The short-course treatment for MDR tuberculosis

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Introduction

- Resistance to anti-TB drugs is an important challenge in global TB control. Resistance is an innate characteristic of *M. tuberculosis,* related to genetic mutations that occur naturally in large populations of microorganisms.

- In the wild state, where specific antimicrobial agents have never been used, this resistance has no clinical significance.

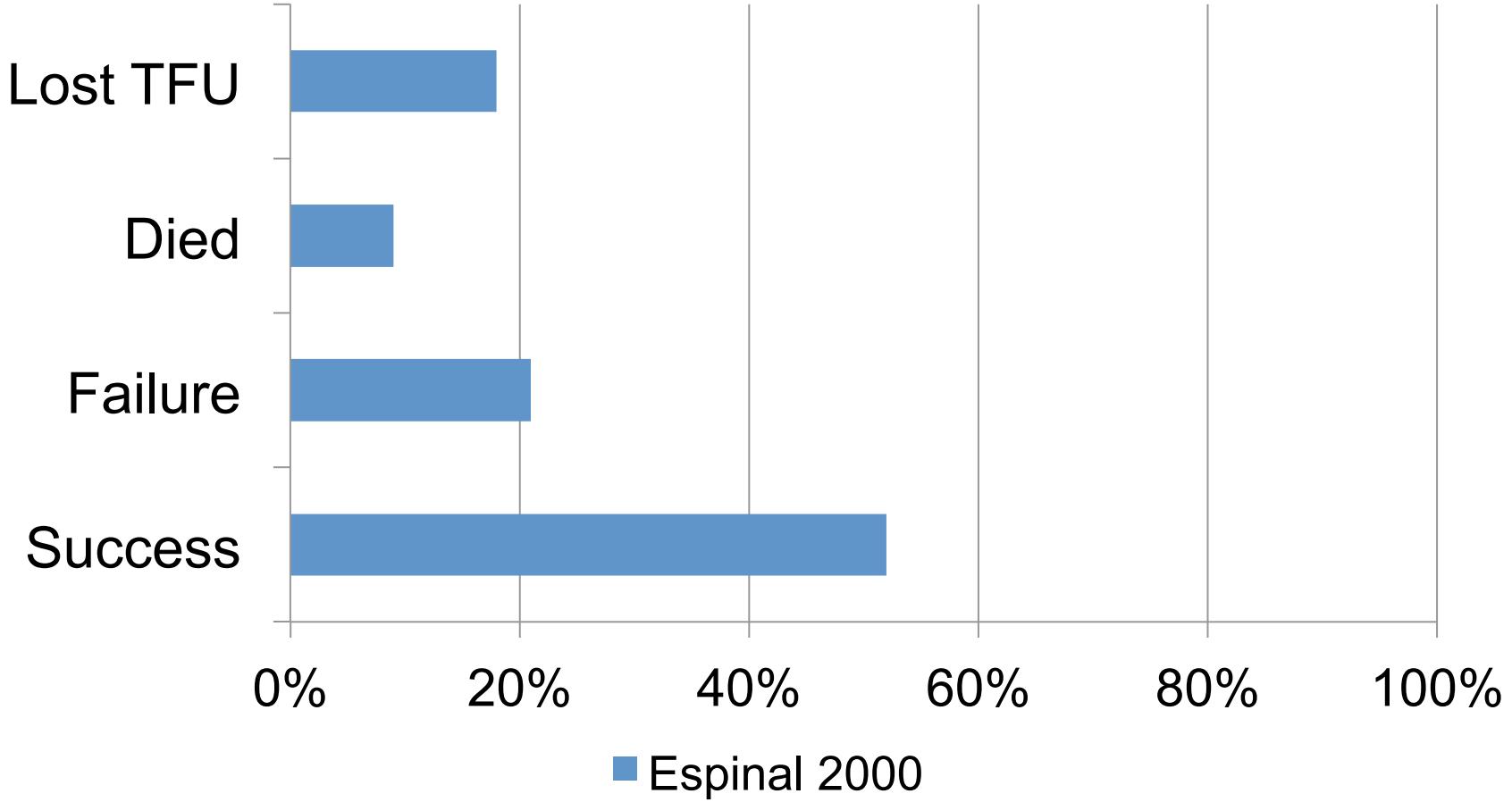
- At the human population level, clinically significant drug resistance has its origins in the incorrect use of anti-TB drugs and is in this sense a ‘man-made’ phenomenon.

- Since the 90’s, 2RHZE/4RH for almost all the forms of tuberculosis in almost all countries.
- The key drug is Rifampicin (R)
- R was introduced much later than the other drugs, the problem of resistance to rifampicin appeared quite recently

Definitions

- **Mono resistance**: resistant to one drug
- **Poly resistance**: resistant to 2 or more drugs
- **Rifampicin-resistant** tuberculosis: (RR-TB) resistant to at least rifampicin
- **Multidrug-resistant** tuberculosis (MDR-TB): resistant to at least rifampicin and isoniazid
- **Extensively-resistant** tuberculosis (XDR-TB): MDR-TB strain with further resistance to a fluroquinolone and a second line injectable agent (amikacin, kanamycin, or capreomycin).

Outcome of SS+ new MDR-TB cases, treated with First Line Drugs (FLD) 2RHZE/4RH (%)



Espinal MA et al. JAMA 2000;283(19):2537-45

WHO, 2006 Guidelines *(WHO/HTM/TB/2006.361)*

- Minimal recommendation is that the injectable agent (other than streptomycin) should be continued for at least 6 months and at least 4 months after the patient first becomes and remains sputum smear- or culture-negative
- The minimal recommendation is that treatment should last for at least 18 months after culture conversion

- Subsequent updates in 2008 *(WHO/HTM/TB/2008.402)* and 2011 (*WHO/HTM/TB/2011.6)* recommended similar treatment duration.

Example of recommended treatment

Intensive phase: 8 months with 5 drugs

- Injectable : Kanamycin
- Fluoroquinolone
- Ethionamide or Prothionamide
- Pyrazinamide
- Plus 1 drug to which the strain is probably susceptible: Cycloserine or PAS

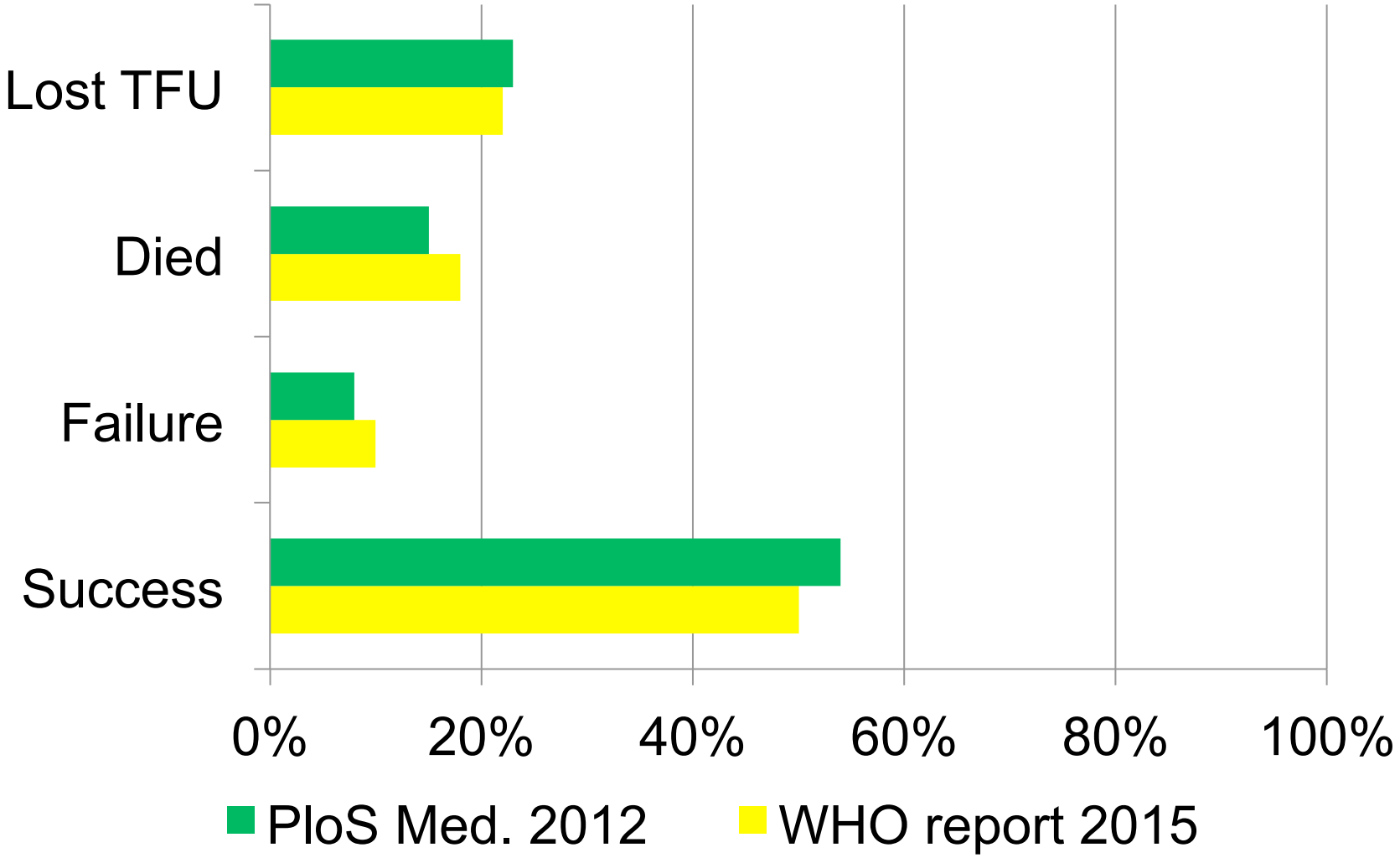
Continuation phase: 12 months minimum with 4 drugs

- Stop the injectable

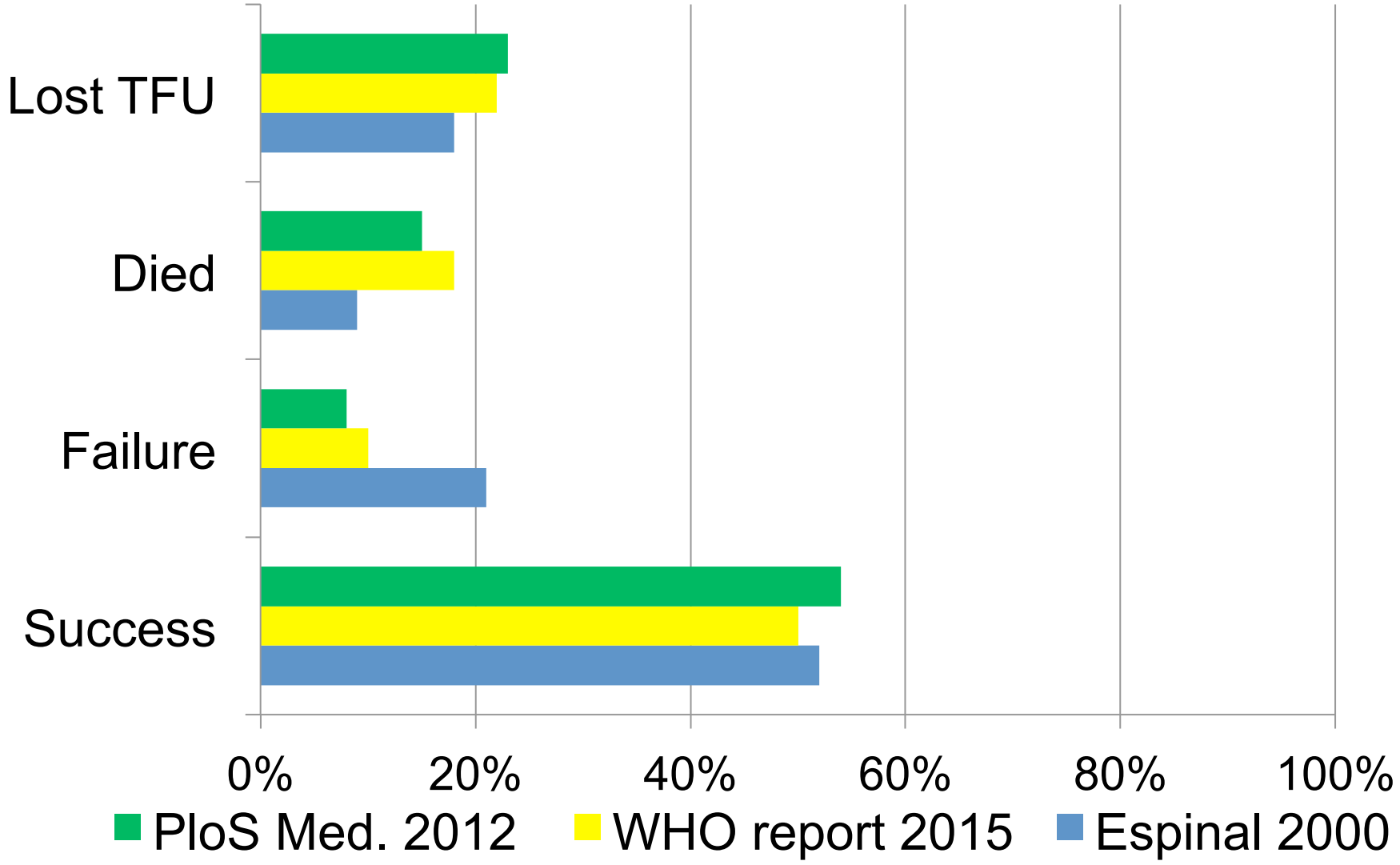
Total: 20 months minimum

WHO/HTM/TB/2011.6, *WHO/HTM/TB/2009*.
WHO Guidelines for MDR management update 2011

Outcome of MDR-TB cases, treated with Second Line Drugs (SLD) (%)



Outcome of MDR-TB cases, treated with FLD or SLD (%)



WHO Grade evaluation system, 2011

Conditional recommendation

- The Guideline Development Group concludes that the desirable effects of adherence to a recommendation **probably** outweigh the undesirable effects.

Very low quality evidence

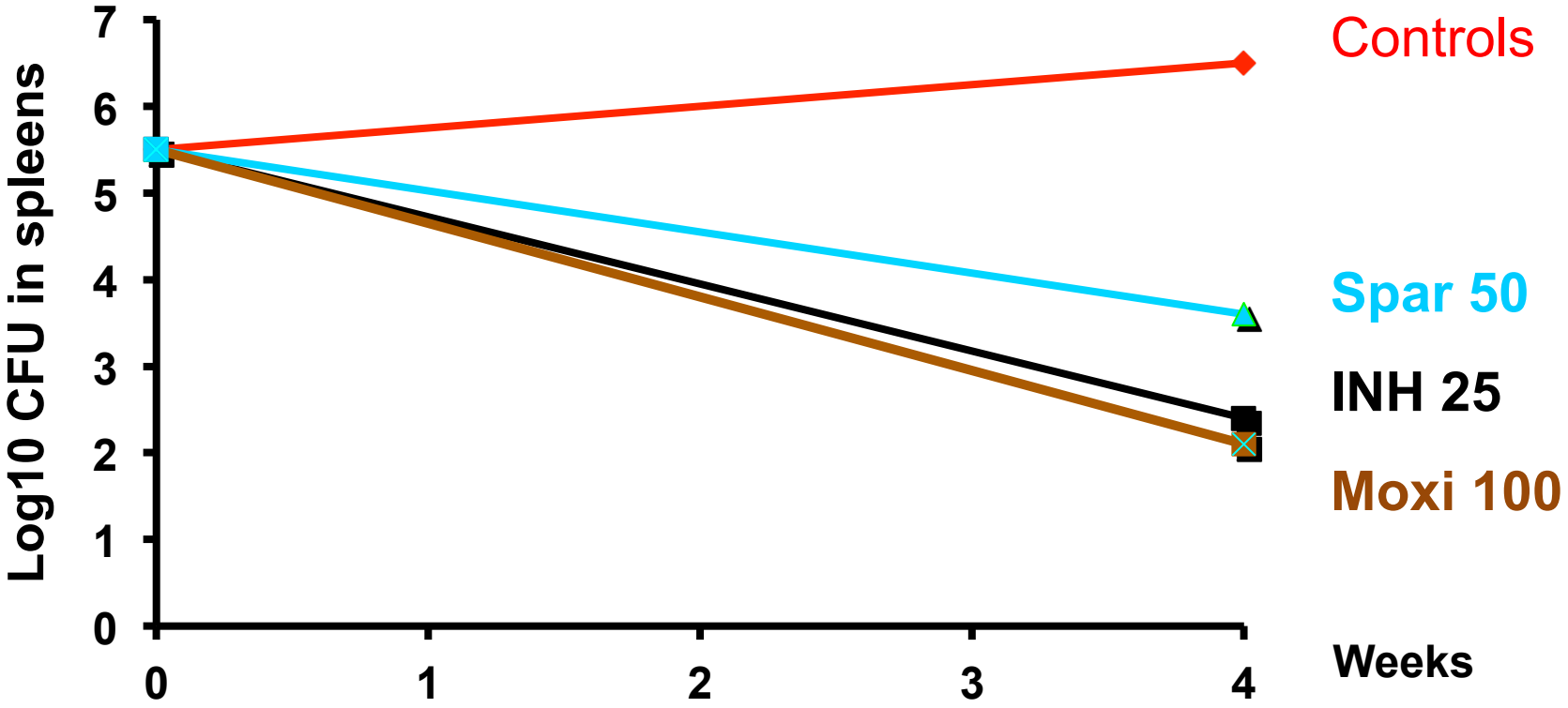
- Any estimate of effect is **very uncertain**

- **Intensive phase of 8 months** (conditional recommendation, ⊕ very low quality evidence).
- **Total treatment duration of 20 months** (conditional recommendation, ⊕ very low quality evidence).

Obviously, it was time to try to do better!

The light came from Bangladesh following some preliminary works

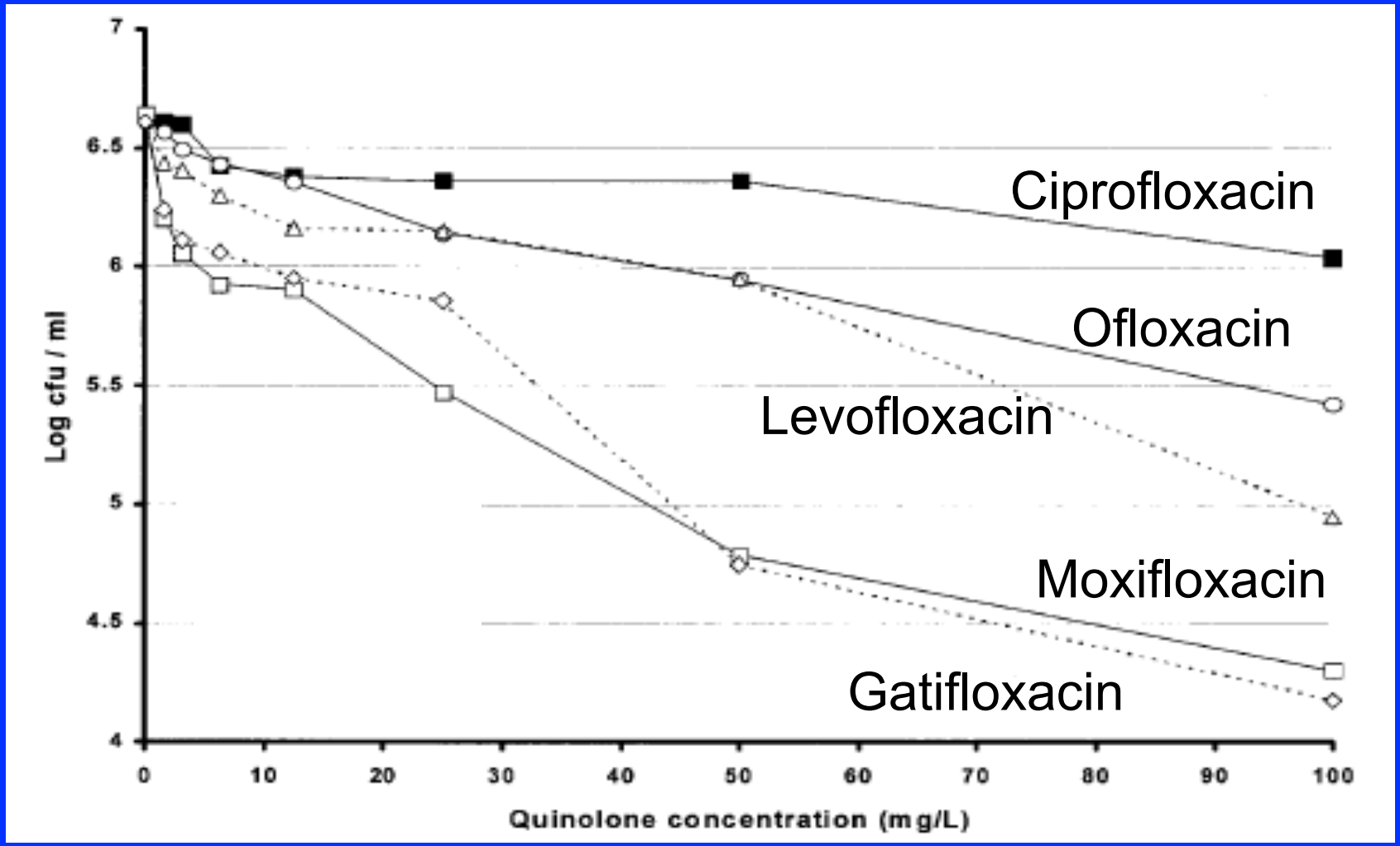
Comparative activities of isoniazid (INH), sparfloxacin (Spar) and moxifloxacin (Moxi) against *M. tuberculosis* in mice



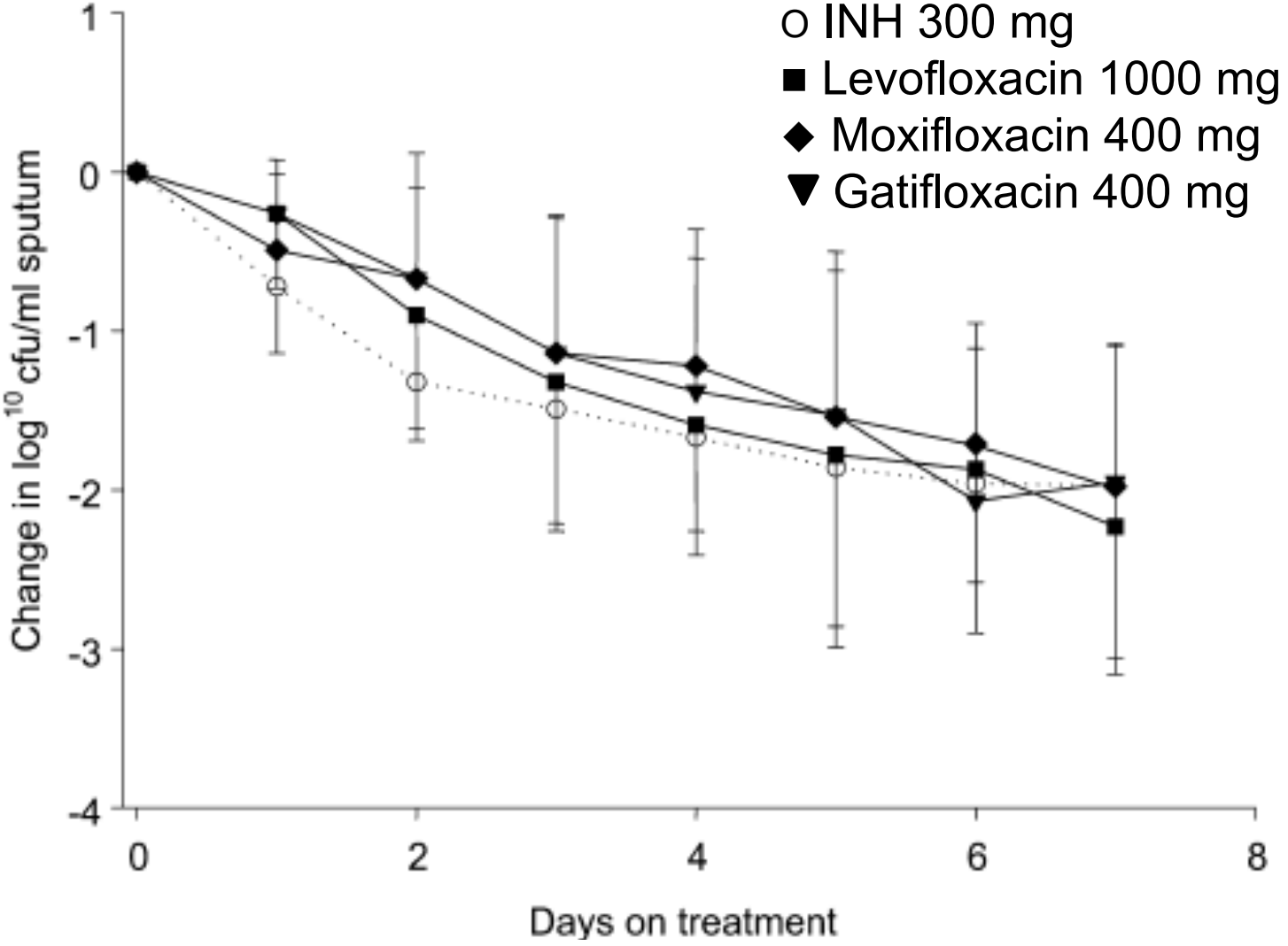
(From Ji et al., AAC 1998; 42: 2066-2069)

Conclusion: the bactericidal activity of moxifloxacin is close to that of isoniazid

Viable counts for 100-day cultures of *M. t* exposed to various concentrations of different fluoroquinolones



Hu, Y., A. R. M. Coates, and D. A. Mitchison. Antimicrob.Agents Chemother. 47 (2003): 653-57.



Early and extended early bactericidal activity of levofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis

(Johnson et al., IJTLD 2006;10:605-612)

The light came from Bangladesh 1997-2007

- **3** Km **Clz** Ofx E H Z Pto / 12 Ofx E H Z Pto / 6 E Pto
- 3 Km Clz Ofx E H Z Pto / 12 Ofx E H Z Pto ~~6 E Pto~~
- 3 Km Clz Ofx E Z Pto / 12 Ofx E Z Pto ~~H~~
- 3 Km Clz Ofx E H Z Pto / 12 Ofx E H Z ~~12Pto~~
- 3 Km Clz Ofx E H Z Pto / 12 Ofx E H Z Clz
- **4 Km Clz Gfx E H Z Pto / 5 Gfx E Z Clz**

Van Deun A, Maug A K J, Hamid Salim M A, Das P K, Sarker M R, Daru P, Rieder H L. Am J Respir Crit Care Med. 2010 Sep 1;182(5):684-92

Bangladesh
4 (6) Km Gfx Pto H Cfz E Z / 5 Gfx Cfz E Z
Treatment outcome

- Total analysed: N = 206
  - Success 181 (87.9%)
  - Failure 12 (5,8%)
  - Died 11 (5,3%)
  - Lost TFU 1 (0.5%)
  - relapsed 1 (0.5%)

Van Deun A et al. Am J Respir Crit Care Med. 2010

Too beautiful to be true !

Sceptical international reception

Studies launched in Benin, Cameroon and Niger in 2008

Similar regimen than in Bangladesh, but **lasting 12-months**:

Identical intensive phase: 4 months Km Gfx Pto H Cfz E Z

Prolonged continuation phase : 8 months Gfx Cfz E Z

(*Pto added in the continuation phase in Cameroon and Benin)*

	Niger*	Cameroon**
N	**65**	**150**
Cured	58 (89%)	134 (89%)
Failure	0	1 (1%)
Died	6 (9%)	10 (7%)
LTFU	1 (2%)	5 (3%)

*Piubello, IJTLD, 2014

**Kuaban, IJTLD 2015

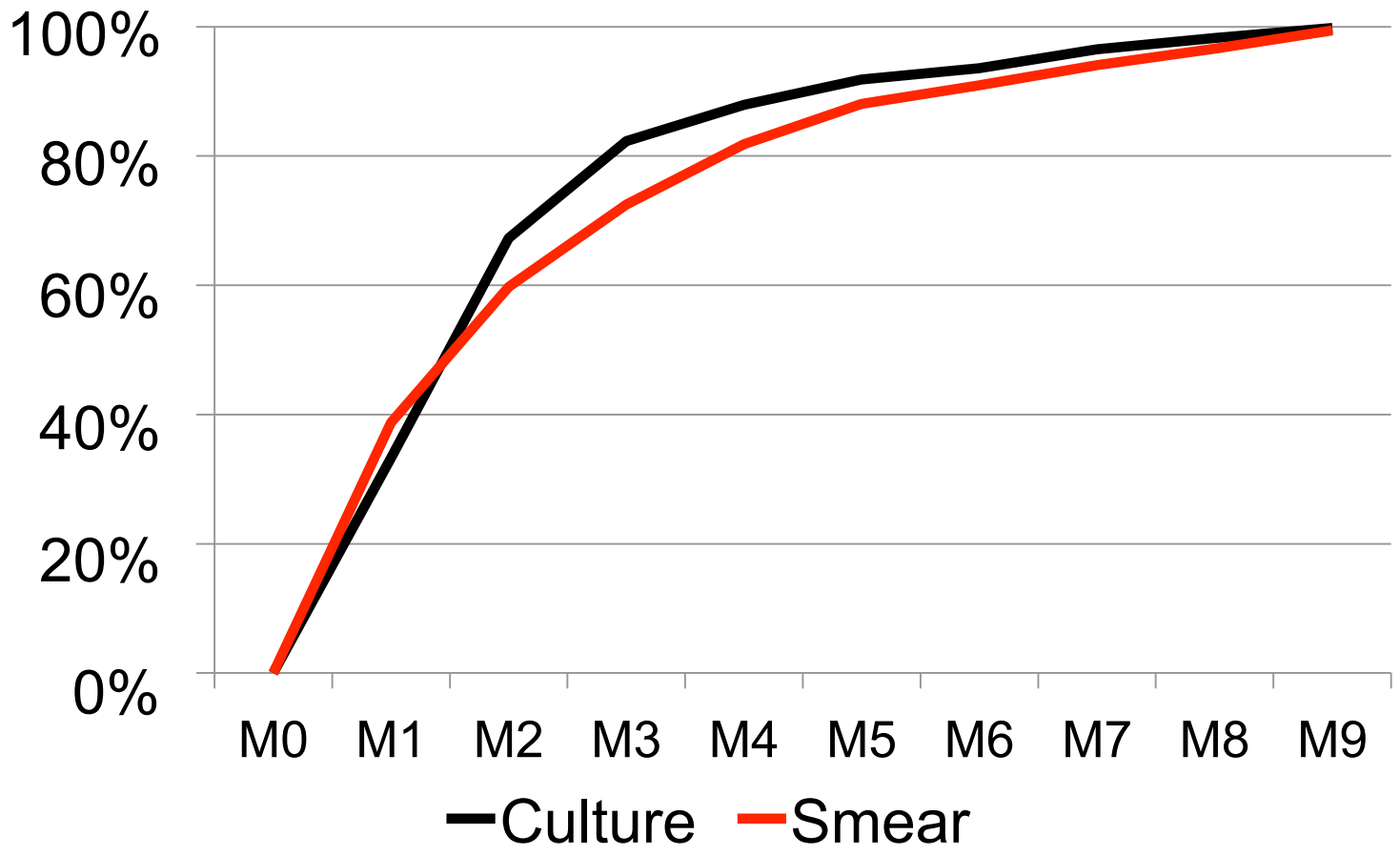
New study launched by The Union in 9 countries in sub-Saharan Africa in 2013

- Same 9-month regimen than in Bangladesh, with gatifloxacin high dosage replaced by moxifloxacin normal dosage
- 4 Km Mfx Pto H Cfz E Z / 5 Mfx Cfz E Z
- Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Côte d'Ivoire, DR Congo, Niger, Rwanda
- All patients with rifampicin resistance confirmed by molecular or phenotypic testing included, except for:
  - patients aged <18 years,
  - those previously treated by 2nd line drugs
  - pregnant women
- Strict daily Directly Observed Treatment whole treatment

Study population (N= 1,006)

Median age (min – max)		35.2 yrs [18 - 80]
Sex	Female	34%
Patient's category		
	Failure of cat. II	31 %
	Failure of cat. I	28 %
	Relapse	23 %
	New case	13 %
	Other	5 %
Lung area affected (N=948) > 50%		65%
HIV (N=1,006)	positive	20%
BMI < 16.0 (Severe thinness)		28%

Smear and culture conversion



Conversion at month 4 : 87% for culture; 82% for smear

Treatment outcome

	N = 1,006	
Cured	738	73%
Treatment completed	70	7%
Success	808	80%
Relapse	15	1,5%
Failure	60	6%
Died	78	8%
Lost to follow-up (LTFU)	45	4%

Definitions following 2013 WHO recommendations with

Cure = treatment termination without evidence of failure and ≥ 3 consecutive negative cultures after the last positive result

Failure = any positive culture at 6 months or later (except if preceded by ≥ 1 and followed by ≥ 2 negative cultures)

Outcomes according to HIV status

	HIV Pos N=200	HIV Neg N=806
Success	145 (73%)	663 (82%)
Failure	9 (5%)	51 (6%)
Died	38 (19%)	40 (5%)
Lost to follow-up	8 (4%)	37 (5%)

Among patients who survived, treatment success did not differ significantly by HIV status: 90% in HIV-positive and 87% in HIV-negative patients

Median time to death: 64 days for HIV pos : 53 days for HIV neg

Success rates according to initial resistance

Initial resistance	N	Success	p value
INH			
Susceptible	100	89 (89%)	p<0.02
Resistant	558	439 (79%)	
FLQ			
Susceptible	571	459 (80%)	p<0.01
Low level resistant	9	6 (67%)	
High level resistant	18	8 (44%)	
SLI			
Susceptible	580	458 (79%)	NS
Resistant	15	11 (73%)	
PZA			
Susceptible	182	142 (78%)	NS
Resistant	193	153 (79%)	

Risk factors for failure

Item		N	Failures	RR (95% CI)
FLQ	Resistant	27	10 (37%)	6.6
	Susceptible	571	32 (6%)	(4.2 – 23.4)
SLI	Resistant	15	1 (7%)	1.0
	Susceptible	580	43 (7%)	(0.2 - 6.7)
INH	Resistant	558	39 (7%)	6.8
	Susceptible	100	1 (1%)	(0.9 – 49.0)
PZA	Resistant	193	18 (9%)	1.9
	Susceptible	182	9 (5%)	(0.87 – 4.5)

HIV, BMI, Extension: no statistically significant difference.

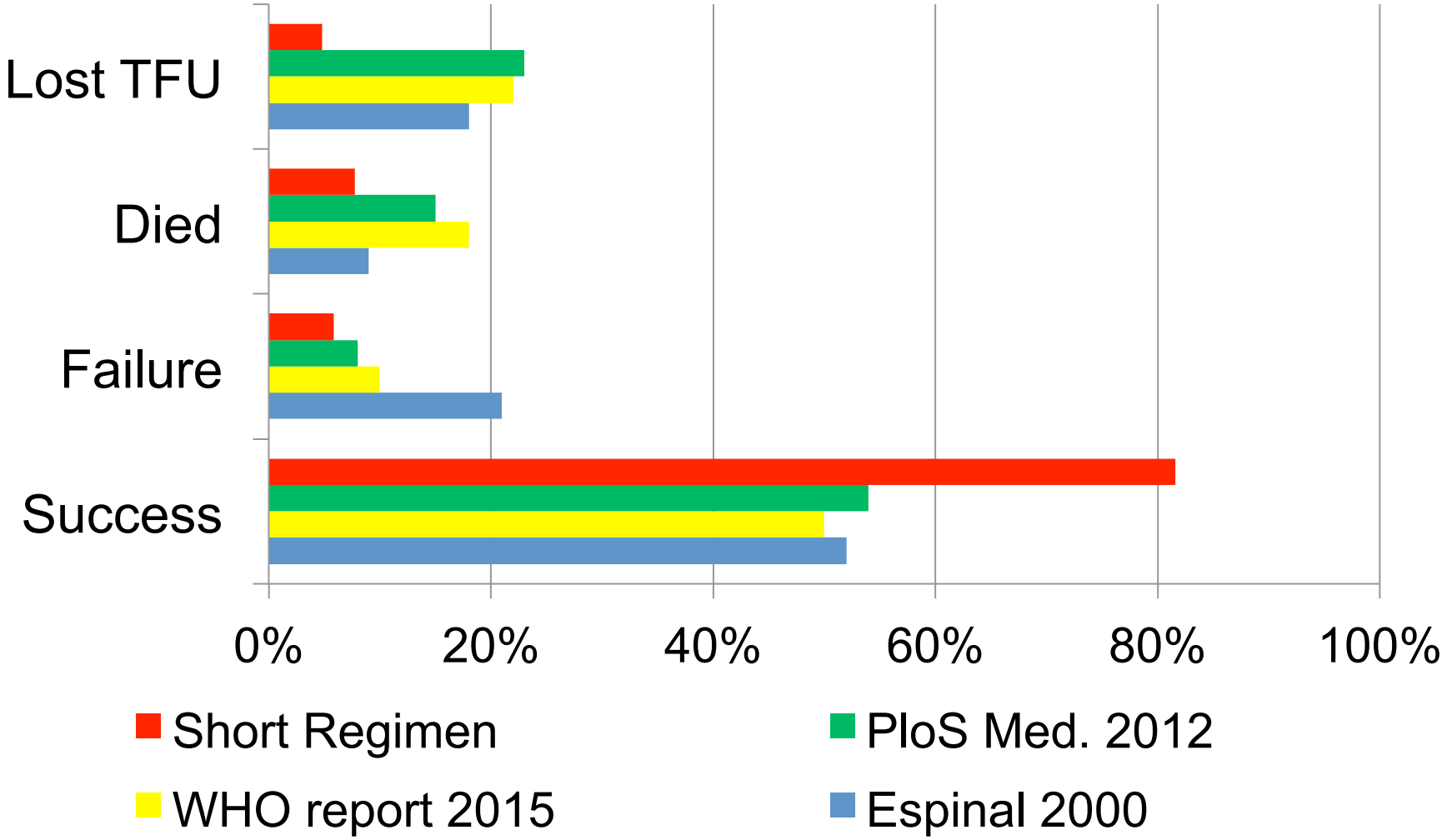
Excluding deaths and LTFU, in multivariate analysis, only resistance to INH and FLQ remained associated with risk of failure

- **Risk factor for death**. Low BMI, large radiographic extent of pulmonary lesions, and older age. All increased the risk of death independently of HIV status, but not the microbiological effectiveness of the regimen.

- **Adverse events.** The most important adverse drug event was hearing impairment: 11% severe hearing deterioration at month 4. HIV infection was significantly associated with severe hearing loss.

- **Amplification.** We documented 8 cases with acquisition of high FQ resistance out of 559 patients who were susceptible at the initiation of treatment (1.4%), which is a substantially larger proportion than the single case documented in Bangladesh over more than 500 cases

Trébucq A, Schwoebel V, Kashongwe Z, et al. Int J Tuberc Lung Dis. 2018;22: 17.-25



Huge improvement with the 9-month MDR treatment regimen

12 May 2016, Geneva, update October 2016
(WHO/HTM/TB/2016.04.)

"In patients with RR-TB or MDR-TB who were not previously treated with second-line drugs and in whom resistance to fluoroquinolones and second-line injectable agents was excluded or is considered highly unlikely, a shorter MDR-TB regimen of 9–12 months may be used instead of the longer regimens (conditional recommendation, very low certainty in the evidence)".

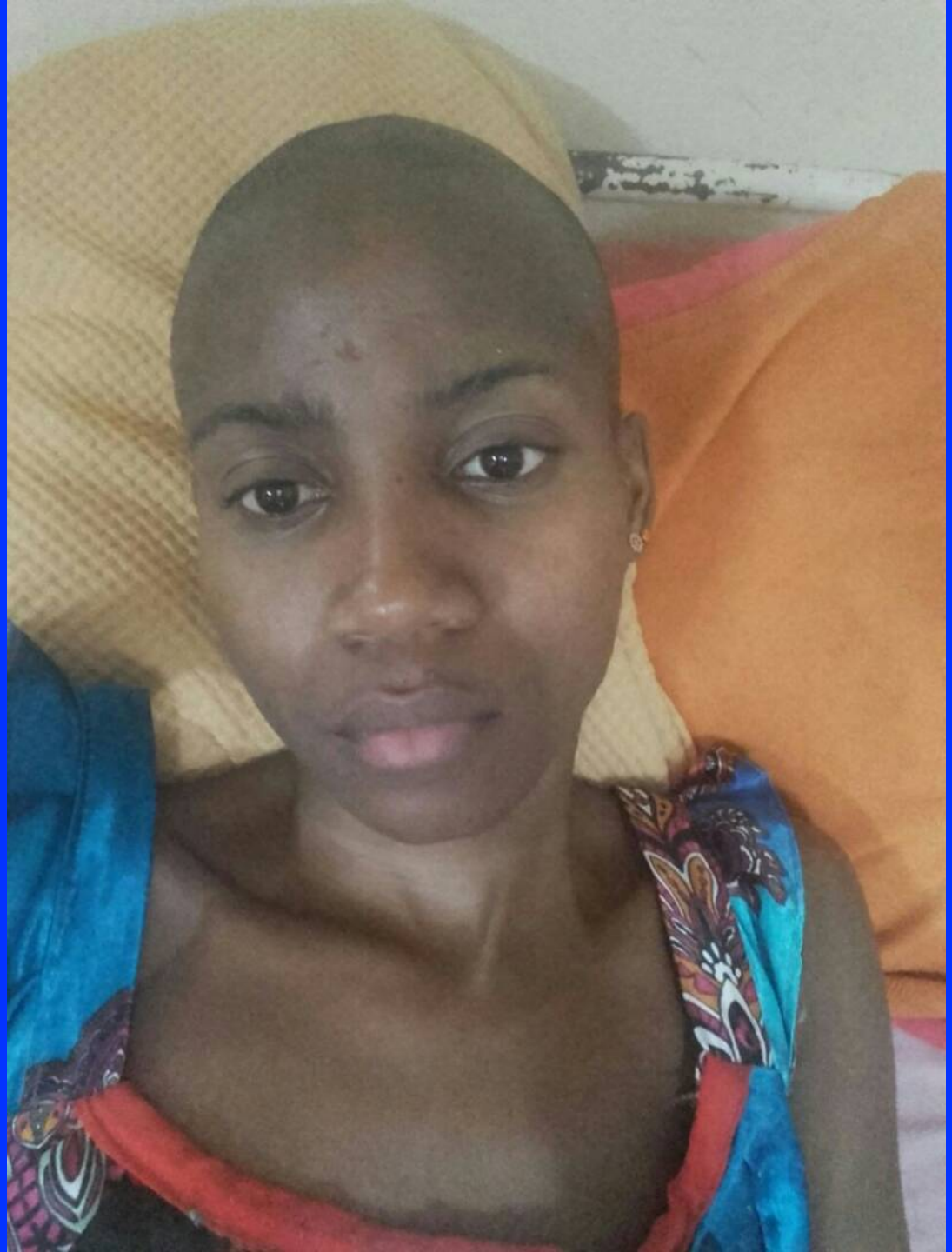
Conclusions (1)

- First need to treat/cure RR-TB, communication is lab responsibility +++
- The 9-month regimen is now recommended by WHO
- It works even if resistance to PZA or ETO or EMB
- Fluoroquinolone is THE KEY DRUG, not recommended if resistance to fluoroquinolones
- Probably better to use high dose of moxi or gati or levo
- Cost is not so high: 600 US $

Conclusions (2)

- Surveillance of hearing is important +++
- Surveillance of QT on ECG if high dose of moxi
- Directly Observed Treatment +++ to avoid XDR-TB

- WHO is publishing an update with some new recommendations. MDR-TB treatment is still a “moving field”. However, most patients with MDR-TB will benefit from the 9-month regimen, huge improvement!



Thank you for your attention

Principal actors for the study in Africa

Benin	Burkina Faso	RCA	Côte d'Ivoire
Martin Gninafon	Martial Ouedraogo	Valentin Fikouma	Alimata Bakayoko
Dissou Affolabi	Souba Diandé	Manuella Onambele	Raymond Nguessan
Ferdinand Kassa	Gisèle Badoum	Olivia Mbitikon	Timothée Ouassa
Wilfried Bekou	Emile Birba	Yvon Ngana	Lucien Koffi Maxime
Burundi	Tandaogo Saouadogo	**RDC**	Olivier Kouakou Adade
Thadée Ndikumana	**Niger**	Zacharie Kashongwe	Djangoné Bi
Nyandwi Stany	Souleymane Hassane	Michel Kaswa	Ibodé Valéri Oulai
François Ciza	Bassirou Souleymane	Léopoldine Mbulula	**Rwanda**
Michel Sawadogo	Zélika Hamidou	Jules Toloko-Risasi	Michel Gasana
Cameroon	Soumaila Morou	**The Union**	Eliane Makanzi
Christopher Kuaban	Ibrahim Boukary	Arnaud Trébucq	Habimana-Mucyo Yves
Sara Eyangoh	Alberto Piubello	Hans Rieder	
Jürgen Noeske		Valérie Schwoebel	
Charlotte Kamgue		Ghislain Koura	