Considering emergence of drug resistance in development of novel drug regimens

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TB MAC Prevention Meeting

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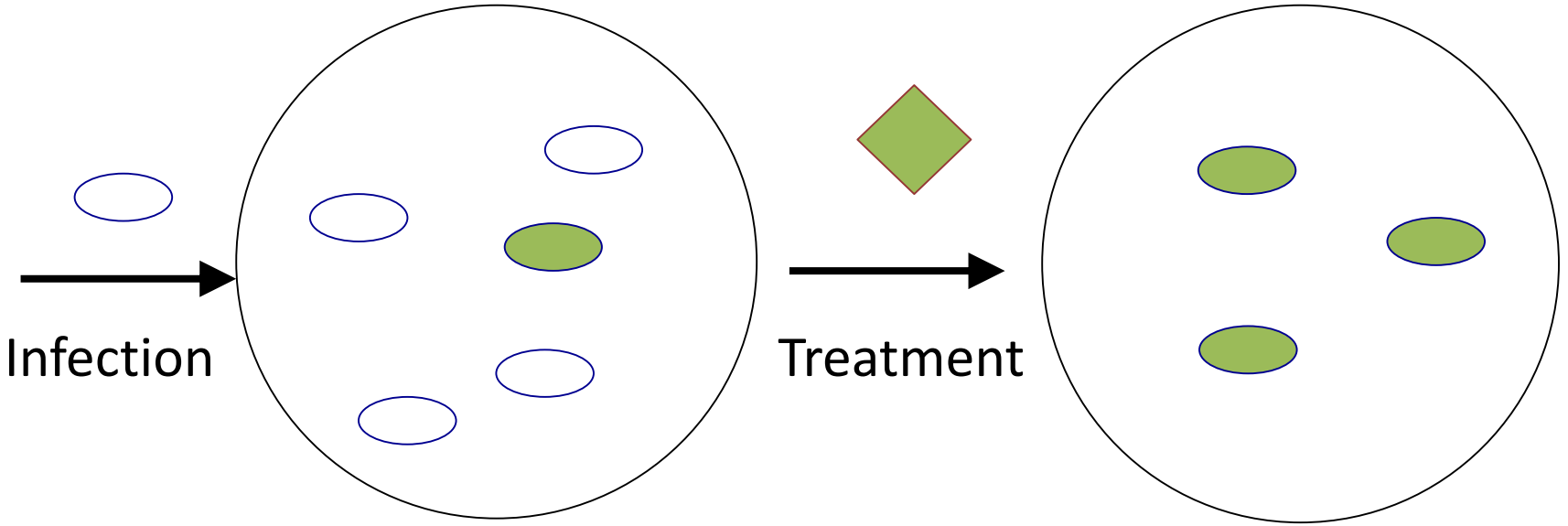
What we know:
Building from theory

1. Acquisition of Resistance

- Known: People receiving a TB drug are at risk of acquiring resistance to that drug
  - Tuberculosis chemotherapy centre (1960): ~100% of positive samples resistant to isoniazid after 6 months of treatment with isoniazid alone
  - Lew (2008): 0.8% of pan-sensitive strains acquired resistance



1. Acquisition of Resistance

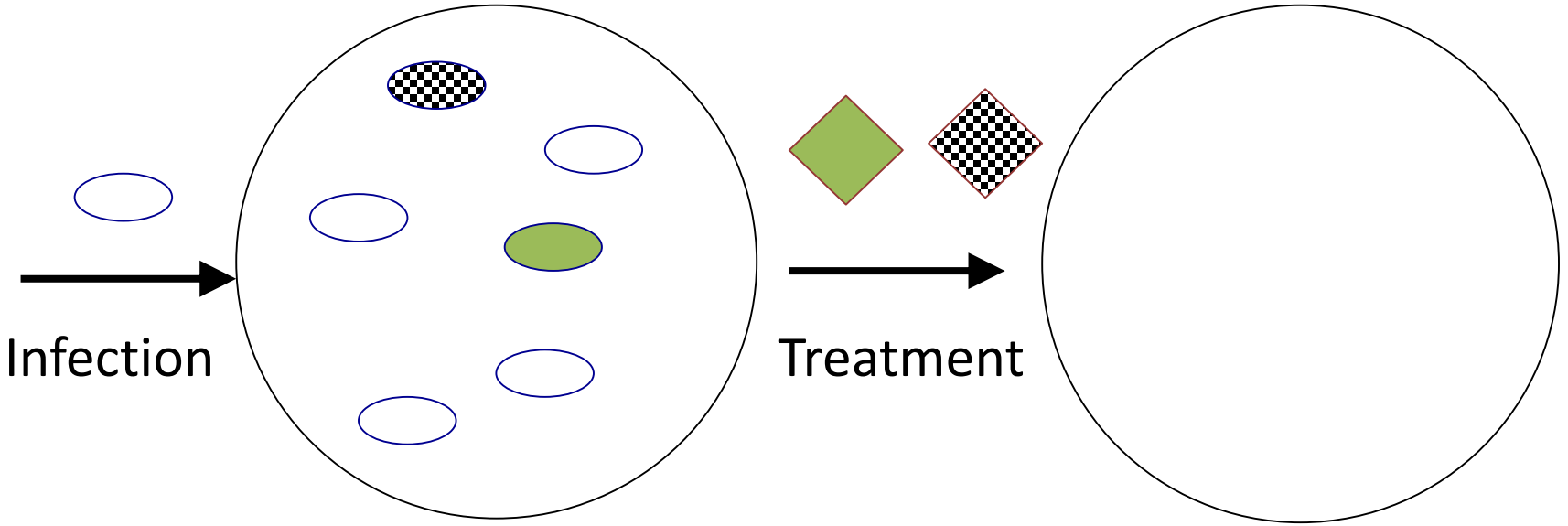
- Implication: People receiving a new TB drug are at risk of acquiring resistance to that drug

	BDQ Available for			
% Acquiring	All MDR	PreXDR+XDR	XDR Only	None
BDQR	**5·88 (2·18, 9·45)**	**3·91 (1·44, 6·29)**	**3·50 (1·30, 5·62)**	**0**
XDR	2·56 (1·09, 7·68)	6·59 (5·84, 8·94)	9·82	9·82
XDR+BDQR	3·44 (1·29, 6·15)	3·20 (1·20, 5·23)	3·50 (1·65,5·62)	0

Kunkel, A., Cobelens, F.G., & Cohen, T. (2016). Tradeoffs in introduction policies for the anti-tuberculosis drug bedaquiline: a model based analysis. *Plos Med 13*(10)

2. Protection by Multi-Drug Regimens

- Known: Regimens with a greater number of effective drugs (with different mechanisms of action) lead to less resistance
  - Lew (2008): 0.8% of pan-sensitive strains acquired drug resistance, compared to 6% single-resistant strains and 14% polydrug resistant strains



2. Protection by Multi-Drug Regimens

- Implications:
  - Using a new drug in combination with other new/existing drugs will help prevent resistance to new drug
  - Adding a new drug to a regimen can help prevent resistance to existing drugs

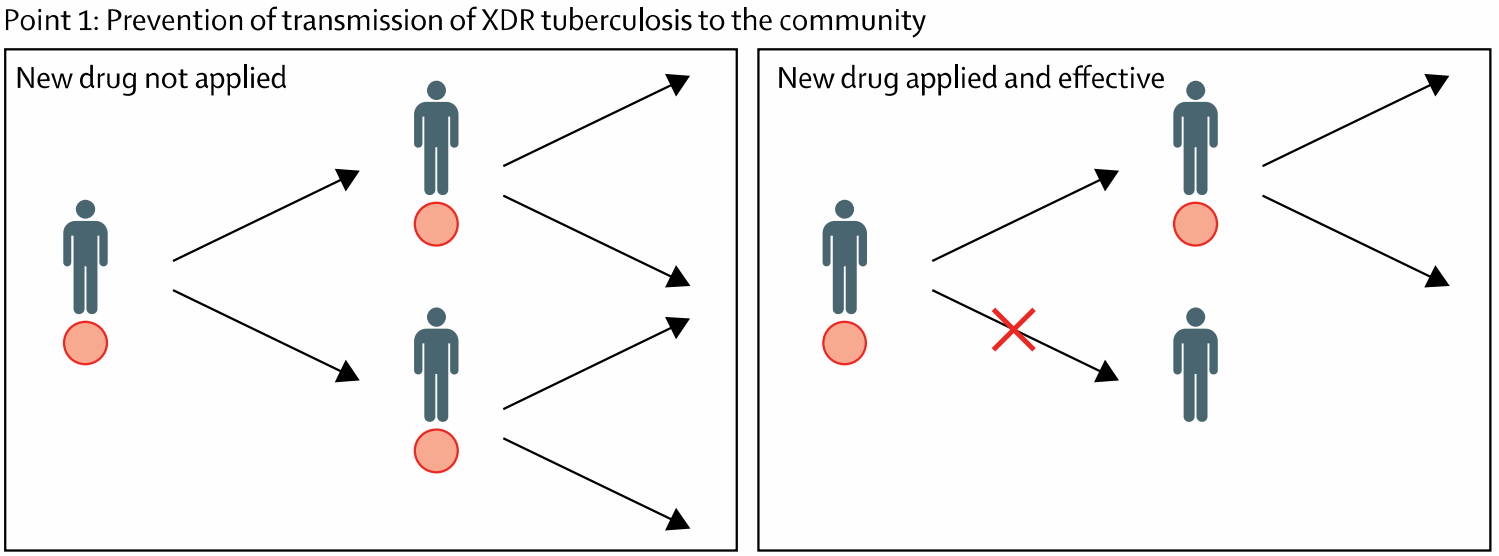
	BDQ Available for			
% Acquiring	All MDR	PreXDR+XDR	XDR Only	None
BDQR	5·9 (2·2, 9·4)	3·91 (1·4, 6·3)	3·5 (1·3, 5·6)	0
XDR	**2·6 (1·1, 7·7)**	**6·6 (5·8, 8·9)**	**9·8**	**9·8**
XDR+BDQR	**3·4 (1·3, 6·2)**	**3·2 (1·2, 5·2)**	**3·5 (1·7,5·6)**	**0**
XDR+BDQR (rapid DST)	**3.4 (1.3, 6.2)**	**3.7 (1.4, 6.4)**	**5.3 (2.0, 8.4)**	**0**

3. Spread of Resistance

- Known: Actively infected individuals can spread their resistance pattern… but effective treatment rapidly stops transmission
  - Shah (2017): Transmission of XDR TB
  - Dharmadhikari (2014): effectively treating MDR TB prevents infection among guinea pigs

3. Spread of Resistance

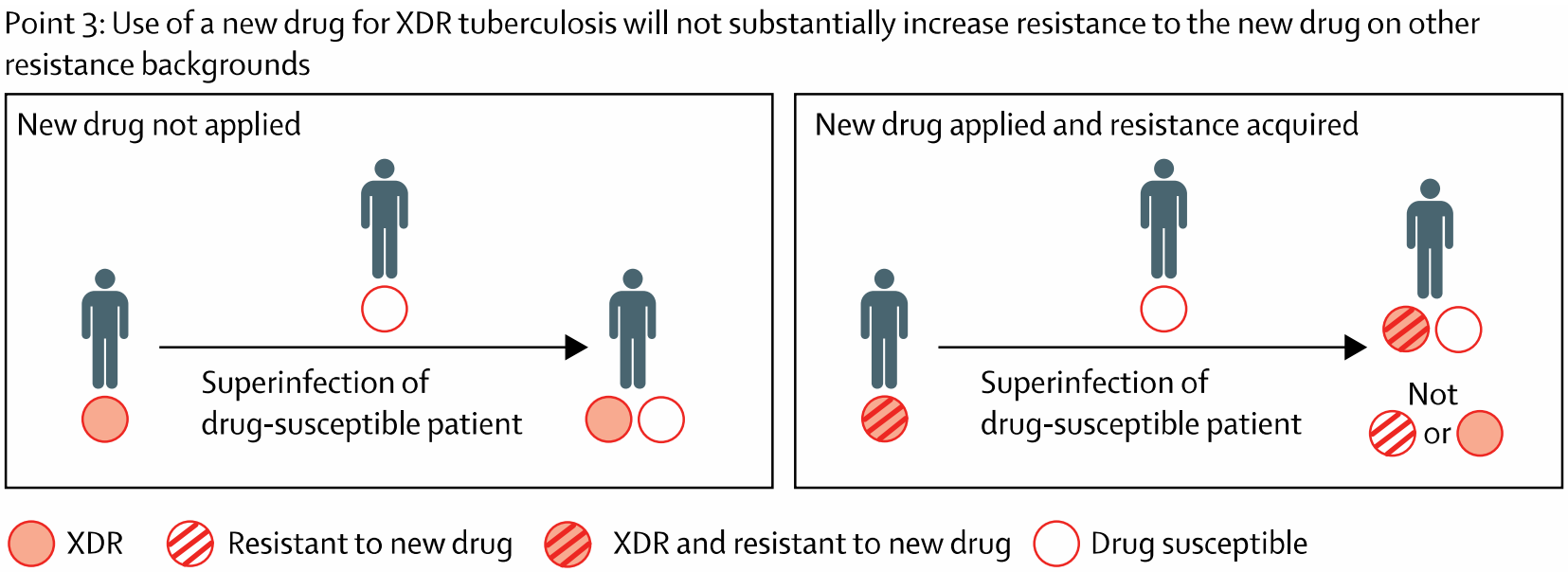
- Implication: Resistance to a new drug could spread to others… but using a new drug could halt the spread of existing resistance



Kunkel, A., Furin, J., & Cohen, T. (2017). Population implications of using bedaquiline in persons with extensively drug resistant tuberculosis: are fears of resistance justified? *Lancet Infect Dis 17*(12)

4. Resistance Mechanisms

- Known: Resistance in TB develops through chromosomal mutation (Eldholm 2016)
- Implication: New drug resistance will not spread beyond the background for which it is used (slight exception for mixed infections)

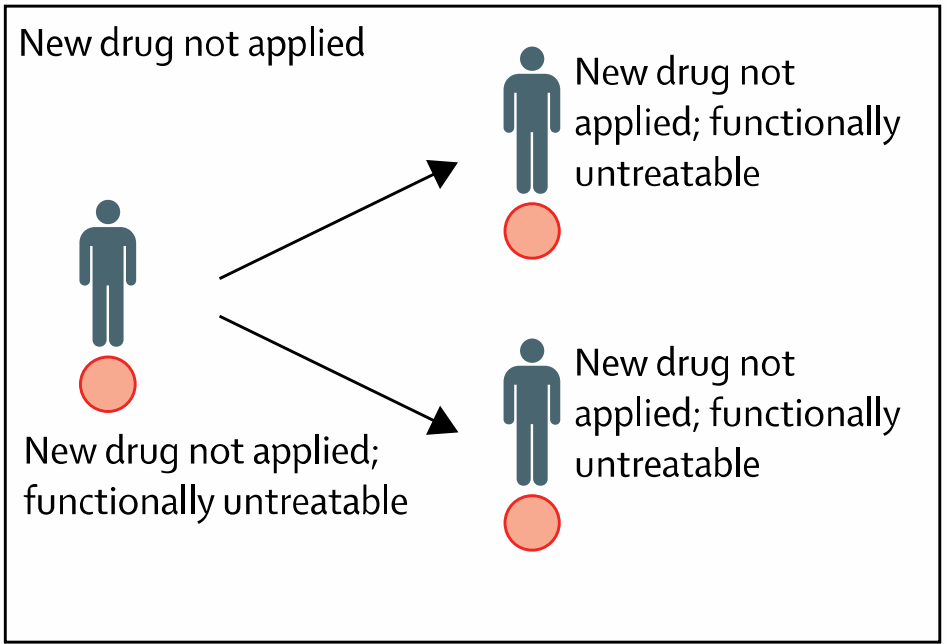


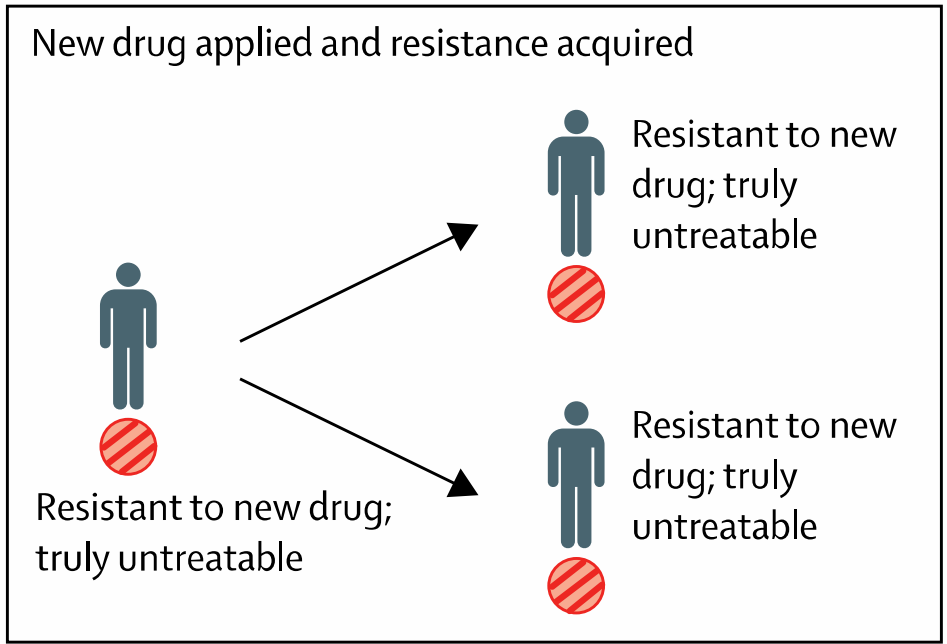
5. Resistance vs. Susceptibility

Known: Successful outcomes depend on receiving drugs to which one is susceptible (Ahmad 2018)

Implication: More pertinent than "resistance" is the number of available, effective drugs

Point 2: Even if new drug resistance is acquired, secondary cases no worse off than if the drug is not used in the absence of other policy changes





What we don’t know:
Need for data and specifics

Resistance Parameters

- Key parameters for a single drug include:
  - How likely are people to develop resistance to the new drug? (What is the background? Clinically relevant definition of resistance?)
  - How well will the new drug protect existing drugs?
- Alternatives: borrow information from other drugs, test wide ranges

Setting and Customization

- Would like to make decisions about drug/regimen change in the context of existing resistance
- Even a universal regimen will not stay universal – how will we treat failures?
- Need for country (or lower-level) specific data on first and second-line drug resistance

Drugs, Regimens, and “In Between”

- Role for decision models that take into account the probability of other possible future events (drugs currently in early phase trials/preclinical development)?
- Updating recommendations as future becomes closer/more certain
- Role of modeling in identifying vs. evaluating combinations of interest

Conclusion

- Existing knowledge can take us part of the way to modeling resistance to new drugs/regimens
- But still lots of work to be done

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