranial IRIS) while in hospital.

- Family is now looking after Owe – she is continuing to do well

Key Messages

- The time has come…..
- Lets prioritize our children and adolescents and ensure they have access to new drugs and the most tolerable regimens inline with emerging evidence
- New drugs need to by accompanied with intensive support for children, adolescents and parents
- DRTB effects the whole family


ACCESS DENIED
JUST
BECAUSE
YOU'RE
MEANS YOU
CANNOT GET
NEW + BETTER
TREATMENT
FOR DR-TB
MEDECINS SANS FRONTIERES
DOCTORS WITHOUT BORDERS
Photo: John Freeman

Thank you