Molecular methods for TB drug resistance testing: what is needed?

Experience from Khayelitsha, Cape Town, South Africa

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MEDECINS SANS FRONTIERES
DOCTORS WITHOUT BORDERS

Burnet Institute

Khayelitsha

- Peri-urban township
- Population 0.5 million
- Antenatal HIV prevalence ~30%
- Patients on ART: 10, 000 started, >9000 in care
- MTCT HIV+ rate: 4.5 %
- TB case notification rate 2007:

  ~1,500/100,000/year
- 10 health facilities providing TB diagnosis and treatment
- TB outcomes (76% cure rate and 83% success rate)

Rapid Molecular Screening for Multidrug-Resistant Tuberculosis in a High-Volume Public Health Laboratory in South Africa

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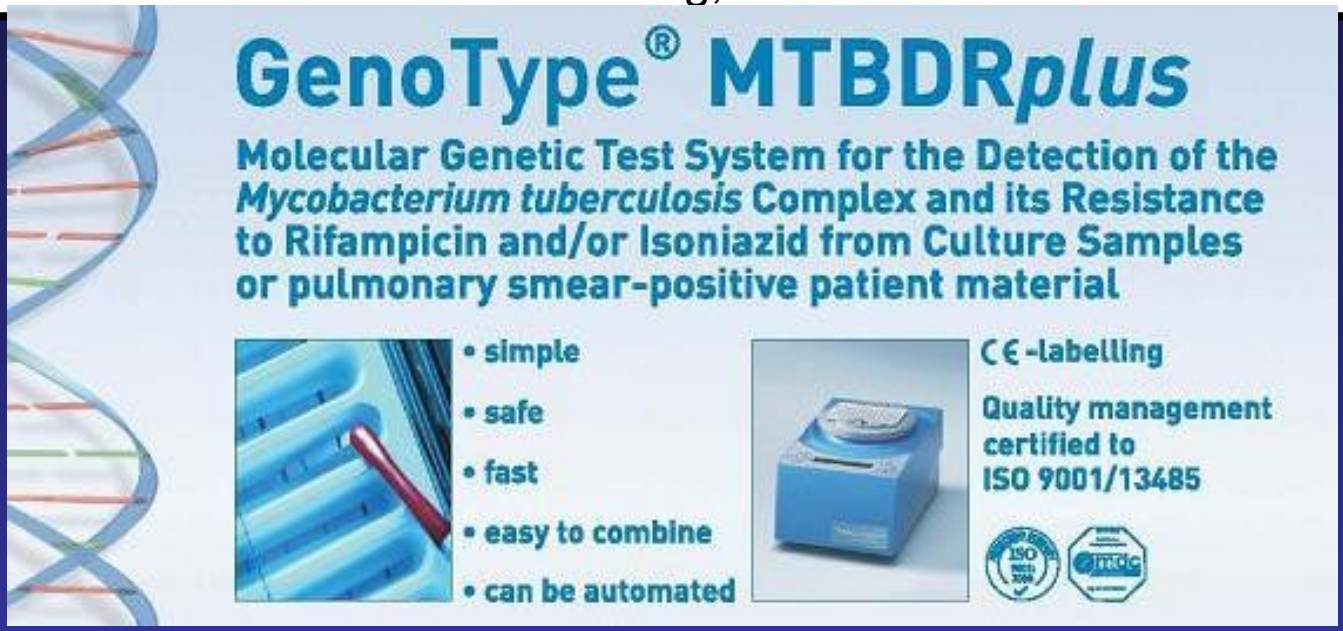
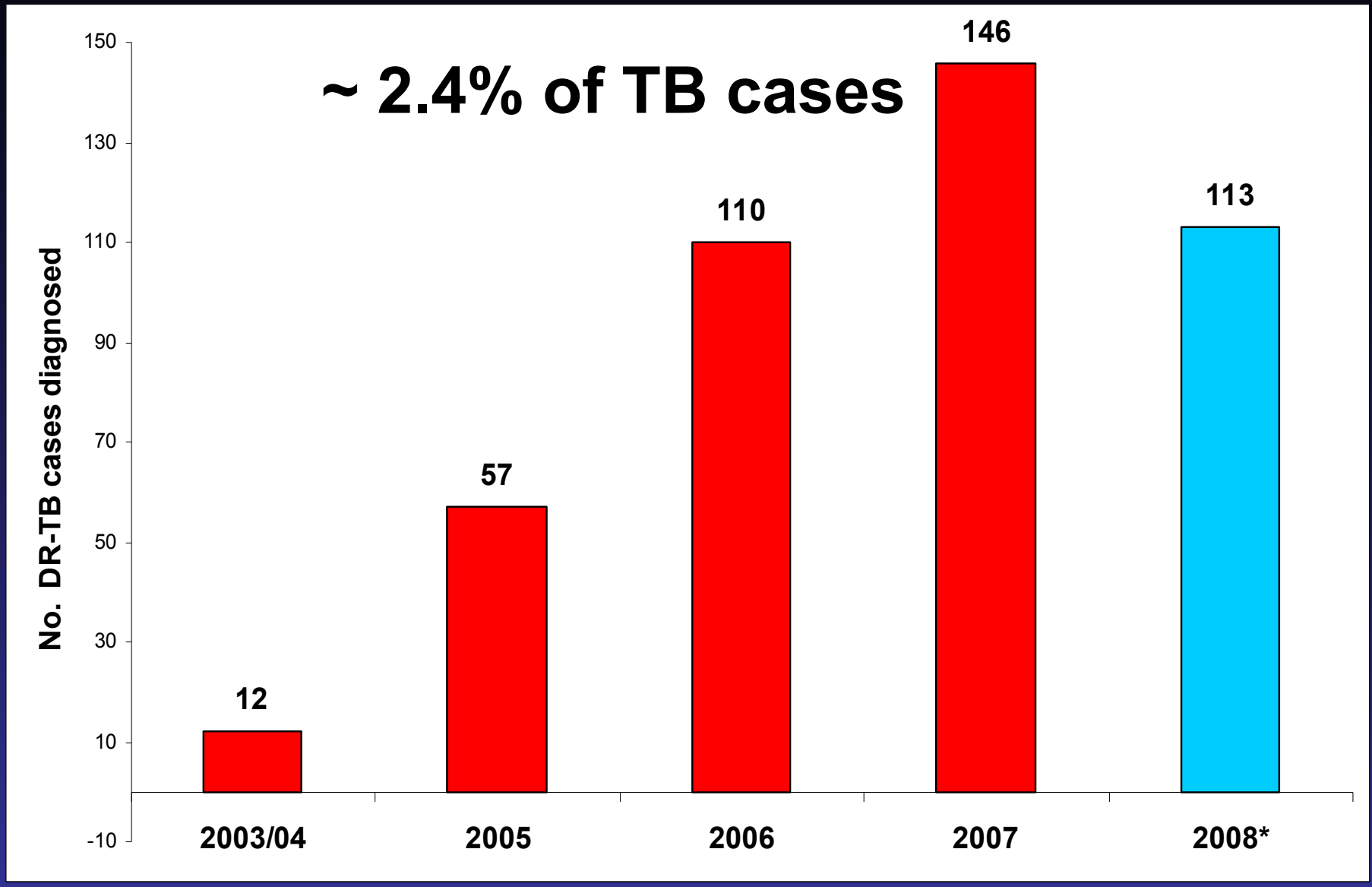



HAIN
LIFESCIENCE
MTBDRplus 96
RMP
INH

DR-TB in Khayelitsha



MDR burden?

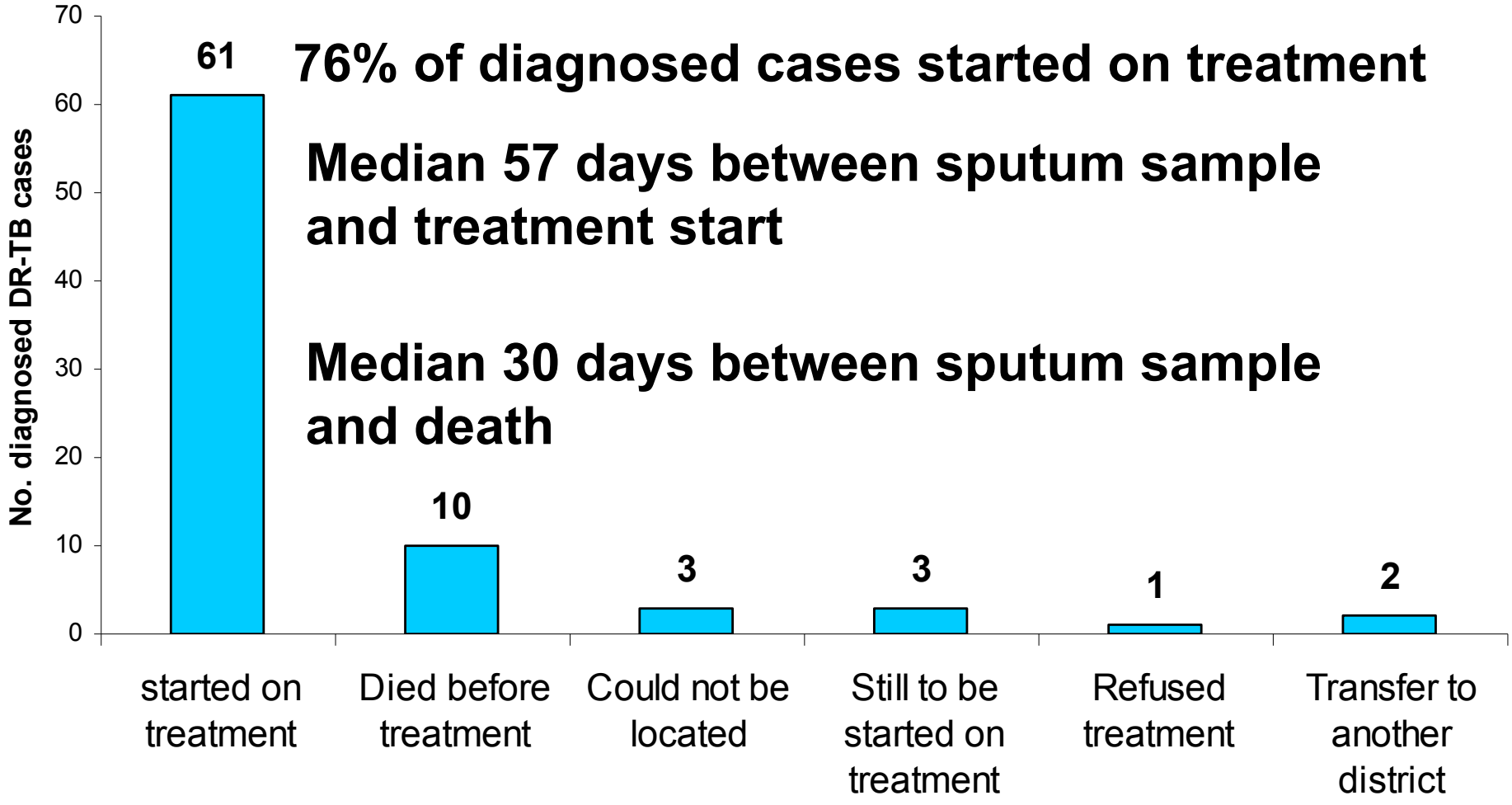
- Routine DST only for previously treated and high MDR risk TB cases
- Therefore likely to be poor overall case detection
- Case detection of 150-200 cases/year = incidence 30-40/100,000/year

	Population (Millions)	**Est. MDR cases**	**% MDR among TB cases**	**MDR incidence /100,000**
South Africa	43.8	14034	2.6	32.1
Russian Federation	140.7	36037	19.4	25.6

Source: WHO 2008

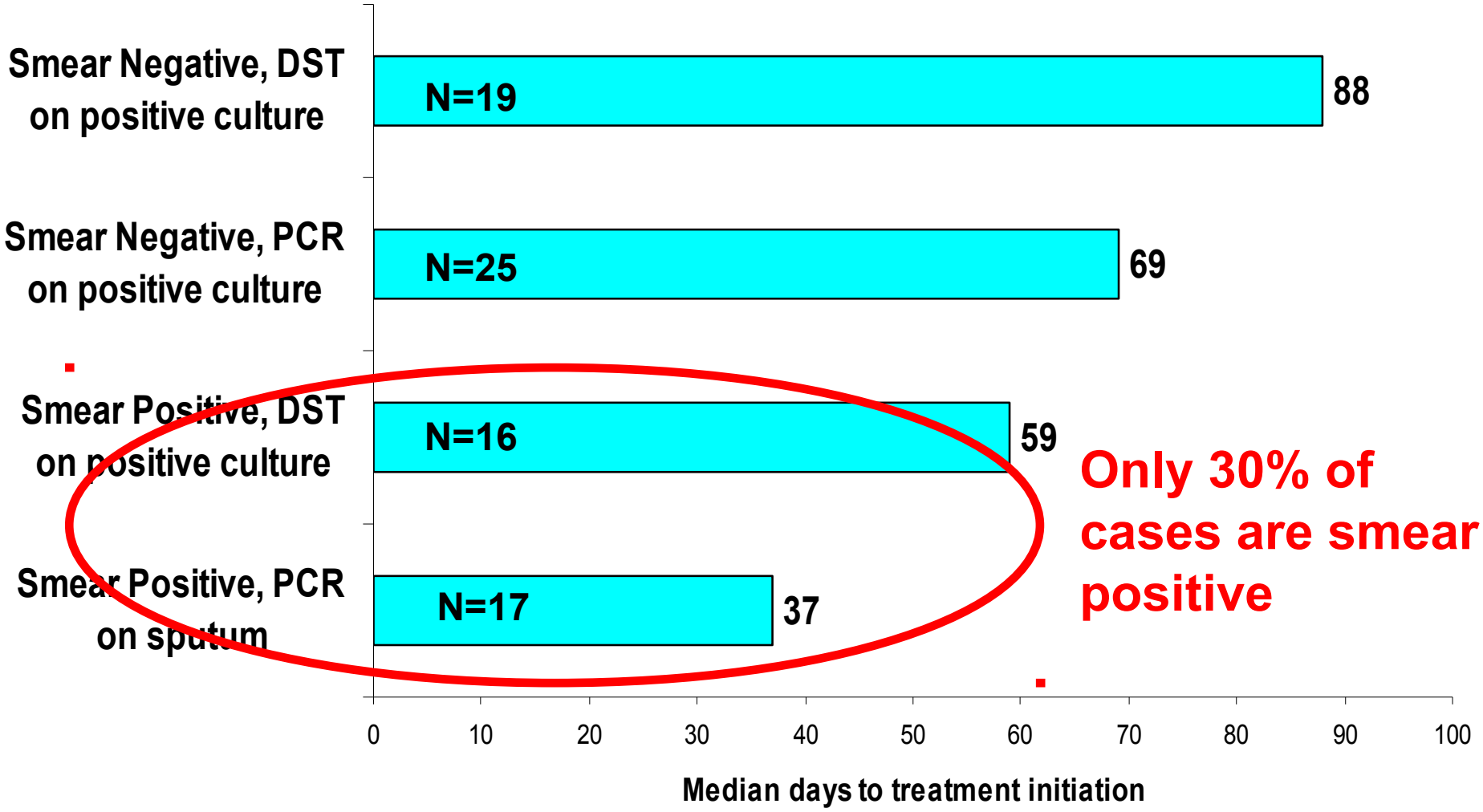
The need for rapid diagnosis

80 DR-TB cases diagnosed in Q1 & 2, 2008

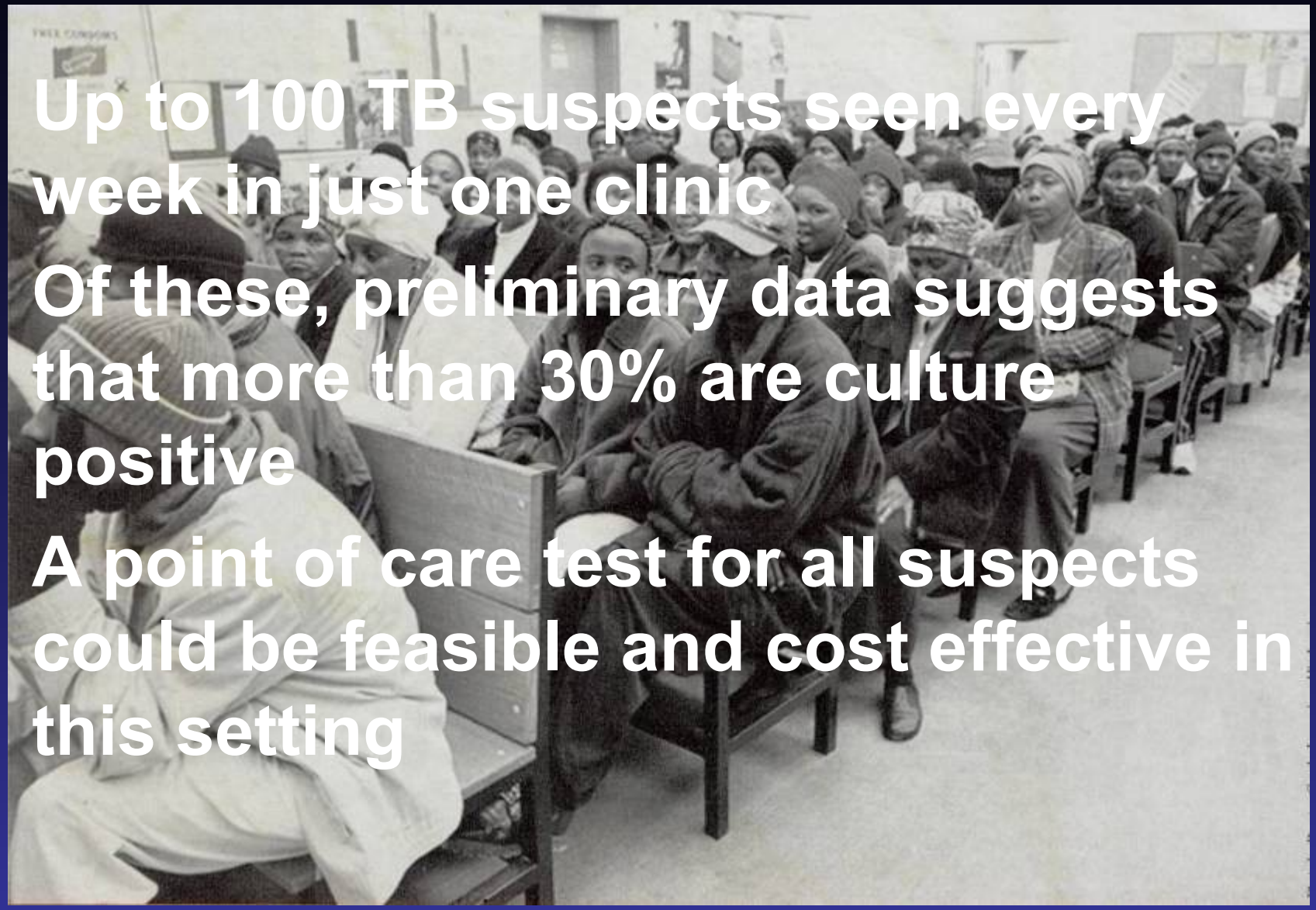


Genotype MTBDR test impact?

Cases diagnosed between September 2007 and June 2008



Need to test ALL TB cases not just the smear positives…



- **Up to 100 TB suspects seen every week in just one clinic**
- **Of these, preliminary data suggests that more than 30% are culture positive**
- **A point of care test for all suspects could be feasible and cost effective in this setting**

Laboratory burden

- 18 MGIT machines
- ~18,000 cultures a month
- Culture not offered to all TB cases
- Reliance on culture requires centralised laboratory

Current constraints to PCR (Hain genotype)

- Logistically not straightforward
- Requires 3 rooms, preferably one with negative pressure to reduce the risk of cross contamination
- Not a closed system, thereby increased risk of cross-contamination
- As yet, no reliable systems to assess cross-contamination
- Lack of clinical trust
- User-dependent, lack of human resources

Clinical trust in PCR

Case: 16 year student

- Negative smear at the end of regimen 1 in March 2008
- Symptoms reappear in April, sputum taken 10th April.
- DST requested as previously treated case
- PCR result from pos culture on 19th May shows MDR
- Started on MDR treatment on 2nd June by clinic doctor, after counselling
- Referred to specialist MDR clinic and seen a week later
- Patient told doctor that he had no symptoms now and X-ray findings inconclusive
- Treatment stopped on the 9th June by specialist doctor, request new sputum and to see again in 2 months
- Patient failed to attend clinic despite repeated attempts to recall; lack of trust in clinic doctor
- Patient died after massive haemoptysis on 16th July

Conclusions

- **Culture is not the answer in this setting**
  - **Too slow and too burdensome on lab**
- **Molecular rapid test has reduced the time to treatment initiation and appears feasible in this setting**
  - **But, there are some drawbacks…**

What is needed for a molecular test?

- Robust technology
- Able to be decentralised to some extent
- Not reliant on highly trained (and motivated) personnel
- High throughput required, whilst reducing the risk of cross-contamination during amplification

Needs to work directly on all sputum specimens!

Is it possible?

- PCR tests for TB have been around for a decade, why are they only now starting to be used routinely in high burden settings?
  - Lack of commitment
  - Lack of understanding of real needs
- Promising developments
- Need to be trialled in terms of programmatic impact

Acknowledgments

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