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Diagnosis of Tuberculosis in Endemic Settings: an Epidemiologist to the Modeler(s)

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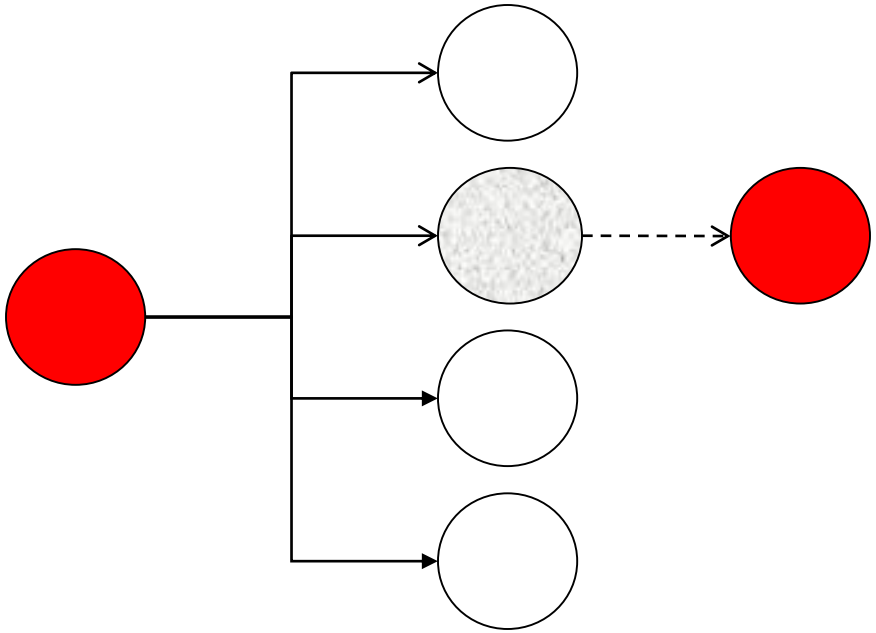
Diagnosis

Diagnosis of infectious diseases is the fulcrum of medicine and public health

- Medicine
  - Identify disease to start effective therapy
  - Direct benefit to the individual
- Public Health
  - Interrupt transmission going forward
  - Indirect benefit in the population
    - Children
    - HIV-infected contacts

Replacement Principle of Tuberculosis

As long as one case of tuberculosis is replaced by another, elimination of tuberculosis cannot be achieved



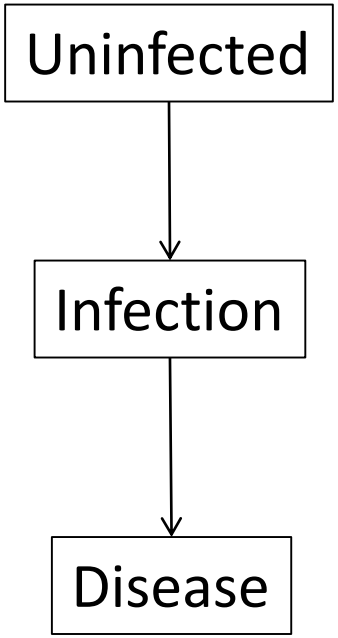
NextGen Principle of Infectious Diseases

For most infectious diseases, the next generation of cases is created through transmission before the diagnosis is made and treatment begun in an infectious index case.

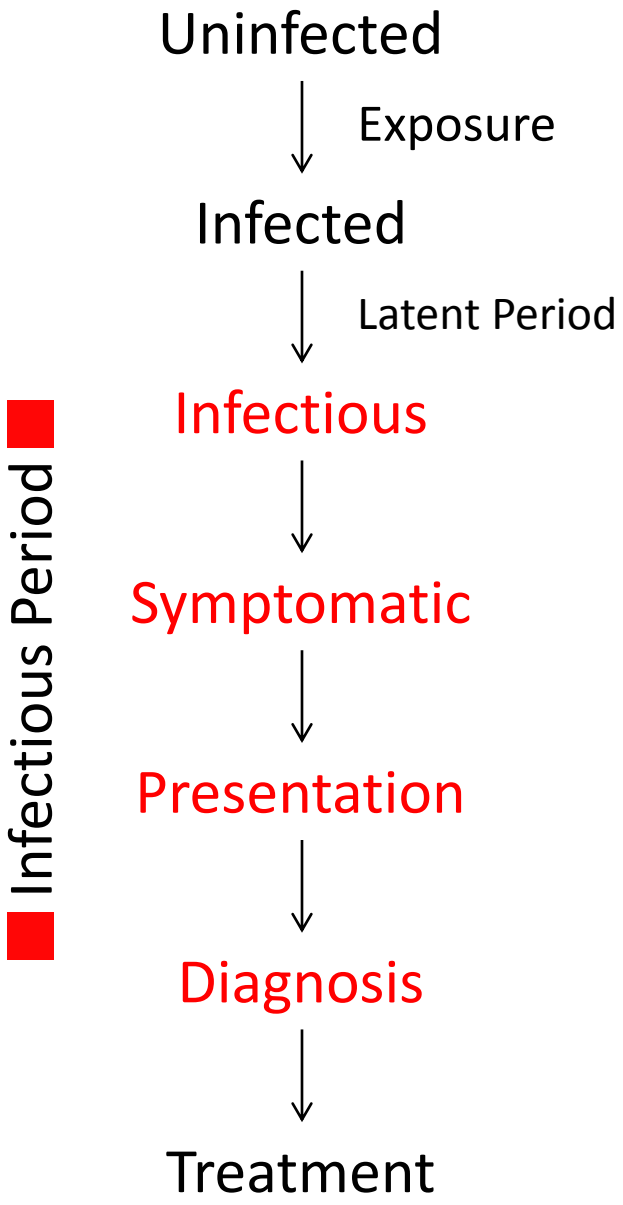
Earlier diagnosis ››› Less transmission

Natural History of Tuberculosis

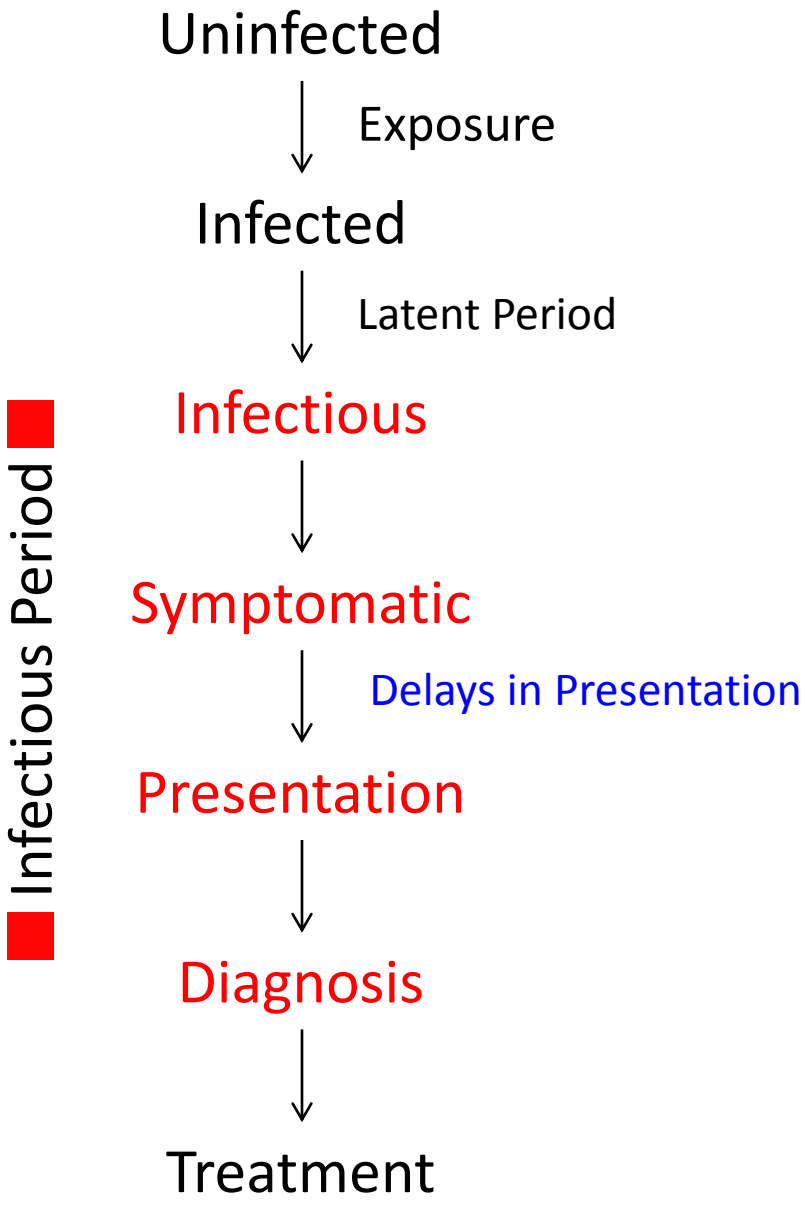
Two stage process: infection and disease Comstock 1972



Transmission Cascade

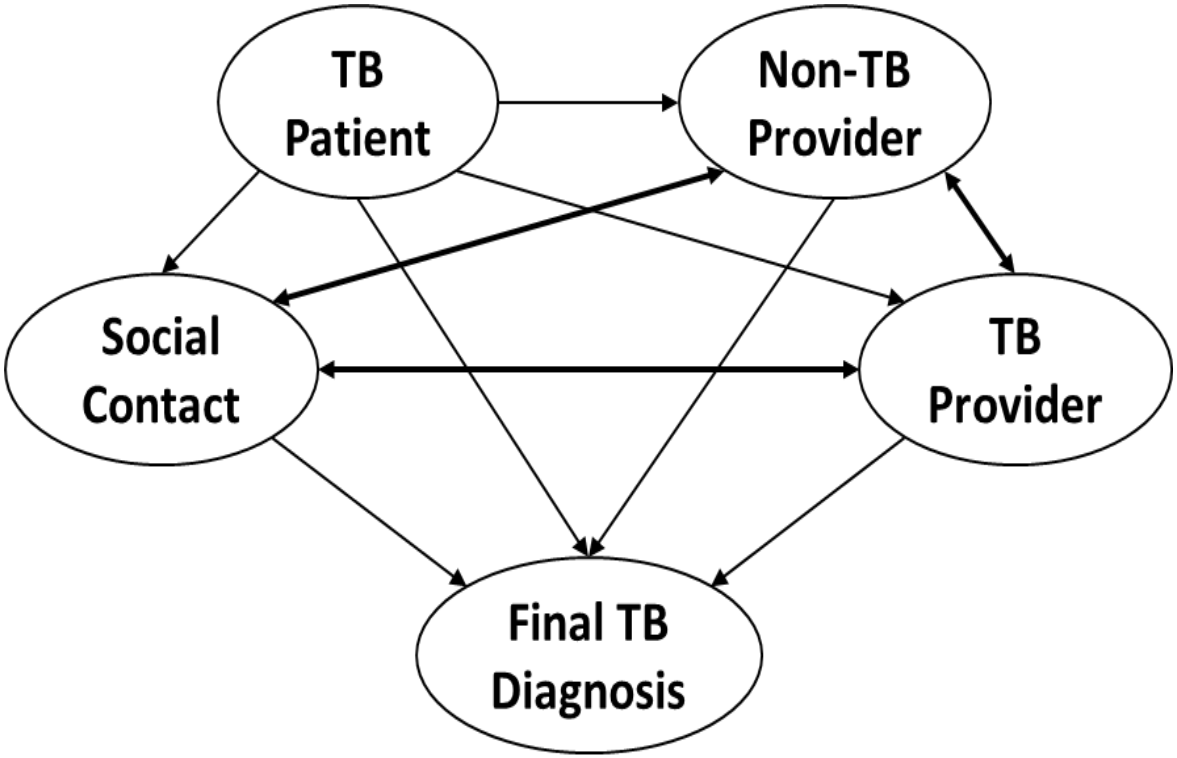


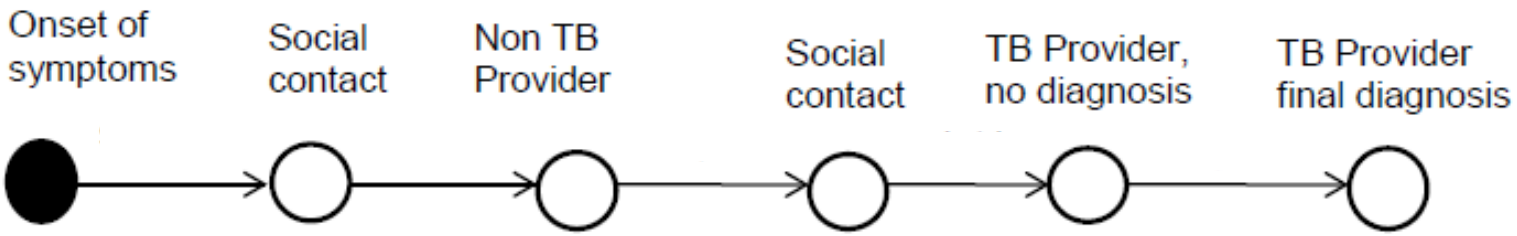
Transmission Cascade



4 Degrees of Separation

Cough to Diagnosis of TB





Sekandi et al. BMC Infectious Diseases 2015

Delays in Presentation

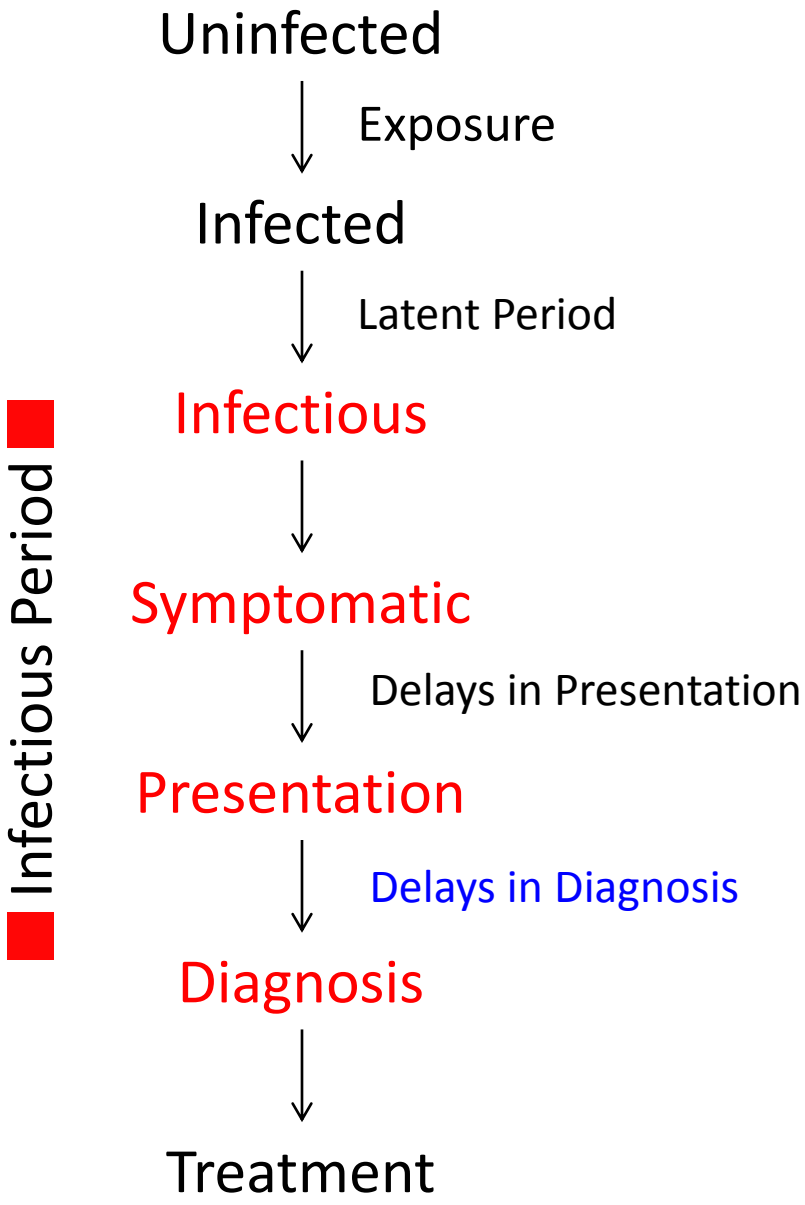
Characteristic	Steps to Diagnosis (median)	Day to Diagnosis (median)
Overall	4	70
TB Category		
New	5	84
Retreatment	3	46

Delays in Diagnosis

- New vs. retreatment cases
- HIV seronegative vs. seropositive
- Initial presentation to general health care provider vs. social contact

Sources of Delay	%
Acknowledgement of symptoms	41
Presentation to general health provider	34
Social contacts within personal network	14
Presentation to TB control program	11

Transmission Cascade



Delays in Diagnosis:
Need for Point-of-Care (POC) Diagnosis

Author	Overall	Patient	Health System
	----- *Delay in Days (IQR)* -----		
Sekandi 2015	28 – 140	16 – 58	7 – 30
Getnet 2017	30 – 367	4 – 199	2 – 129

Effects of Delays in Diagnosis

- Prolong disease morbidity
- Effective therapy delayed
- Prolong the infectious period
- Increase likelihood of infecting new contacts

Test	Time Required (d)
Acid-fast bacilli microscopy	1
Nucleic acid amplification, detection	1
Nucleic acid amplification, drug resistance	1 – 2
Growth detection Liquid Solid	42 – 56 10 – 14 21 – 28
Antigen detection, e.g., LF-LAM	1
Identification by DNA probe or HPLC	1
First-line drug susceptibility testing (DST; liquid)	7 – 14
Second-line and novel compound DST	7 – 28

Lewinsohn D, et al. AJRCCM 2017

Point-of-Care Diagnostics:

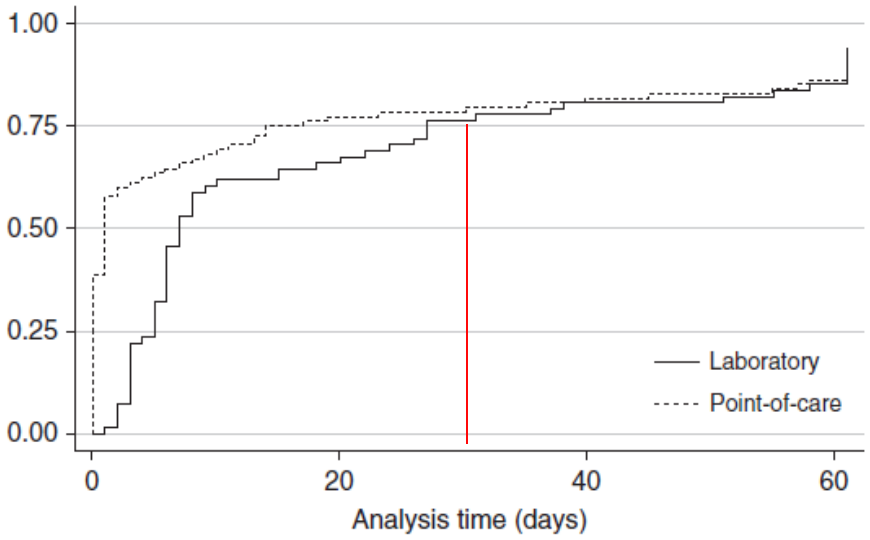
Xpert MTB/RIF

Cluster-randomized trial of adults with suspected pulmonary TB/DR-TB to evaluate the performance of centralized versus point-of-care Xpert MTB/RIF on initiation of appropriate TB treatment. Lessells RJ et al. AJRCCM 2017

Key findings

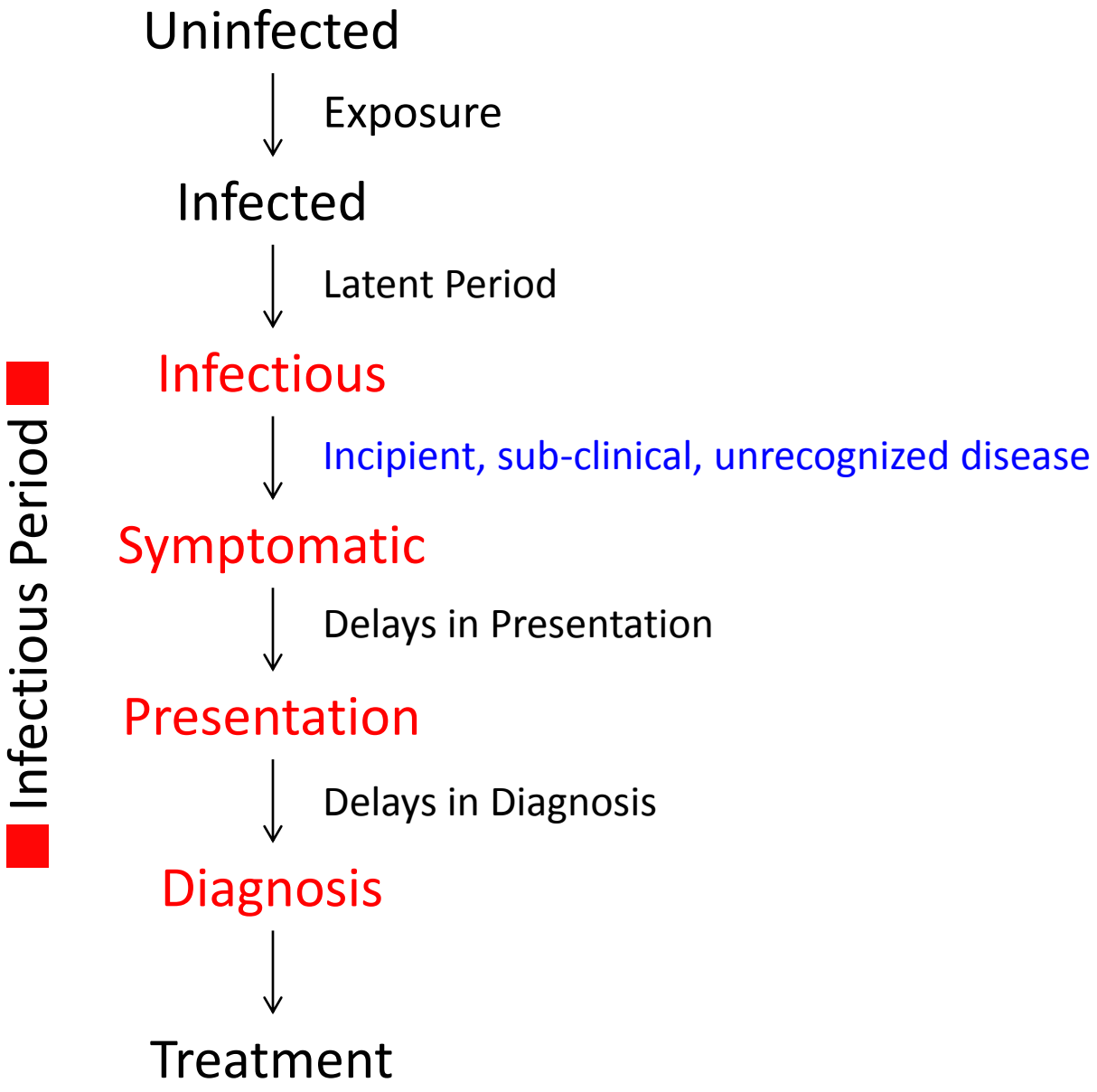
- 80% and 77% of culture positive cases were on therapy at 1 month (RD = 3.1, NS)
- Median time to initiation of treatment was earlier in POC than in centralized testing (1 versus 7 d)
- POC testing led to earlier treatment

Time to initiation of appropriate tuberculosis treatment in culture–positive patients



Number at risk							
Laboratory	68	(45)	23	(10)	13	(9)	10
Point-of-care	88	(68)	20	(3)	17	(7)	12

Transmission Cascade



Active Case Finding in African Communities

DETECTB (Corbett EL et al. Lancet 2010)

- Cluster-randomized trial in Zimbabwe to compare mobile van with door-to-door active case finding
  - Mobile van improved ascertainment of cases by 48%
  - Both types of active case finding reduced tuberculosis prevalence in the community by about 40%.

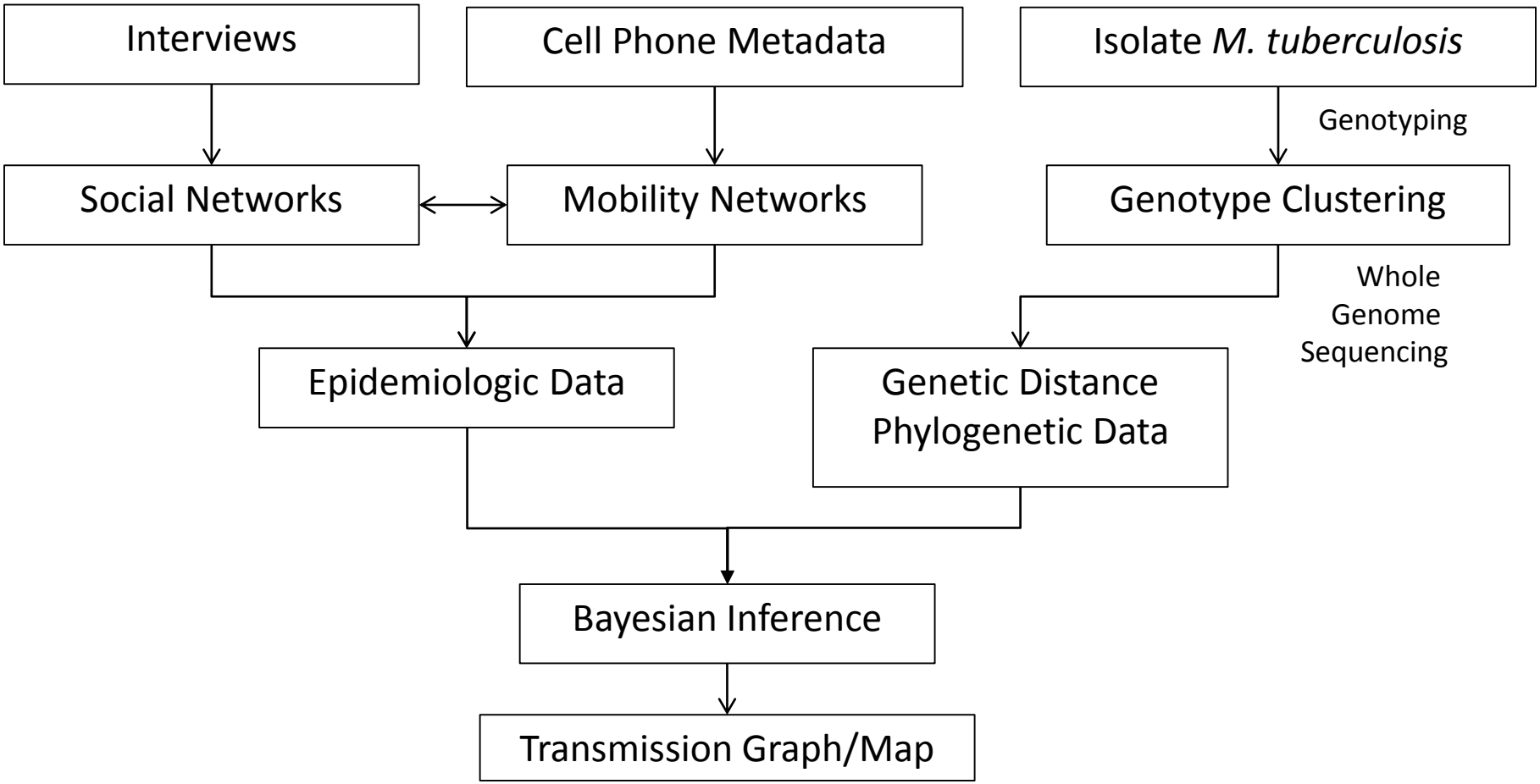
ZAMSTAR (Ayles H et al. Lancet 2013)

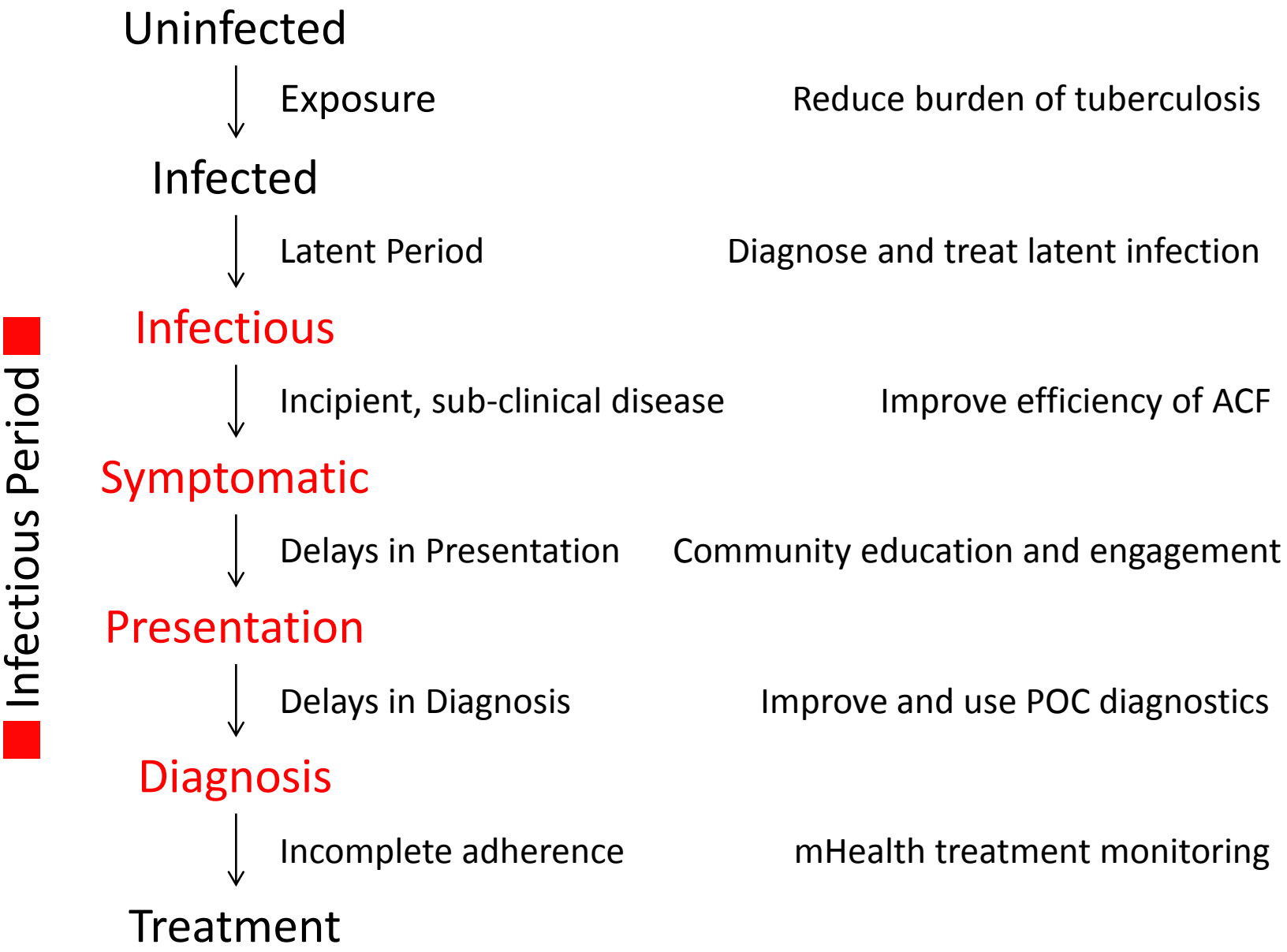
- Community-randomized trial in Zambia and Western Cape to compare enhanced case finding (ECF) with household tuberculosis-HIV care
- Household intervention performed better than ECF
  - Prevalent disease: reduced by 18% in household intervention; no effect with ECF
  - Incident infection: reduced by 55% in household intervention; no effect with ECF

Challenges of Active Case Finding in the Community

- Challenges
  - Active case finding in the community is *inefficient*
    - Depends on local epidemiology
  - Improve efficiency by targeting case finding to areas where infectious cases may be
- Potential solutions
  - Where is *M. tuberculosis* transmitted in community?
    - Reconstruct the movement of index cases in the weeks and months before diagnosis using archival cellular telephone information

Estimating Tuberculosis Transmission in African City Post-Modern Epidemiology




Uninfected
Exposure
Reduce burden of tuberculosis
Infected
Latent Period
Diagnose and treat latent infection
Infectious
Incipient, sub-clinical disease
Improve efficiency of ACF
Symptomatic
Delays in Presentation
Community education and engagement
Presentation
Delays in Diagnosis
Improve and use POC diagnostics
Diagnosis
Incomplete adherence
mHealth treatment monitoring
Treatment
Infectious Period

Questions for modeling

- What is the effect of compressing the infectious period on the course of an epidemic?
  - What yields the greatest benefit: reducing patient delays or diagnostic delays, or pre-symptomatic case finding? And at what cost?
- How is spatial information incorporated into models?
  - Local factors, such as mobility, may affect the epidemiology of tuberculosis. How can these be integrated to generate spatial models with ‘local’ epidemiology?

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