TORCH
Tuberculosis Omics ResearCH

NUMBER OF EFFECTIVE DRUGS IN THE SHORT COURSE MDR-TB REGIMEN ACCORDING TO STANDARD OF CARE DRUG SUSCEPTIBILITY TESTING AND WHOLE GENOME SEQUENCING

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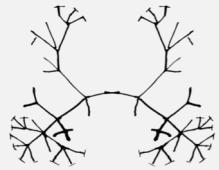
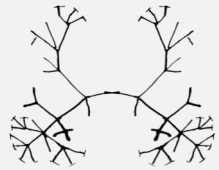
RIFAMPICIN RESISTANT TB



- Global burden: 600 000 of the 10.4 million annual TB cases
- Treatment success rate: 54% compared to 83% for all TB
- Important determinant of treatment success is the number of effective drugs administered
  - Treatment success improves stepwise as the number of effective drugs increases
  - PZA and FQ are important components of the MDR-TB treatment
- Key = timely, comprehensive knowledge of drug resistance profile
  - Phenotypic DST slow, not standardized for all drugs
  - Incomplete implementation of standard of care DST
  - Targeted sequencing and molecular assays target a small number of genomic regions

Cegielski J. P. et al., 2016, Clinical Infectious Diseases; Courtney M. Y. et al., 2015, PLOS Medicine; Chang K. C. et al., 2013, AJRCCM

WHO GUIDELINES FOR MANAGEMENT OF RR-TB



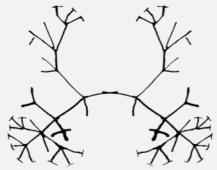
At least 5 effective drugs:

- PZA
- 1 Fluoroquinolone
- 1 Second line injectable
- ≥2 Other core second line drugs

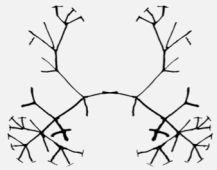
Table 6. Medicines recommended for the treatment of RR-TB and MDR-TB[a]

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

MANAGEMENT OF RR-TB: SOUTH AFRICAN STANDARD OF CARE



RESEARCH QUESTIONS

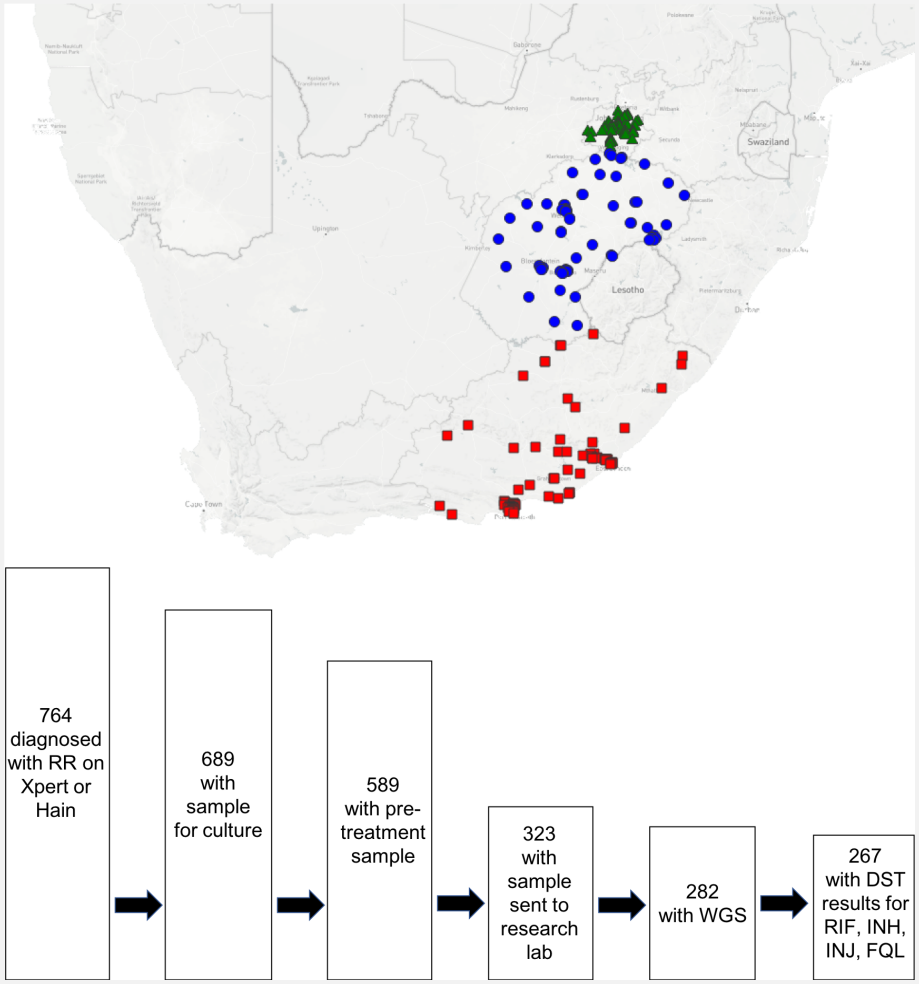


1. Determine the drug resistance profile
   - SOC as implemented
   - SOC as intended
   - WGS
2. Determine the number of effective drugs in the starting regimen
   - Standard 20-24 month regimen
   - Standard short course (9 month) regimen
   - New injectable free regimen (recommended in SA since June 2018)

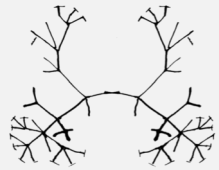
METHODS

Secondary analysis: cohort study: **E**valuating **X**pert **I**mpact on **T**B outcomes-**Rif** Resistance" (EXIT-Rif)

- Prospective cohort of patients diagnosed with RR TB
- Collection of routine data
- Comprehensive assessment of routine MTB isolates at research laboratory



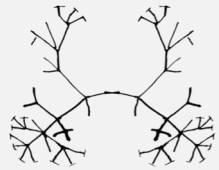
METHODS: DETERMINE THE RESISTANCE PROFILE



- SOC "as implemented"
  - Review of medical files and electronic lab data
- Simulating the SOC "as intended"
  - INH → MTBDR*plus* (simulate using Sanger sequencing of katG and inhA)
    - inhA promotor mutation → low level INH resistance
    - katG mutation → high level INH resistance
  - Injectables → pDST
  - Fluoroquinolones → pDST
- WGS
  - Illumina sequencing of MTB culture isolates
  - Resistance calling using the list suggested by Coll F. et al.

Coll F. et al., Nature Genetics, 2018

METHODS: DETERMINE THE NUMBER OF EFFECTIVE DRUGS

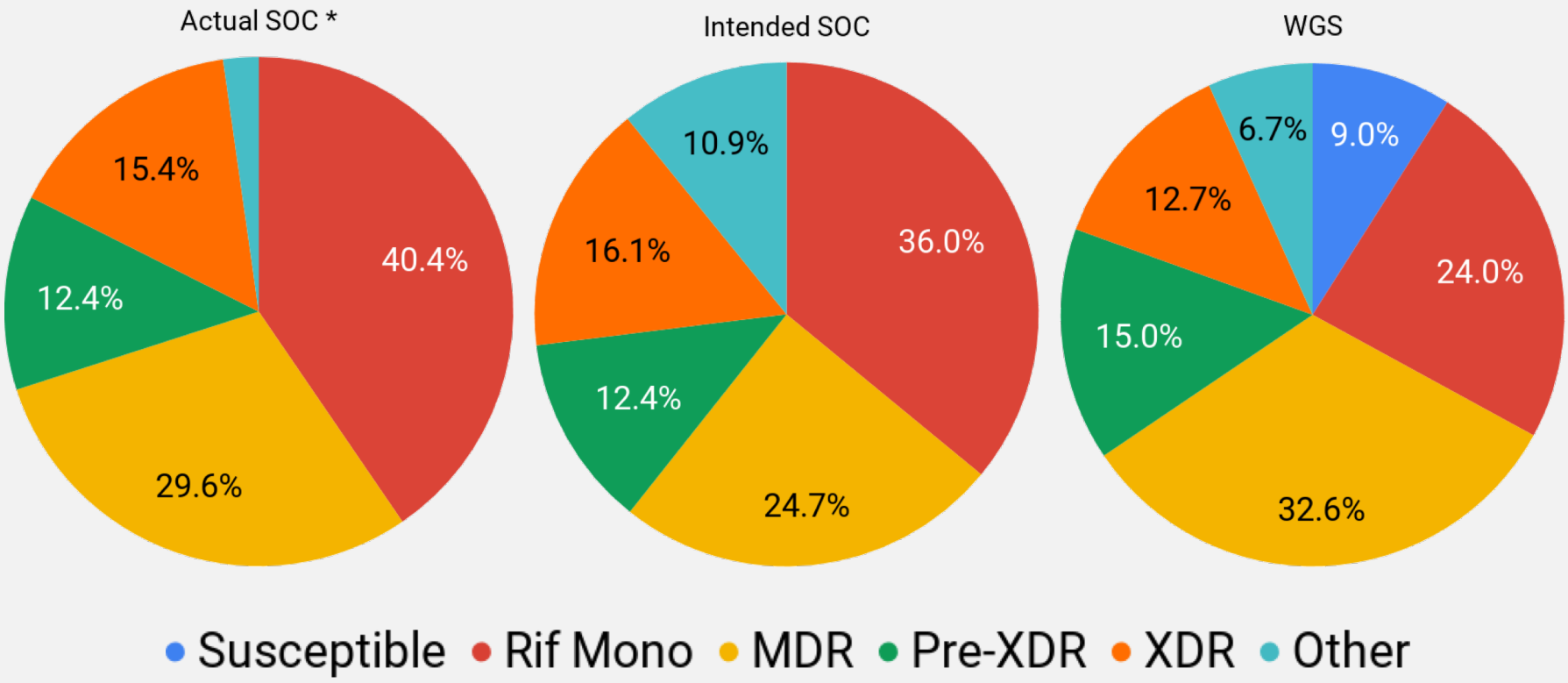


Comparison of number of effective drugs between methods of diagnosis (routine SOC, optimal SOC, WGS) in three different treatment regimens:

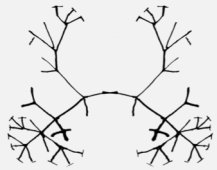
- Standard 20 months standard WHO approved regimen
- Short 9 month WHO approved regimen
- New SA injectable-free regimen (since June 19 2018)

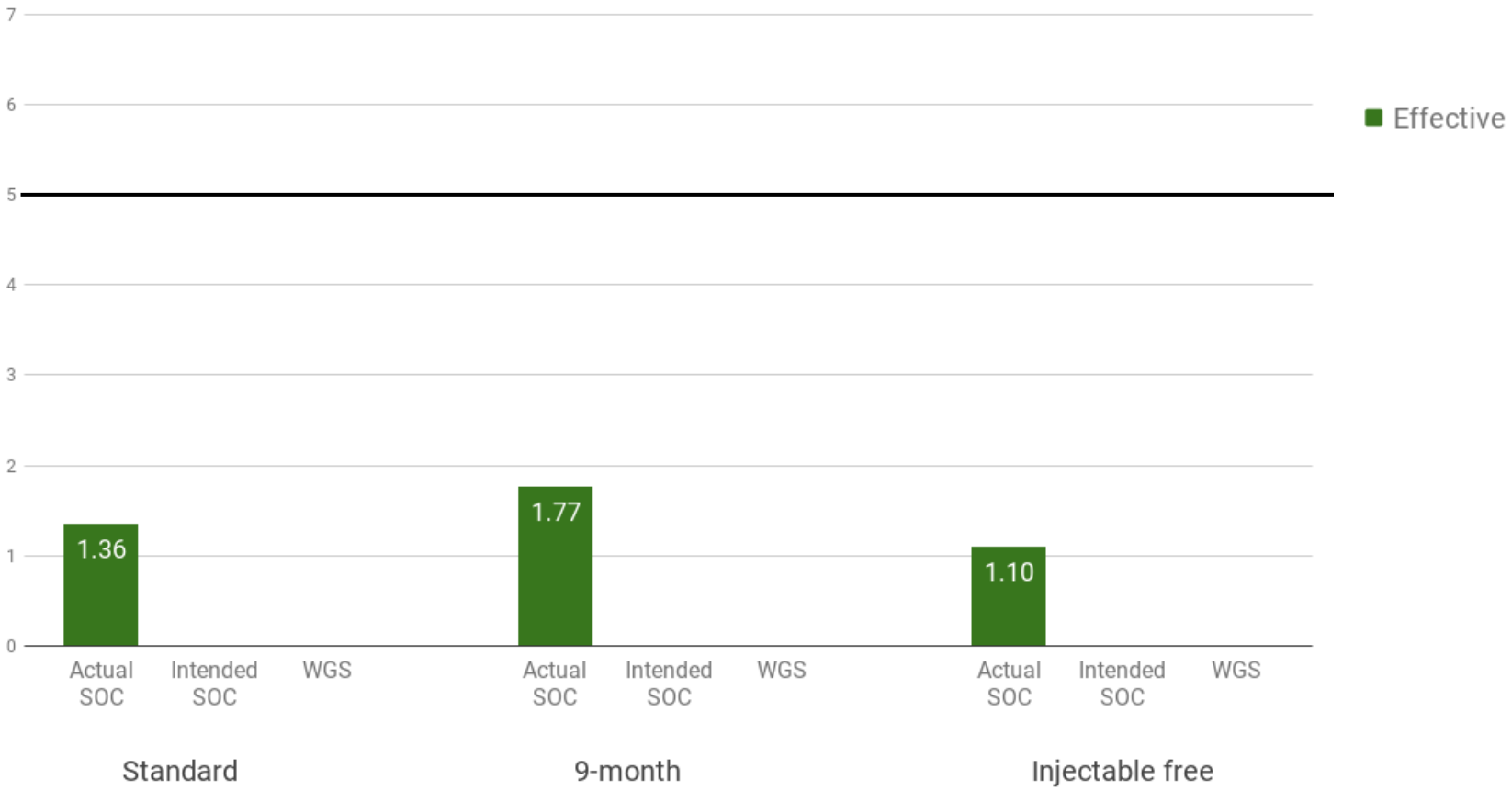
Drug	Standard	Short 9-month	Injectable free
Ethionamide	X		
Pyrazinamide	X	X	X
Kanamycin (INJ)	**X**	**X**	
Moxifloxacin (FLQ)	**X**	**X**	**X**
Terizidone	X		
Prothionamide		X	X
Ethambutol		X	X
Clofazimine		X	X
Isoniazid (high dose)		**X**	**X**
Bedaquiline			X

RESULTS: DRUG RESISTANCE PROFILE



RESULTS: MEAN NUMBER OF EFFECTIVE DRUGS





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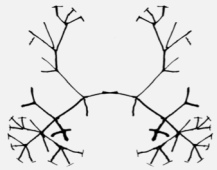

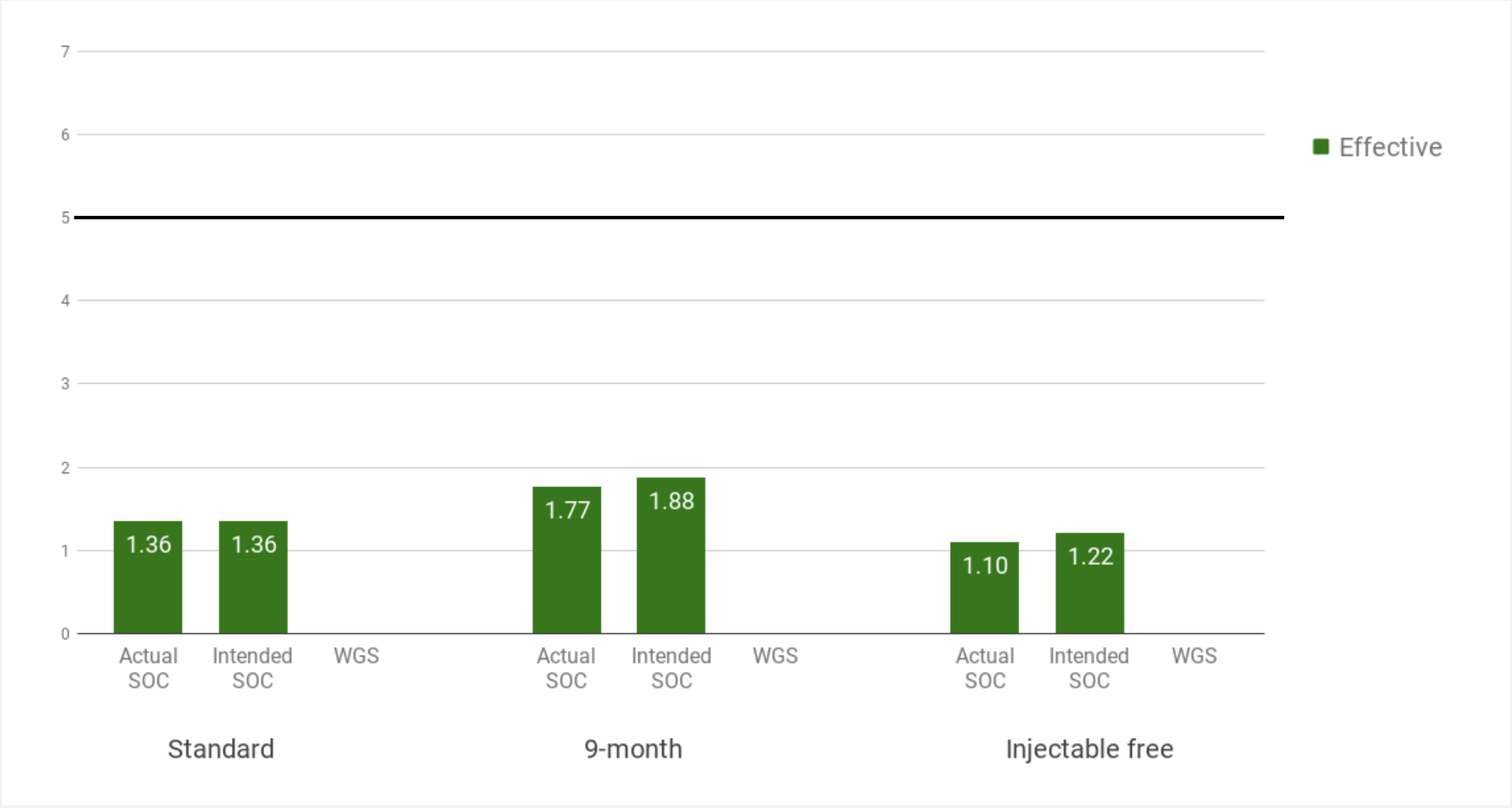

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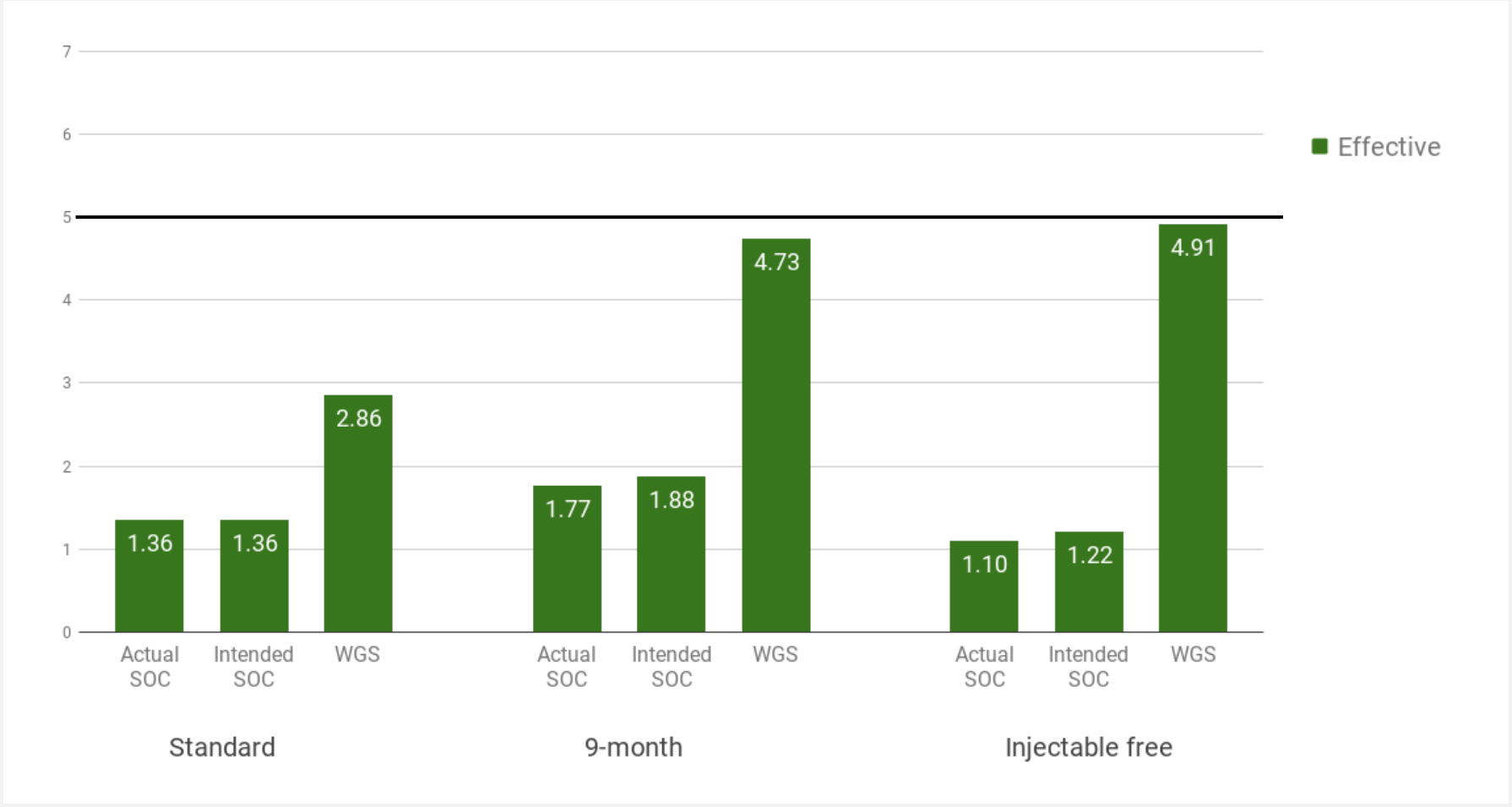

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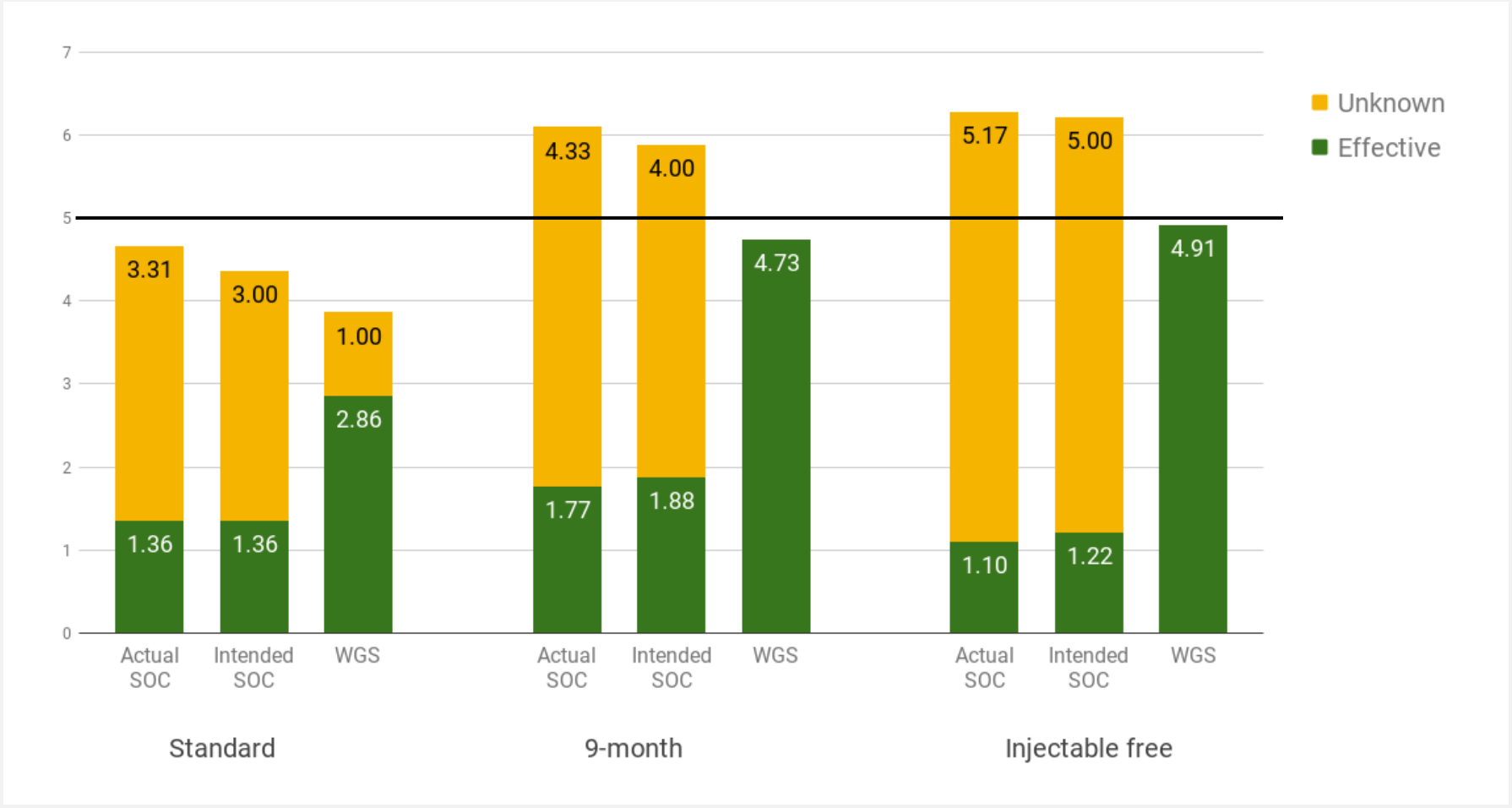
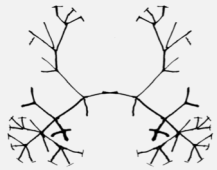


RESULTS: MEAN NUMBER OF EFFECTIVE DRUGS

STRENGTHS AND LIMITATIONS



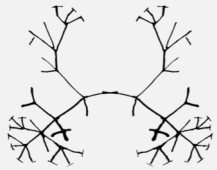
Strengths:

- 3 regimens and 2 standards of care
- 3 provinces
- Most recent (2018) resistance conferring variant list

Limitations:

- Missing culture isolates → selection bias
- SOC defined based on guidelines → implementation varies
- SA is not representative for the world
- Knowledge on DR variants is incomplete

CONCLUSION



Conclusion:

- Standard of care is rarely accurately followed → patients may receive suboptimal treatment (ineffective or unnecessarily toxic)
- Even under optimal SOC, MDR-TB regimen is initiated without sufficient knowledge of the resistance profile of the patient → increased risk for acquired resistance to drugs
- Uncertainty of drug resistance profile under SOC could compromise new drugs
- Changes in regimen recommendations requires a flexible DST approach → WGS is rapid, easily adaptable, and provides the most complete resistance profile

Future direction:

- Public health perspective → WGS could improve patient care
- Research perspective → replicate the study in settings with different drug resistance patterns

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