Conceptualizing subclinical TB and its role in transmission at the population level

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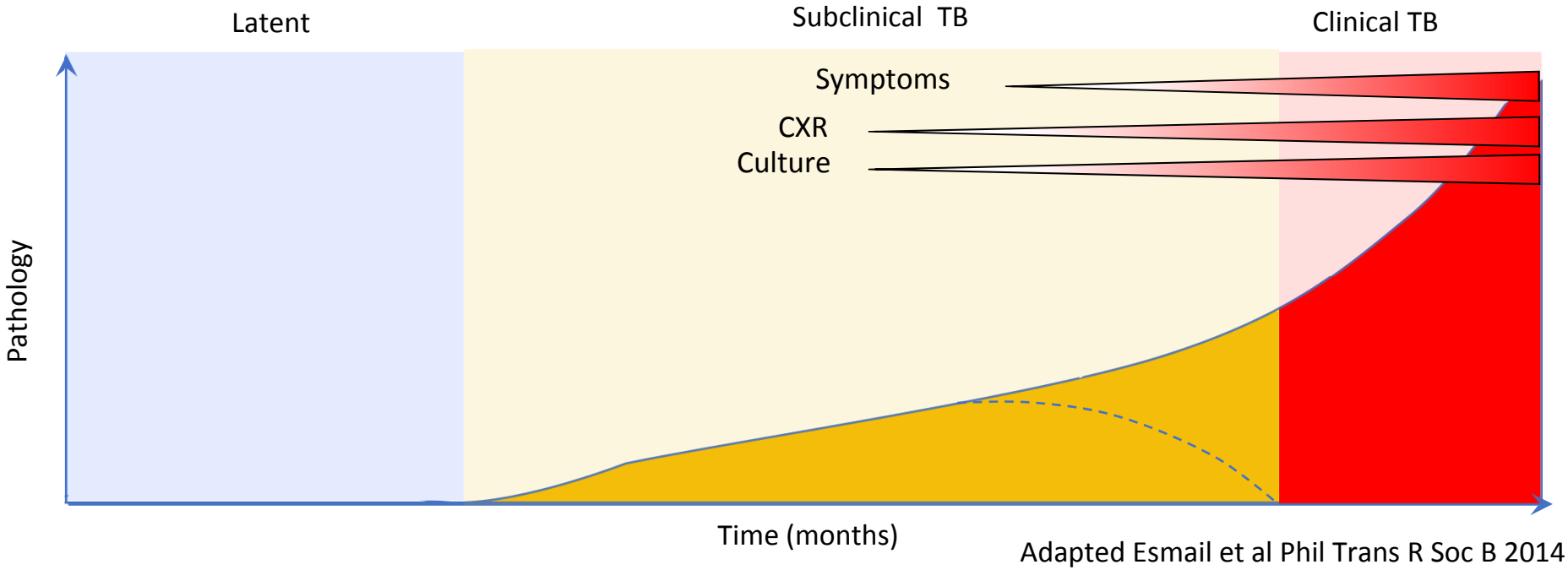
Subclinical disease progression



Adapted Esmail et al Phil Trans R Soc B 2014

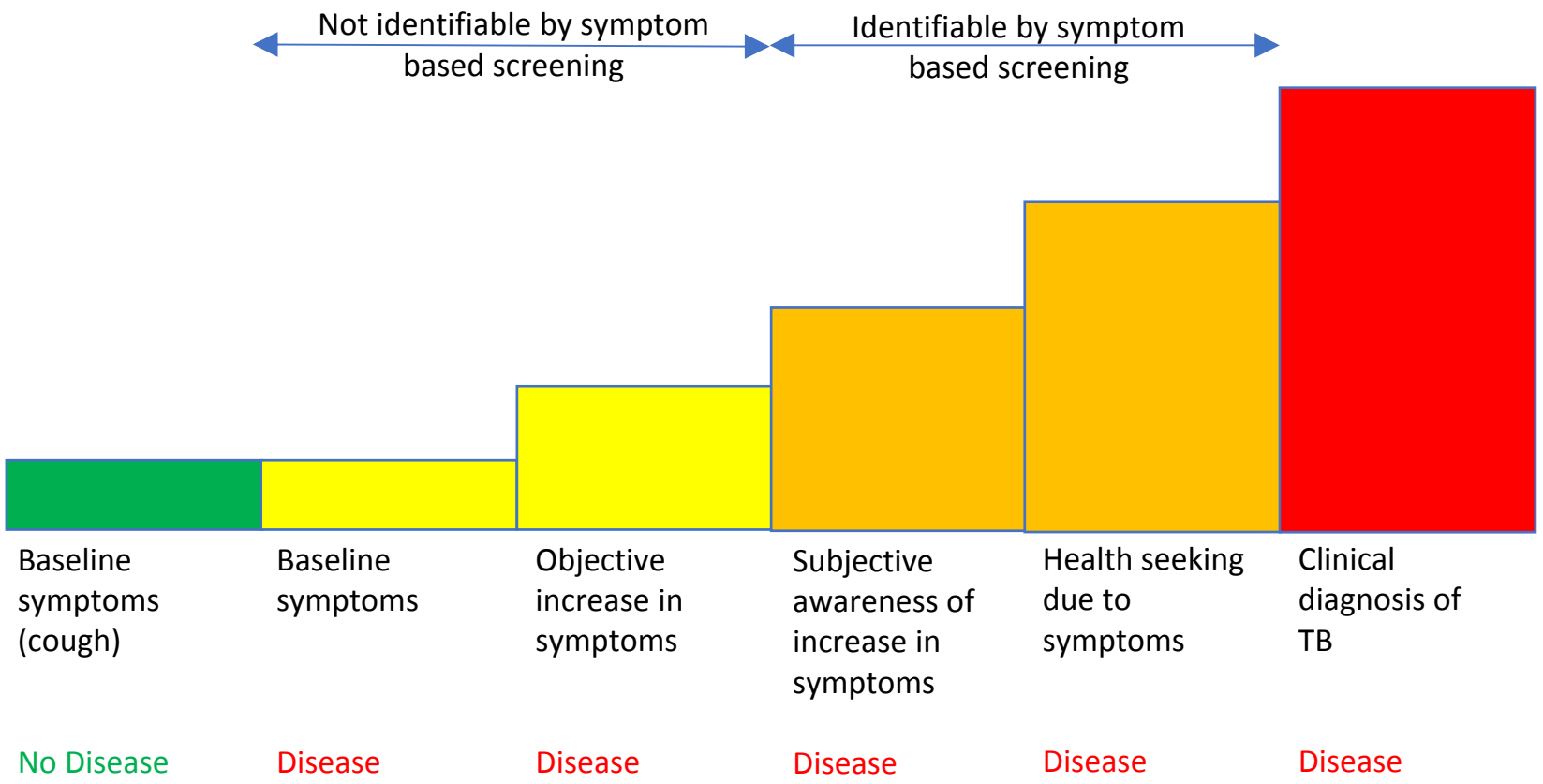
During subclinical phase

- TB pneumonia develops as the earliest event in active pulmonary TB

- Pathology evolves – may become visible radiographically
- Bronchogenic spread of disease → shedding of Mtb in resp secretions
- Cytokines and inflammatory mediators → development of symptoms

- May spontaneously improve

Symptom progression



Infectiousness and transmission

- Mol epi studies in settings with very high participation and coverage can be informative
- Smear positive disease relative transmission rate 4x that of smear negative – Tostmann et al CID 2008
- Very difficult to take this to determine transmission related to subclinical disease

Key factors in transmission of subclinical TB

- What is the number of infectious particles produced <u>spontaneously</u> in subclinical disease
  - Concentration of bacilli in sputum
  - Rate of spontaneous droplet nuclei production
- Duration of time with viable bacilli in sputum

Infectiousness $\propto$ conc. bacilli in sputum X rate of droplet nuclei production

Concentration of bacilli in sputum

Community prevalence in Western Kenya 2006-7 – n=20,566 screened

- Symptom screen, sputum smear, CXR on all
- Sputum culture on Abn CXR, positive symptoms, smear positive

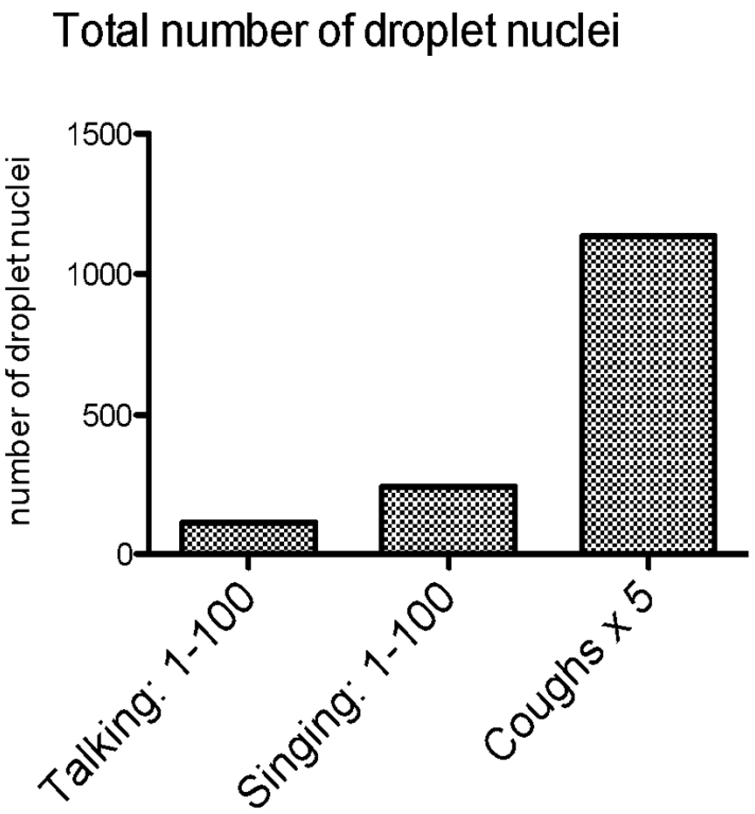
Van't Hoog et al Plos One 2012

	All Participants		Suspects§		Cases		HIV-infected	Smear+
Presence of	*n*	*(%)*	*n*	*(%)*	*n*	*(%)*	**n(%)**¶,**	**n(%)**¶
	20,566		7,342		123		52/101 (51)	51 (41)
Cough								
≥2 weeks	2,264	(11)	2,264	(31)	64	(52)	36/56 (64)	37 (58)
8–13 days	317	(2)	317	(4)	4	(3)	2/3 (67)	2 (50)
1–7 days	5,973	(29)	1,913	(26)	26	(21)	11/20 (55)	9 (35)
None reported	12,006	(58)	2,846	(39)	29	(24)	3/22 (14)	3 (10)
Study symptom screening algorithm†‡								
Yes	3,490	(17)	3,481	(47)	75	(61)	40/62 (65)	40 (53)
No	17,076	(83)	3,861	(53)	48	(39)	12/39 (31)	11 (23)

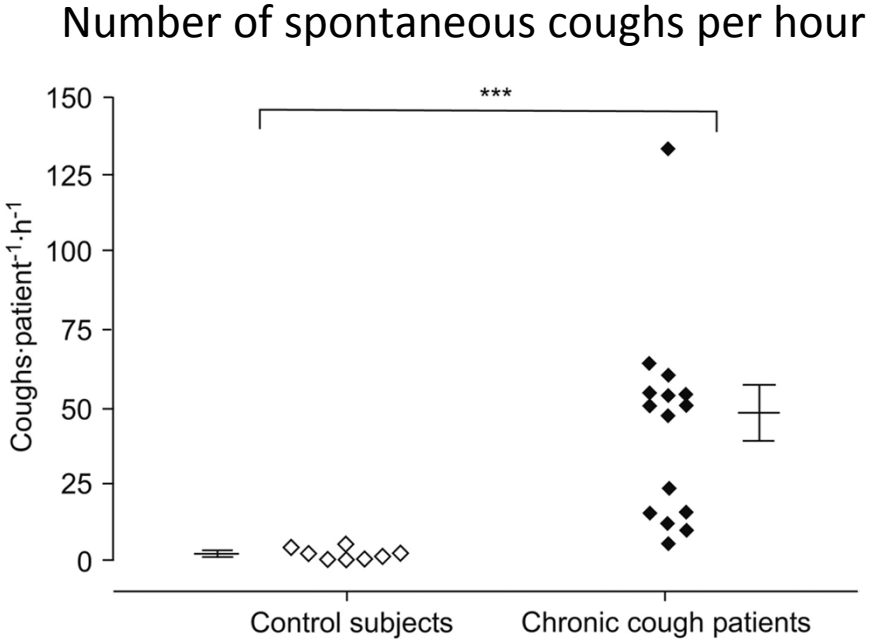
Future studies

- Smear + vs Cult +
- Time to positivity (liquid culture)
- CT values on Xpert (Ultra)

Do healthy people produce droplet nuclei?



Louden and Roberts Am Rev Resp Dis 1967 & 1968



Birring et al ERJ 2008

Prevalence of chronic cough varies in communities

- Postal survey of respiratory symptoms in 44,483 adults living in Finland, Sweden and Estonia

	Chronic productive cough			
	M	W	Total	P
Manual workers in industry				
Finland	14.4	11.8	13.9	F/S $P < 0.001$
Sweden	7.9	10.1	8.2	F/E $P = 0.024$
Estonia	12.6	11.1	12.0	S/E $P < 0.001$
Manual workers in service				
Finland	11.9	12.4	12.2	F/S $P < 0.001$
Sweden	7.2	7.0	7.1	F/E $P = 0.002$
Estonia	9.6	9.3	9.4	S/E $P = 0.043$
Assistant non-manual				
Finland	7.5	11.0	9.9	F/S $P < 0.001$
Sweden	6.5	5.9	6.1	F/E ns
Estonia	10.4	8.1	8.6	S/E $P = 0.001$
Intermediate and professional				
Finland	9.8	9.6	9.7	F/S $P < 0.001$
Sweden	4.6	4.4	4.5	F/E $P = 0.003$
Estonia	8.2	7.2	7.5	S/E $P < 0.001$
Housewives				
Finland	0.0	6.7	6.5	F/S ns
Sweden	0.0	4.2	4.1	F/E ns
Estonia	25.0	4.7	5.2	S/E ns
Self-employed				
Finland	12.0	11.2	11.6	F/S ns
Sweden	8.7	7.6	8.4	
Students				
Finland	7.2	7.2	7.2	F/S $P < 0.001$
Sweden	3.8	3.5	3.6	F/E ns
Estonia	7.5	3.5	4.9	S/E ns

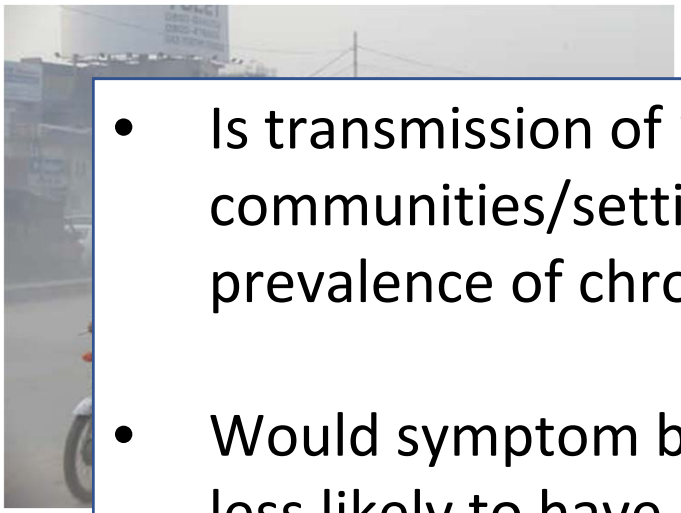
Pallasaho IJTLD 2004

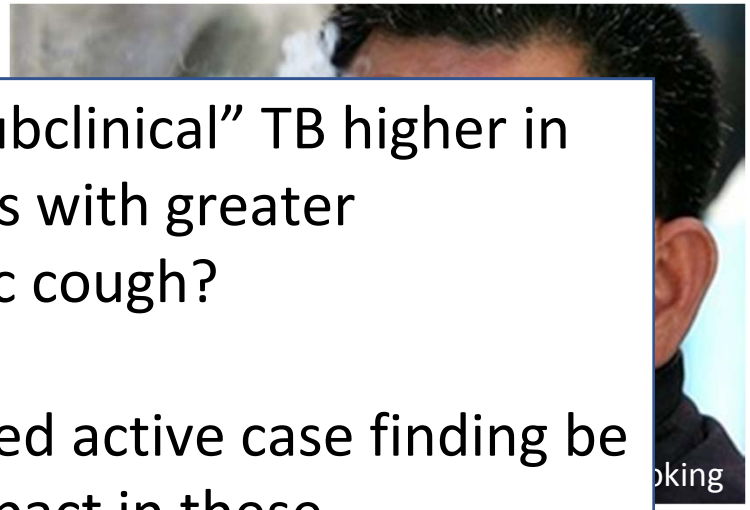
- 10-15% of Nordic population has productive cough most days for > 3 months/ year for at least 2 years
- Manual worker 1.4x more likely to have chronic cough than professional workers

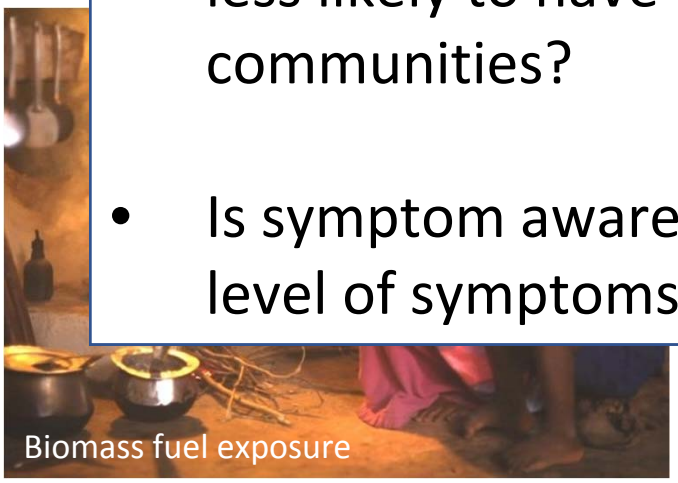

Helsinki, Finland

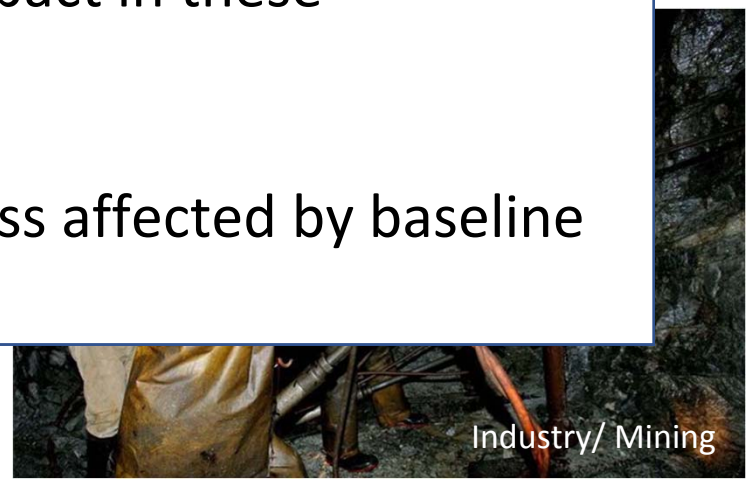
Prevalence of chronic cough in TB high burden setting…..?

- Is transmission of “subclinical” TB higher in communities/settings with greater prevalence of chronic cough?
- Would symptom based active case finding be less likely to have impact in these communities?
- Is symptom awareness affected by baseline level of symptoms?









50.5% of miners without pneumoconiosis – chronic cough

Community rate of respiratory infections

Community study - Michigan USA, 1976-81
5363 person years of observation of 1000 individuals
Medical consultation in 25% of illnesses

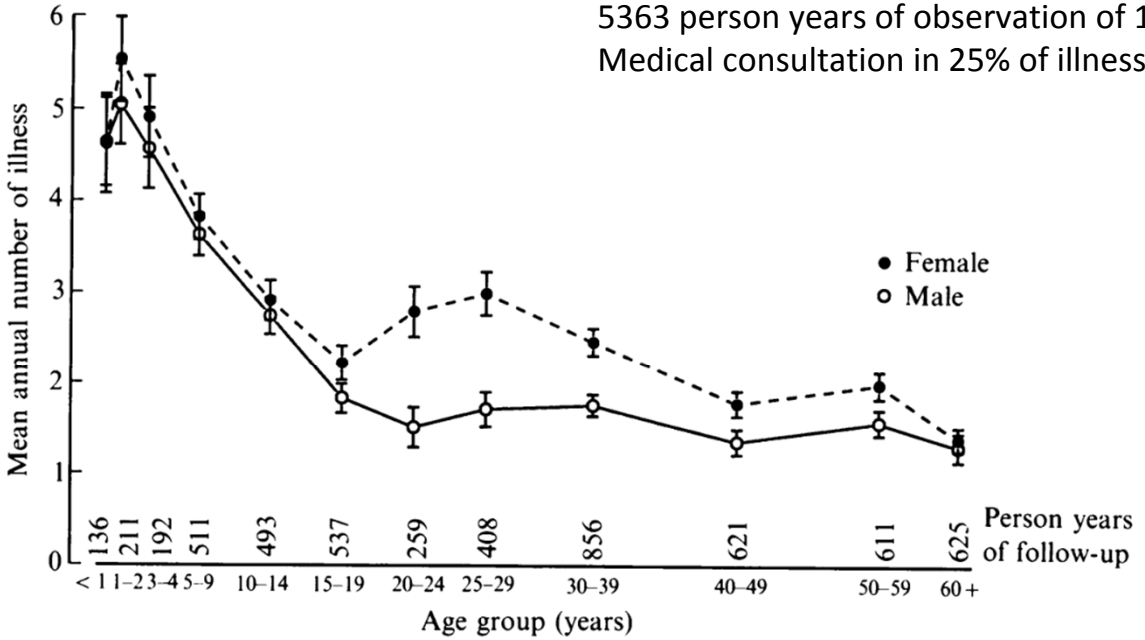
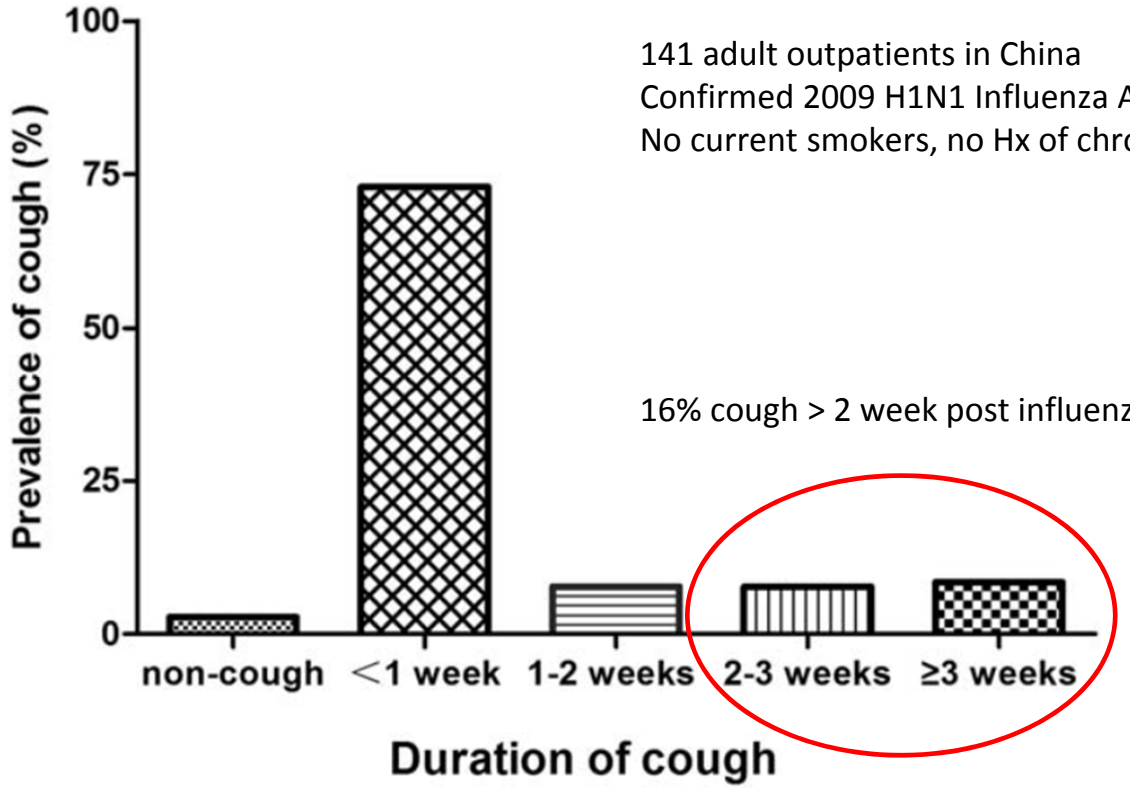


Fig. 1. Mean number of respiratory illnesses (and 95% confidence intervals) experienced per year by age and sex. Tecumseh Michigan, USA 1976–81.

Monto and Sullivan Epidemiol Infec 1993

Duration of cough post influenza



141 adult outpatients in China
Confirmed 2009 H1N1 Influenza A
No current smokers, no Hx of chronic respiratory disease

16% cough > 2 week post influenza

Lin et al Clinical Resp Journal 2015

Duration of infectiousness

- Ratio of undiagnosed prevalent TB to incident TB reflects mean duration of smear/culture positivity

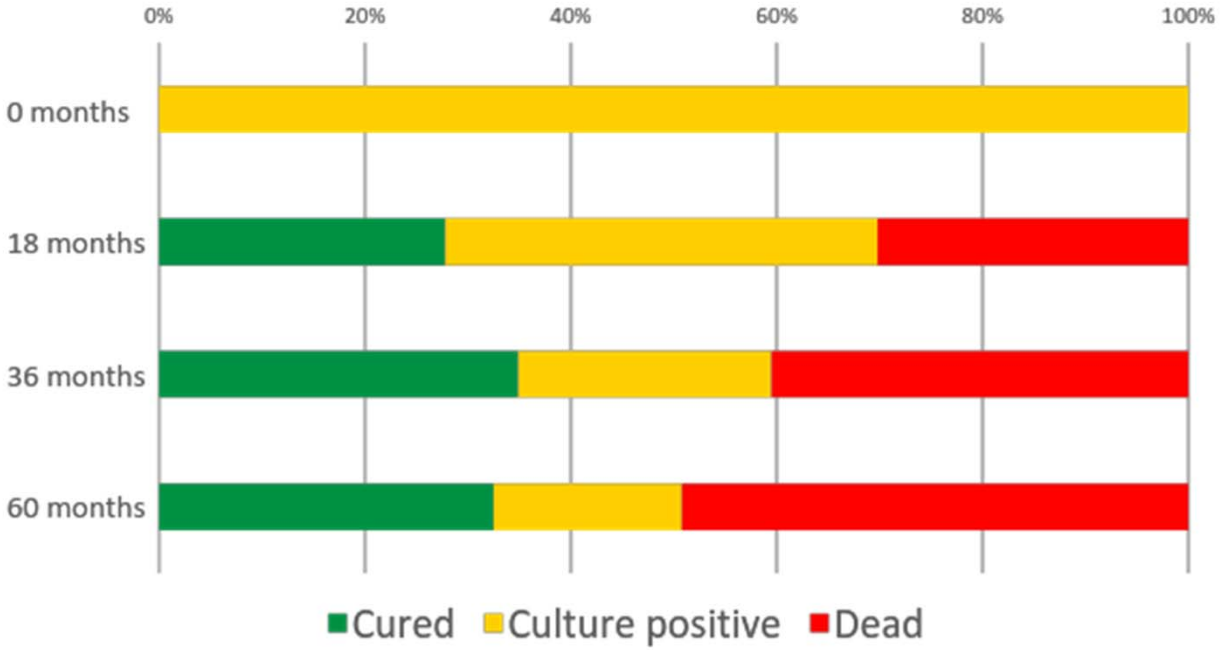
- Corbett et al – duration of Smear positivity
  - HIV+ve – 4.2 - 7.2 months; HIV-ve - 12.7 - 18 months
- Wood et al – Duration of culture positivity
  - HIV+ve – 14.3 months; HIV-ve – 12.2 months

- Dowdy et al (model)
  - Duration cuture positive before diagnosis – 18 months
    - Duration asymptomatic – 9 months
    - Duration symptomatic – 9 months

Corbett et al IJTLD 2009 Wood et al AJRCCM 2007 Dowdy et al AJRCCM 2013

Heterogeneity in disease outcome

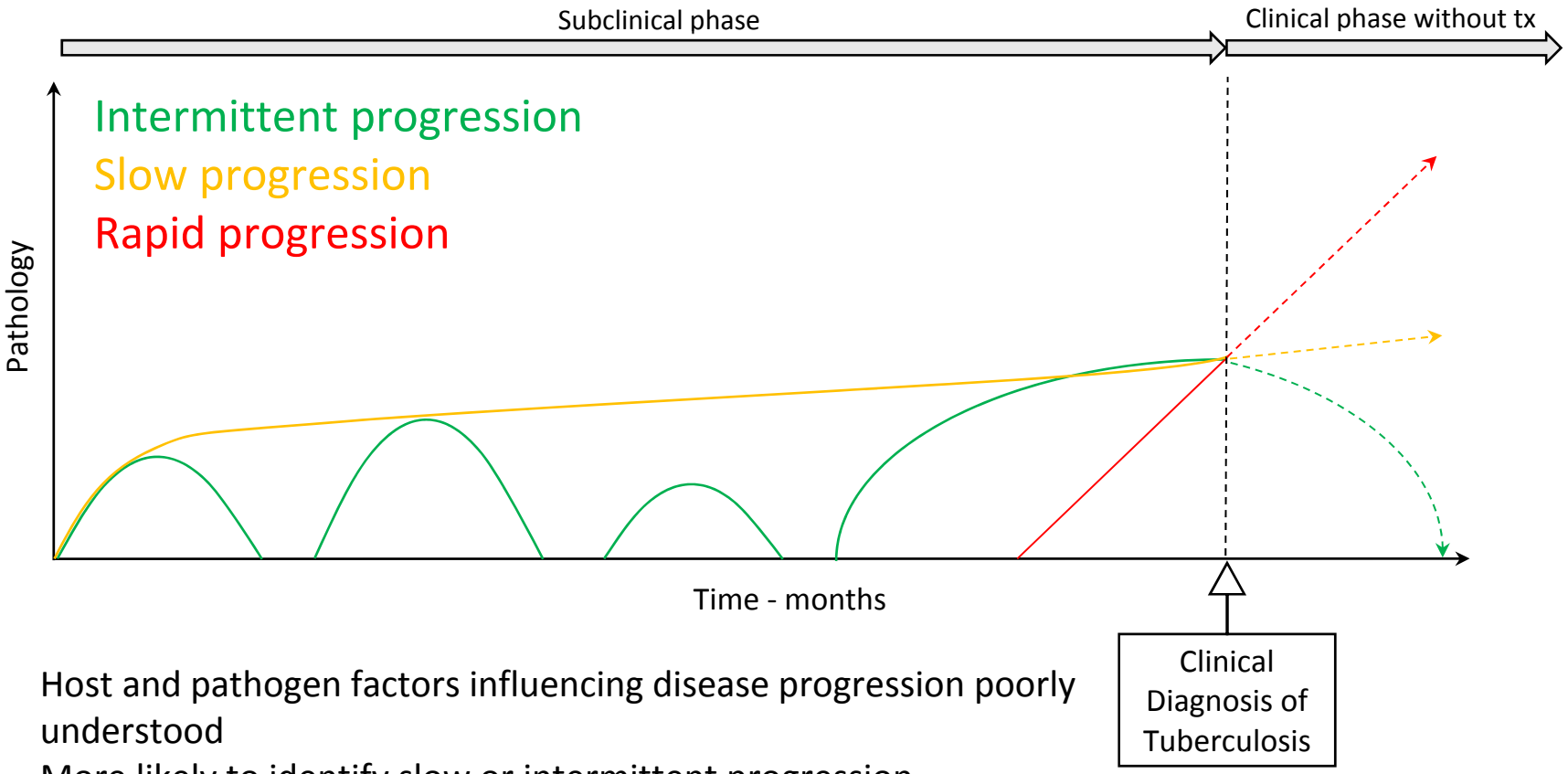
Follow up of 126 people with culture positive TB over 5 years



National Tuberculosis Institute, Bangalore study, 1961 – 1968

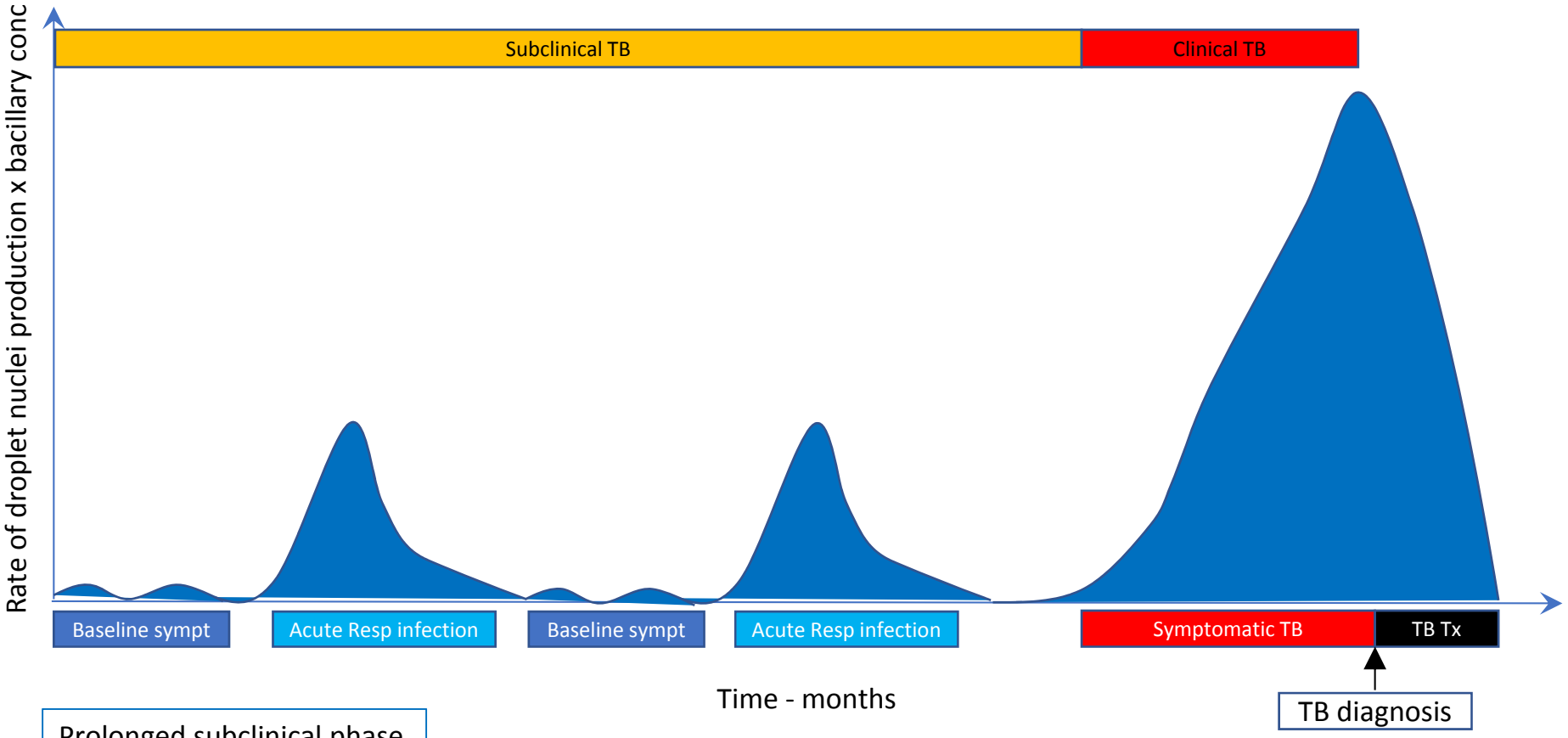
- Community survey (CXR, TST)
- All those with Abnormal CXR screened with 2x sputum culture
- Survey repeated at 18 months, 36 months, 60 months
- No/v. little treatment available

Heterogeneity in subclinical TB progression?



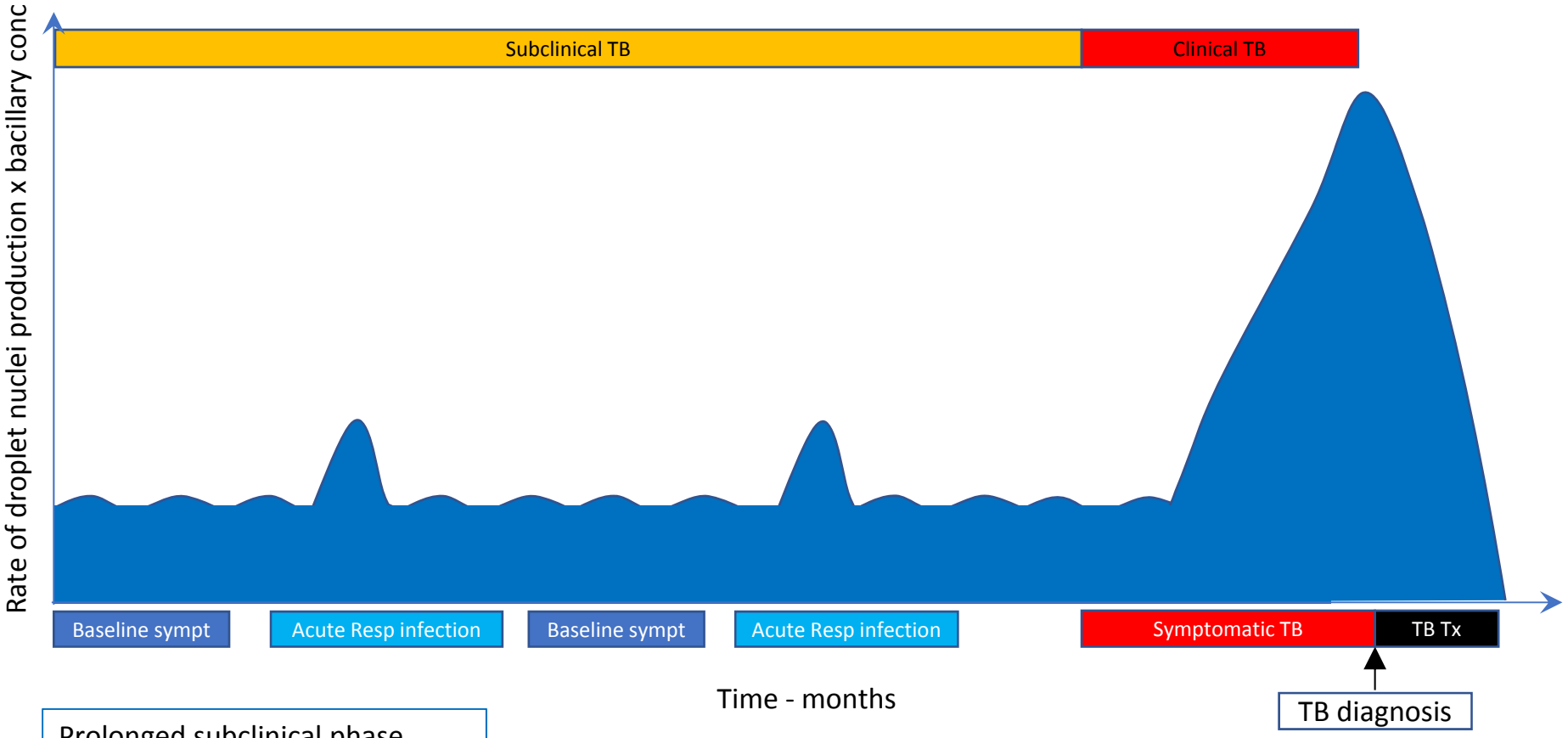
- Host and pathogen factors influencing disease progression poorly understood
- More likely to identify slow or intermittent progression

Transmission potential



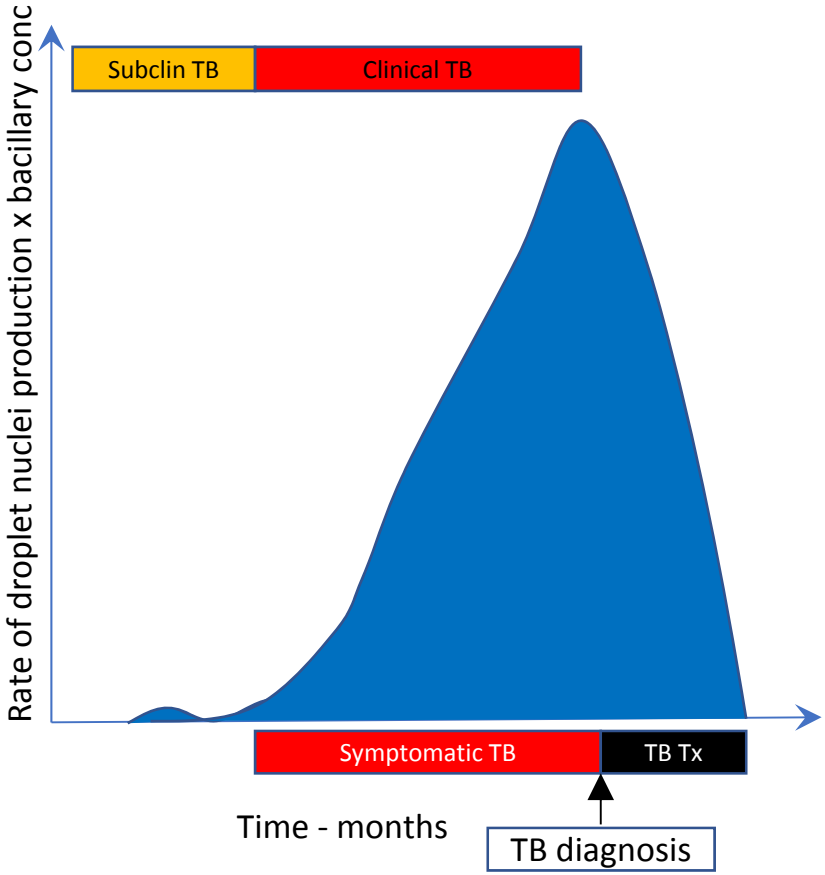
Prolonged subclinical phase
Minimal baseline symptoms

Transmission potential



Prolonged subclinical phase
Chronic cough (unrelated to TB)

Transmission potential



short subclinical phase

Conclusions

- Determining role of subclinical transmission in a population is challenging
- Subclinical transmission will likely be influenced by
  - Duration of subclinical phase
  - Proportion with chronic cough
- Communities/populations with exposure to high-levels of respiratory irritants may may have greater subclinical transmission
- Great understanding needed about heterogeneity of subclinical phase and factors that contribute to progression and self-healing