

Cost-effectiveness and Potential Impact of New TB Vaccines

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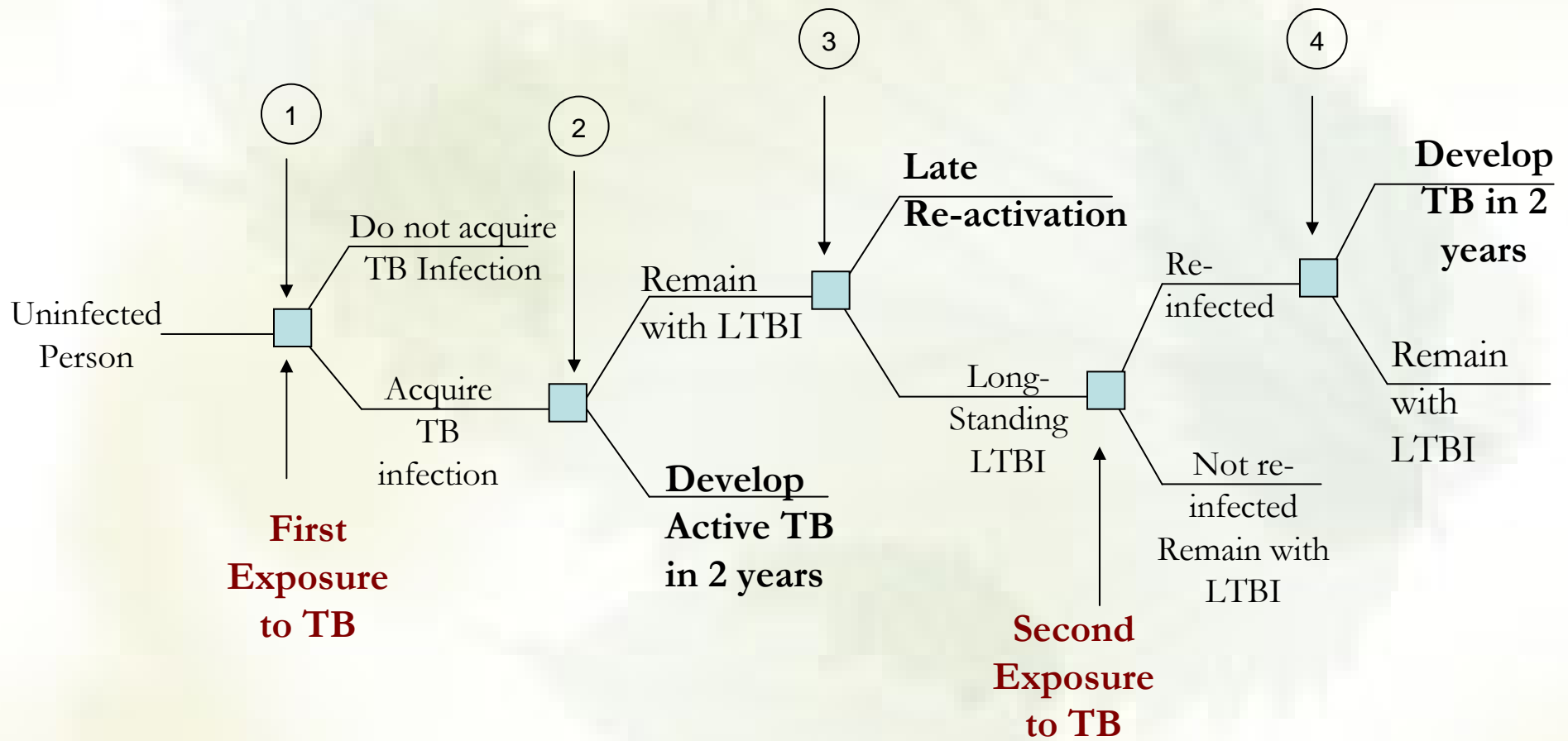
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Outline

- Decision analysis – why? And how?
- How new vaccines could act
- Modeling methods:
 - Countries – India and China
 - Key inputs – costs, epidemiologic parameters
- Main results: Epidemiologic impact, Costs, Savings
- Sensitivity analyses – varying the key parameters
- Conclusions, and future analyses

How & where a new vaccine could act - Conceptual model



How & where a new vaccine could act - Conceptual model

1. Primary prevention – Acts to prevent acquisition of first infection
 2. Prevents early development of disease after first infection
 3. Prevents late re-activation from longstanding latent TB infection
 4. Prevents early development of disease after re-infection
- Natural infection / immunity – Acts by mechanism #2
 - BCG vaccination – reasonable evidence that acts by mechanism #2

Key parameters that will affect modelling of TB vaccine

1. Efficacy (obviously)

- In previously uninfected
 - In preventing early development of disease (within first 2-3 years)
 - In preventing late development of disease (late reactivation)
- In previously infected
 - Preventing early disease – More than natural immunity?
 - Preventing late reactivation – is any effect likely?

Key parameters affecting modelling of TB vaccine

2. Age when given

- If given in infancy
 - Long lag before epidemiologic impact, because no impact on transmission until the infants reach adolescence
 - Hence long lag before any substantial economic benefit”
- If given at all ages (or up to age of 30)
 - Immediate epidemiologic impact (↓ cases, ↓ transmission)
 - Reduced mortality yields immediate economic impact
 - BUT – safety concerns – already HIV, or TB infected

Parameters affecting modelling of TB vaccine

3. Safety in HIV infected

- (Setting aside consideration of efficacy in HIV)
- If vaccine cannot be given safely to HIV infected then
 - Must screen for HIV
 - Adds to cost and complexity
 - Or give only to infants and children (even there some risk)
- We have assumed that new vaccine **COULD** be given safely to HIV infected. Clinical screening only – meaning vaccine would be given to apparently healthy persons without HIV testing.

Parameters affecting modelling of TB vaccine

4. Safety if already infected with latent TB

- If SAFE for already infected (setting aside questions of efficacy) then:
 - Can be given to all ages safely
 - No need for LTBI screening before vaccination
- If UNSAFE for already infected, then:
 - Can be given only in infants and small children
 - Or must screen for LTBI first – adding to cost and complexity

Parameters affecting modelling of TB vaccine

5. Complexity of vaccine (1 dose vs. multi dose)

- Cost issues – Labour costs are greater if multi-doses must be given.
- Compliance – data from India

*Effect of number of doses on success rates
in getting children (12-35 months) fully
immunized in India*

	1 Dose	3 doses	5 doses
Polio	72.6	44.4	
DPT	49.9	29.1	
Non-polio EPI	56.4		18.4

Decision analysis - why?

- Clinical data (trials, observational studies) typically focus on one fully-developed intervention e.g. drug, vaccine, etc.
- In trying to forecast and compare impact of future interventions (or new applications of existing ones), the data are often simply not there
- Particular challenges in examining impacts of combined approaches

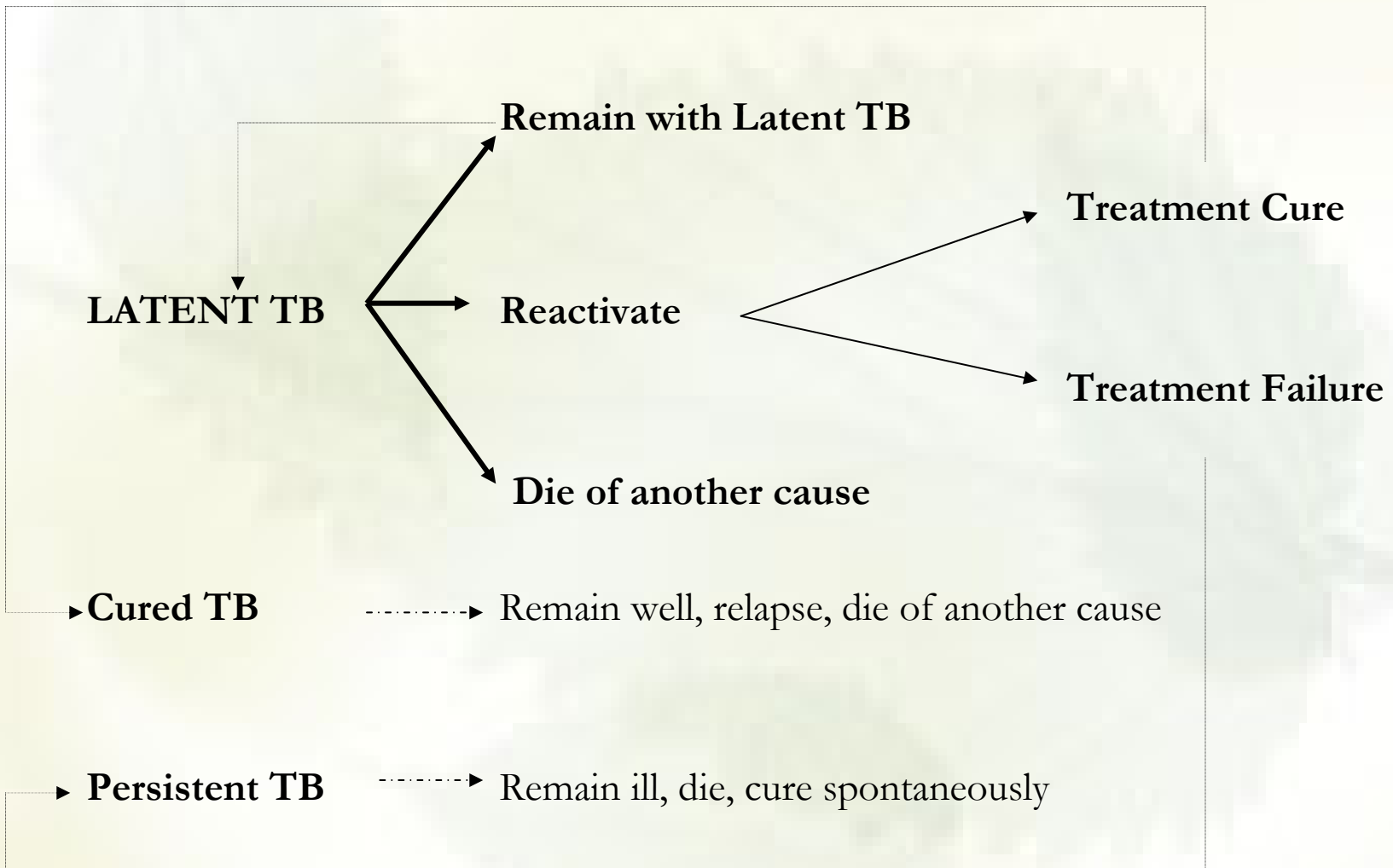
Decision analysis - why?

- Decision analysis techniques allow for prediction as to what would happen if alternate courses of action were chosen
- The process involves building a credible sequence of events after the decision/choice, leading to relevant final outcomes (e.g. TB cases, mortality, costs)
- Equally important is assigning probabilities to each step along the way – taken as much as possible from published data. If “best guesses”, then varied widely in sensitivity analyses

Decision analysis - How?

- Decision analysis model, using multiple Markov processes (“Markov model”)
- A way to capture and use recurrent probabilities of events over time, so as to forecast future events (and associated costs)
- Once built, in principle can run for any number of “cycles” (forecast over any time period)

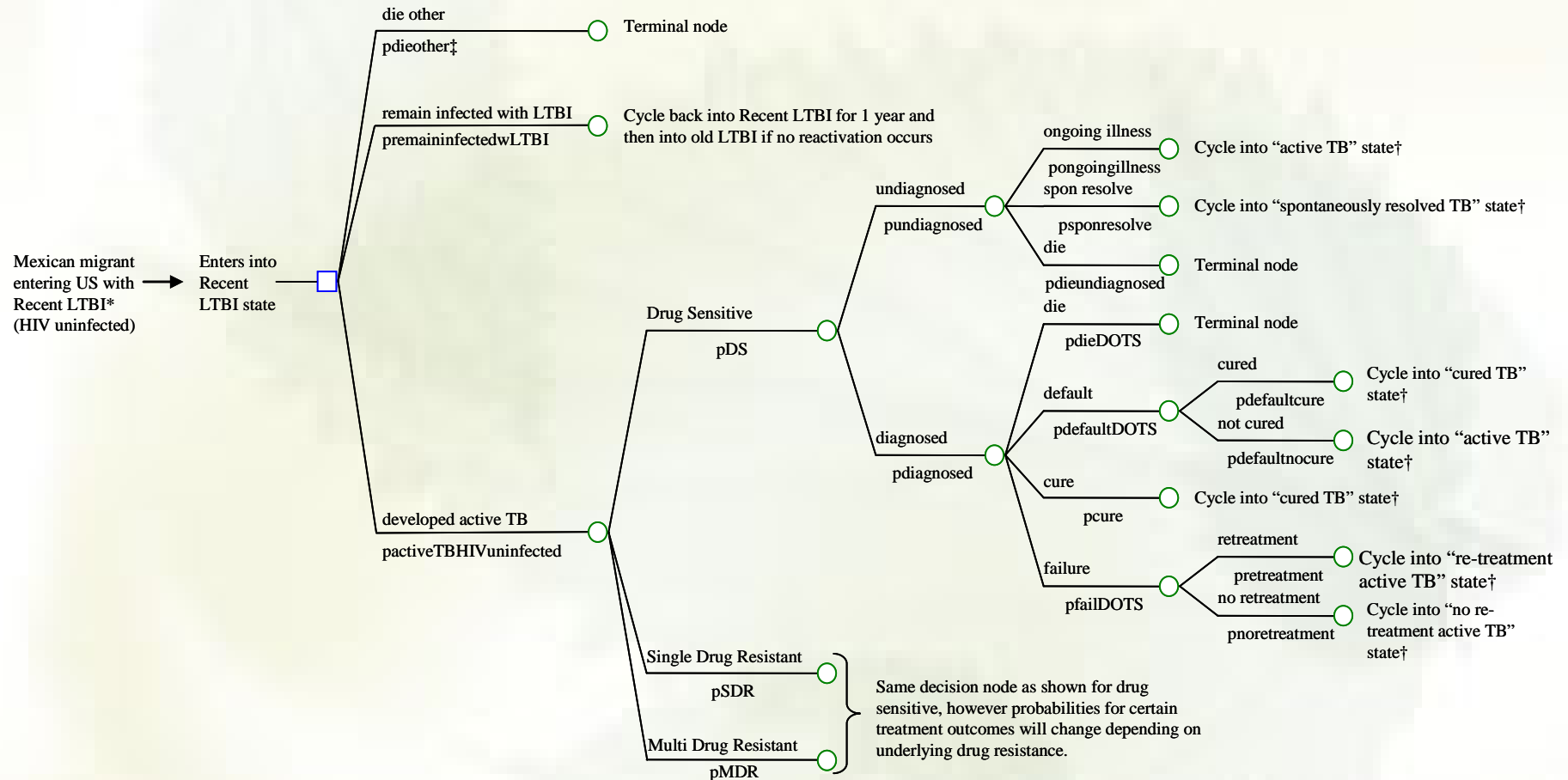
Markov Process



Decision analysis - Markov modeling

- Especially useful for complex processes where probabilities vary over time, in different contexts, or as a function of other parameters
 - Risk of TB infection falls after introduction of a vaccine
 - Risk of TB reactivation varies over time since acquisition of infection
 - Risk of reactivation changes dramatically with HIV infection

Example decision analysis tree for person with recently acquired latent tuberculosis infection



* Probability of having Recent LTBI will fall over time as DOTS expansion occurs in Mexico, and remains unchanged in other strategies

‡ the letter “p” refers to probability. For example p_dieother = probability of dying from other cause.

† states that are entered in subsequent cycles are not shown in figure

Methods: General Approach

- 20 year time frame modeled.
 - 3% discounting after Year 1 (standard)
 - This reduces benefits that occur only after many years
- Analysis conducted from societal perspective
 - Includes health system PLUS patient/family costs
 - Includes costs from disability and mortality
- Analysis considers two high burden countries
 - India – high incidence, and low income
 - China – intermediate incidence and low-middle income

Methods: Outcomes considered

- Only events and costs referable to TB considered
 - Expected TB cases
 - Expected TB-related mortality
 - Costs of development of new vaccines
 - Costs of procurement, training, administration
 - Costs for TB cases – Direct costs of health system
 - Direct costs for patients and families,
 - Indirect costs - Disability, Mortality
- Secondary cases (from transmission) NOT directly modeled (yet)

Parameters of TB vaccine for modelling

1. Efficacy and mode of action will be varied
2. Age of vaccination will be varied
3. Assumed safe in HIV infected
4. Assumed safe in already infected
5. Assumed single dose, with 100% compliance and 100% coverage

Sources of other Data

- Epidemiology from WHO, UNAIDS, World Bank etc.
- Pathogenesis of TB and HIV from review of literature
 - Cohort studies and randomized trials
- Patient and family costs – data from surveys in other low-mid income countries, extrapolated to India/China
 - Interviewer administered questionnaires
- Health system expenditures – data from surveys in other low-mid income countries, extrapolated to India/China
 - Interviewer administered questionnaires at health facilities

Key Assumptions - Disease following TB Infection

Pathogenetic Factor	Base	Range
<u>LTBI more than 2 years (“longstanding LTBI”)*</u>		
HIV uninfected	0.1%/year	0.1-0.2/yr
HIV infected – asymptomatic	3.4%/year	3.4%-8.7%
HIV infected - AIDS	33%/year	33%-67%
<u>Within 2 years of new TB infection (“recent LTBI”)</u>		
HIV uninfected	5%	2%-15%
HIV infected – asymptomatic	33%	33%-100%
HIV infected – AIDS	100%	50%-100%
<u>Within 2 years of a second TB infection (re-infection)</u>		
HIV uninfected – protective effect 80%	1%	
HIV infected – No protective effect	33% or 100%	

Key parameters - HIV un-infected

Outcome	Base	Range
<u>Untreated smear positive tuberculosis</u>		
Mortality – 1 year,	33%,	
Spontaneous remission	25%	
Relapse after spontaneous remission/year	2.5%	1.3%-2.5%
<u>Treated smear positive tuberculosis:</u>		
Relapse after cure (total over 2 years)	3.0%	1.5%-5%
Cure rate if default (SDR or drug sensitive)**	62.4%	
<u>Drug resistance & treatment outcomes</u>		
Relative risk of failure/ if single drug resistant	2.0	
Relative risk of failure/ if multi-drug resistant	10.5	
If MDR – Probability of cure with treatment	48%	48%-73%
– Probability of death with treatment	12%	12%-26%

Key parameters - HIV infected

Outcome	Base	Range
Average survival with HIV infection	9.8 years	7.3-9.8 years
Time spent in HIV asymptomatic state	9.0 years	
Progression of asymptomatic HIV to AIDS/year	7%	7%-9%
Annual risk of death when asymptomatic	4.6%	
Annual risk of death when develop AIDS	22%	
Effect of prior TB on relative risk of death from HIV	2.2	2.2-4.0
Effect of HIV infection on relative risk of death during TB treatment (drug sensitive or single drug resistance)	2.25	
Relapse after Cured	3.1%	3.1%-6.4%

Epidemiologic parameters in 2004

	India	China
Total Population	1.1 Billion	1.3 Billion
-Median age*	25 years	33 years
Gross national income	\$620	\$1,290
Incidence Smear + TB	75 / 100,000	46 / 100,000
-ARI (Styblo)	1.5% / year	0.9% / year
-Case detection rate	60%	65%
-MDR in new cases	2.4%	5.3%
DOTS coverage	84%	96%
HIV sero prevalence		
-General population	0.9%	0.1%
-TB cases	5.2%	0.9%

* Age of cohort assumed to be 15 years

TB control parameters (both countries)

- DOTS coverage 100%
 - Treatment outcomes - New cases
 - Cure/complete..... 85%
 - Die..... 5%
 - Fail..... 3%
 - Default / Transfer..... 7%
- Outcomes if untreated (smear positive)
 - Die..... 33% / year
 - Spontaneous cure.....25% in first year
 - Relapse after spontaneous cure.....2.5% / year

Costs

- Development of new vaccine = \$1,000,000,000
 - Includes research and development, clinical trials
 - Development manufacturing capacity
 - Training and distribution network
- Cost per vaccine dose – Manufacturers cost: \$5 (vary \$1 to \$5)

	India	China
Vaccine Administration	\$2	\$4
TB case – diagnosis and treatment - Direct costs	\$424	\$789

Base case analysis

- Efficacy – 80%
- Vary countries – China & India
- Vary age given
 - Infancy – lag of 15 years until impact
 - Adolescence – immediate impact
- Vary action:
 - Prevents early disease
 - Prevents early disease, and late reactivation

Expected TB cases over 20 years (Millions)

Strategy	India	China
DOTS (100% coverage)	17.0	11.5
Vaccine given to newborns		
Prevents early TB disease	15.6	10.2
Prevents early and late TB	14.5	9.3
Vaccine given at all ages		
Prevents Early TB disease	10.2	5.6
Prevents early and late TB	4.0	4.6

Reduction in cases with New TB vaccine over 20 years (Millions)

Vaccine strategy	India	China	Total
Predicted cases (with DOTS)	17.0	11.5	29
Vaccine given to newborns			
Prevents early TB disease	1.4	1.3	2.7
Prevents early and late TB	1.1	0.8	1.9
-Total	2.5	2.1	4.6
Vaccine given at all ages			
Prevents early TB disease	6.8	5.9	12.7
Prevents early and late TB	1.2	1.0	2.2
-Total	8.0	6.9	14.9

Expected TB related costs over 20 years

	India	China
Vaccine strategy	Total costs	Total costs
Mechanism of effect	(US \$ Billions)	(US \$ Billions)
DOTS (100% coverage)	35.2	46.9
Vaccine given to newborns		
Prevents early TB disease	42.0	51.9
Prevents early and late TB	40.9	50.2
Vaccine given at all ages		
Prevents early TB disease	27.4	30.5
Prevents early and late TB	25.5	27.5

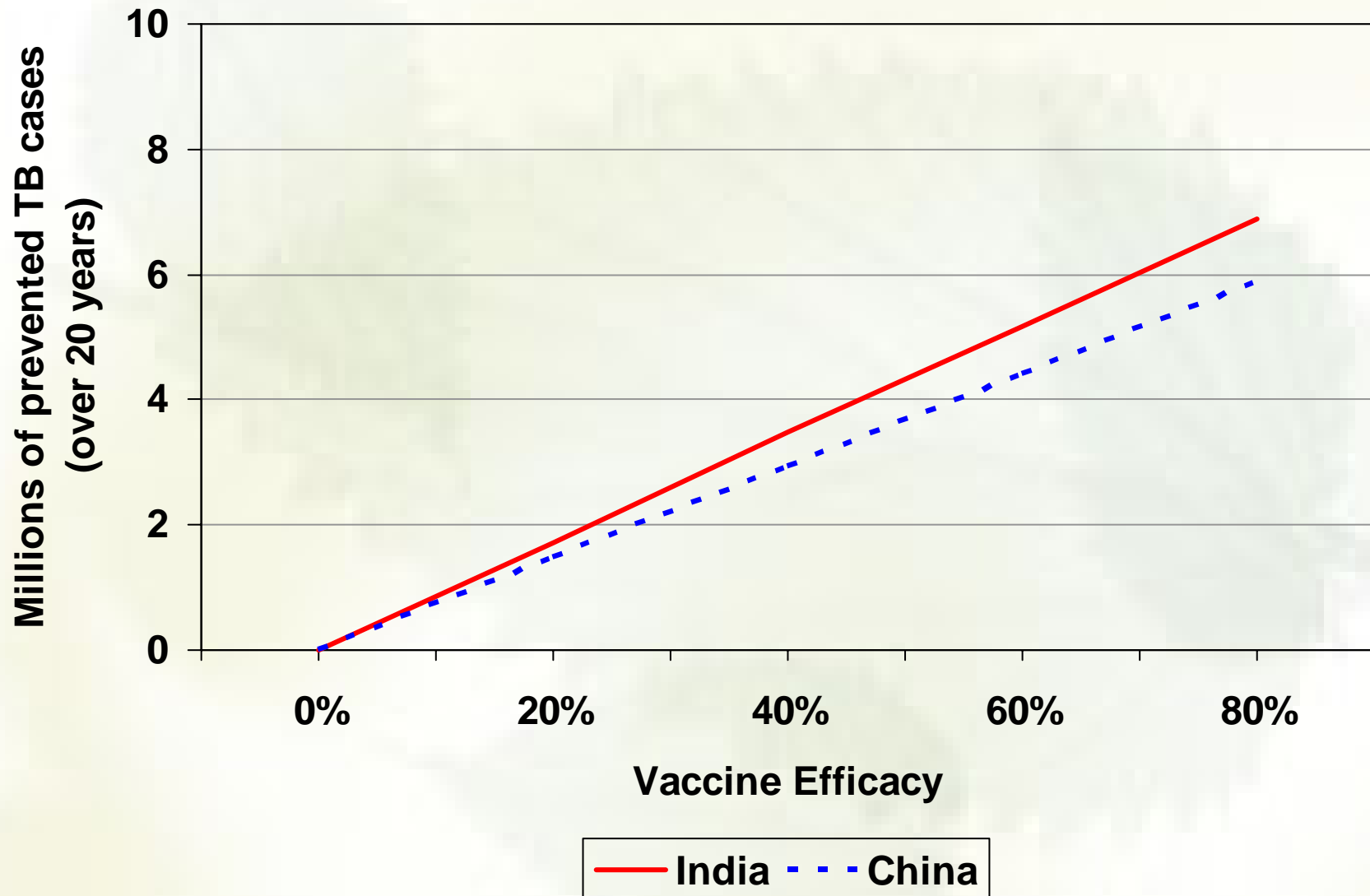
Added Costs or Savings (in parentheses) with New TB vaccine over 20 years (us\$ Billions)

Vaccine Strategy	India	China	Total
Mechanism of effect			
Total predicted costs (with DOTS)	\$35.2	\$46.9	\$82.1
Vaccine given to newborns			
Prevents early TB disease	+6.8	+5.0	+11.8
Prevents early and late TB Difference	(1.1)	(1.7)	(2.8)
TOTAL	+5.7	+3.3	+9.0
Vaccine given at all ages			
Prevents Early TB disease	(7.8)	(16.4)	(24.2)
Prevents early and late TB Difference	(1.9)	(3.0)	(4.9)
TOTAL	(9.7)	(19.4)	(29.1)

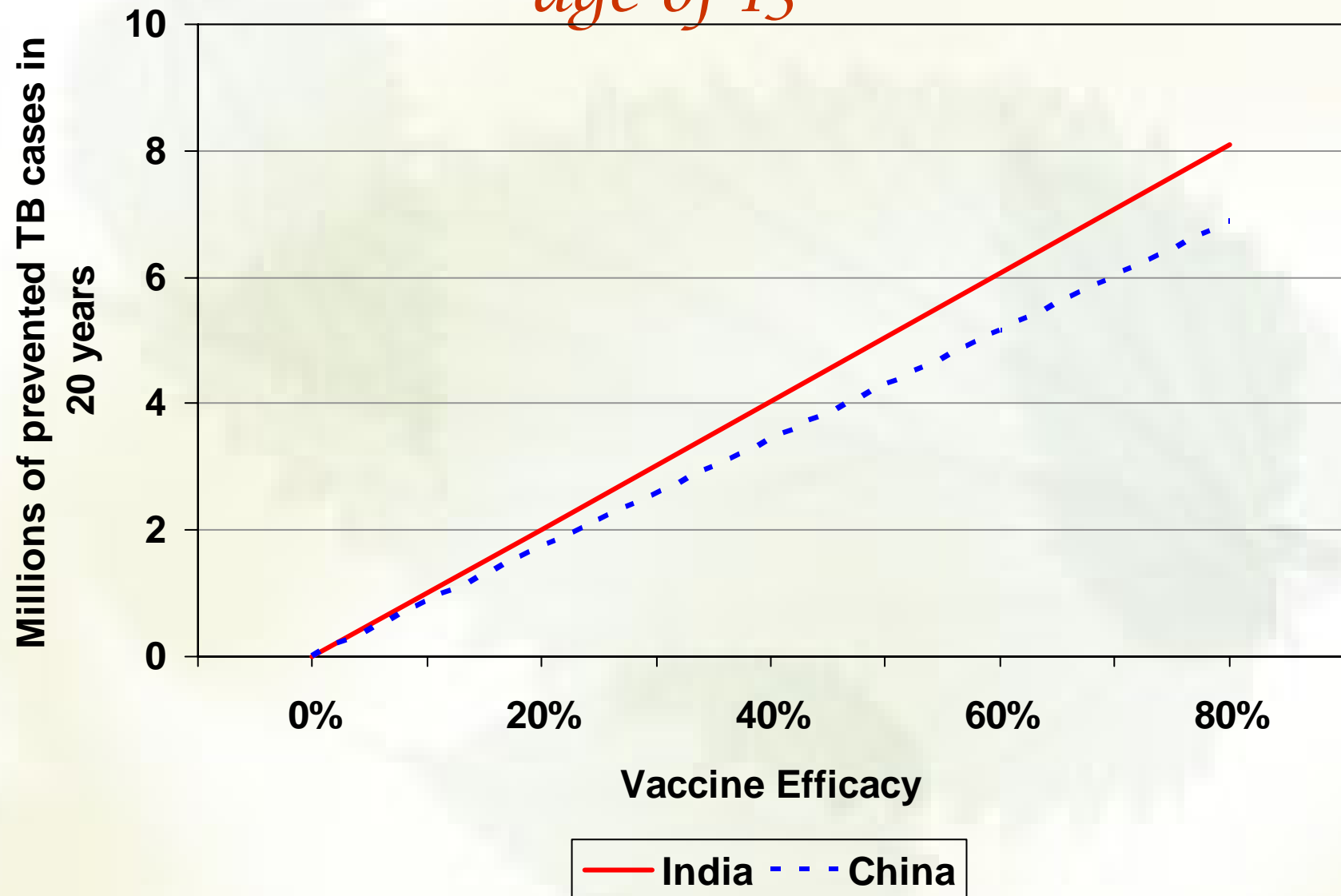
Sensitivity analysis

- Vary efficacy – from 0 to 80%
- Hold constant – age vaccinated
 - Age of 15
- Vary – mode of action
 - Prevents early disease
 - Prevents early & late disease

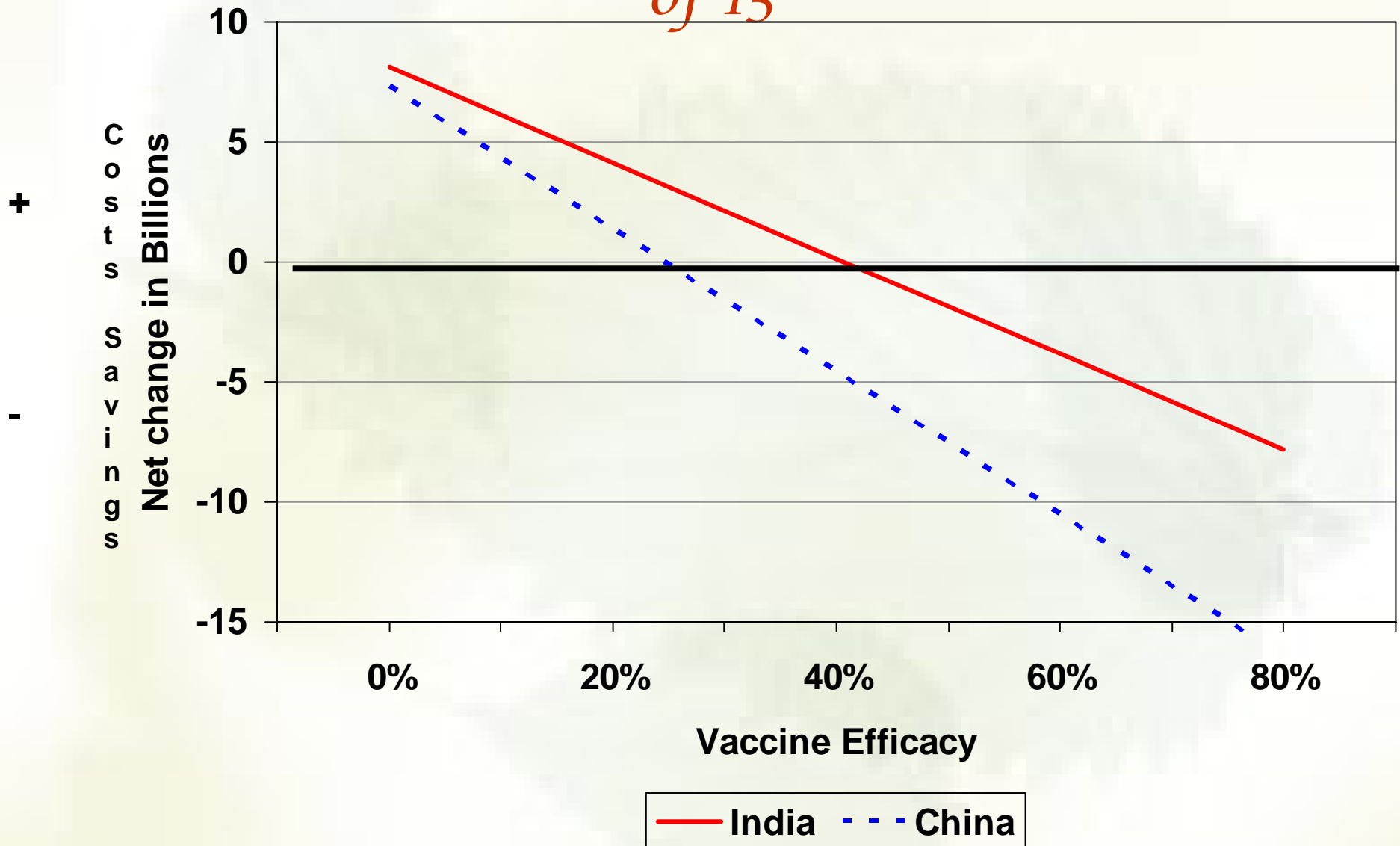
Reduction in TB cases: Vaccine prevents early disease only. Given at age of 15



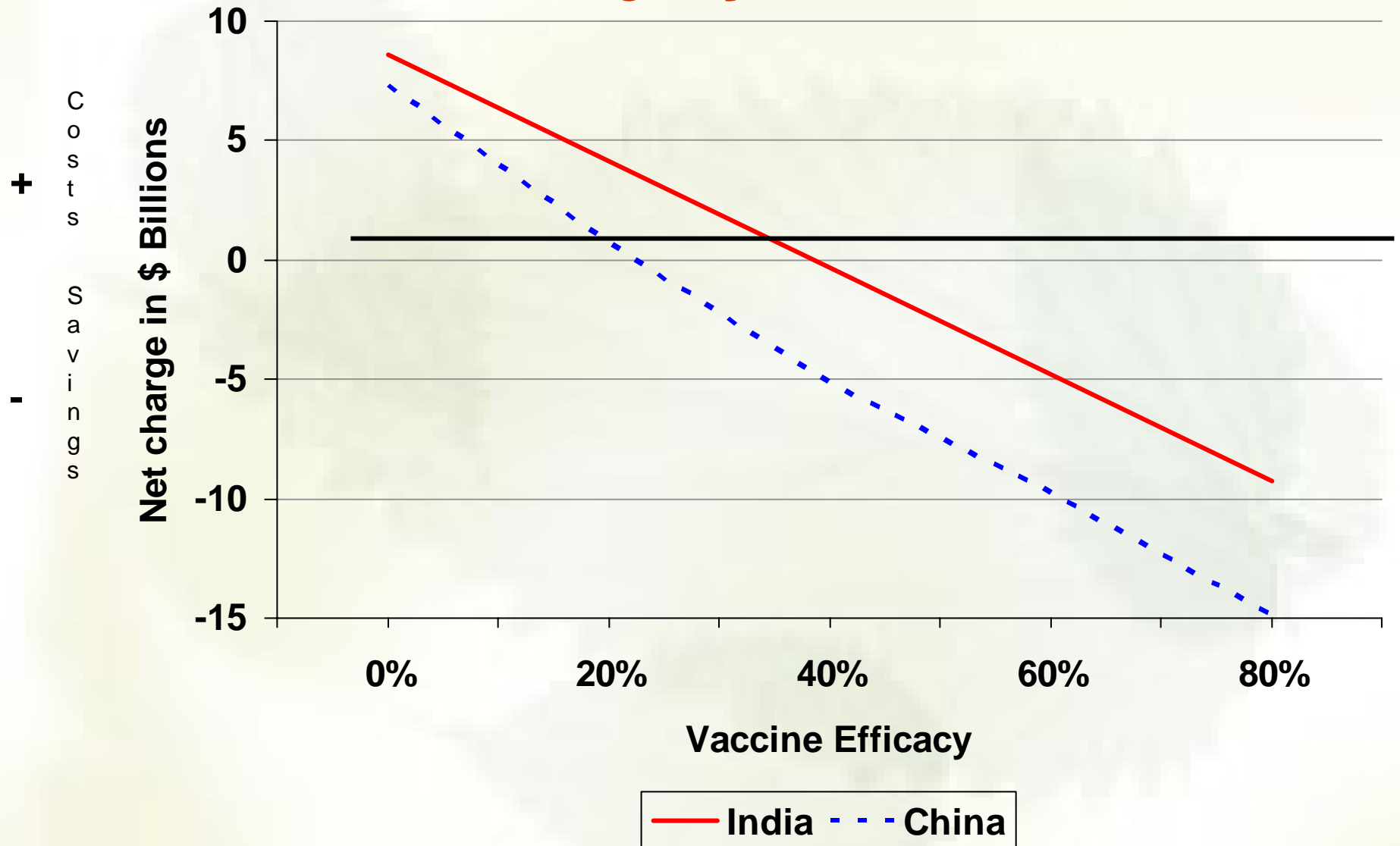
Reduction in TB cases. New vaccine prevents early and late disease. Given at age of 15



Added costs or savings. New vaccine prevents early disease only. Given at age of 15



Added costs or savings. New vaccine prevents early and late disease. Given at age of 15



Sensitivity analysis

- Vary unit cost of vaccine
 - From \$1 to \$9
- Hold constant – age vaccinated
 - Infancy
- Vary – mode of action
 - Prevents early disease
 - Prevents early & late disease

*Varying the unit cost of vaccine
Given in infancy with 80% prevention of early
disease only*

Total Unit Cost	India Net costs/(savings)	Total Unit Cost	China Net costs/(savings)
\$7	+6.8	\$9	+5.0
\$5	+4.6	\$6	+1.1
\$3	+2.4	\$3	(2.8)
\$1	+0.2	\$1	(5.4)

*Varying the unit cost of Vaccine
Given in infancy with 80% prevention of early
and late disease*

Total Unit cost	India Net costs/(savings)	Total Unit cost	China Net costs/(savings)
\$7	+5.7	\$9	+3.3
\$5	+3.5	\$6	(0.6)
\$3	+1.3	\$3	(4.5)
\$1	(0.7)	\$1	(7.1)

Summary and Conclusions:

- A new vaccine could be cost saving if:
 - If given to adolescents or young adults
 - If prevents early disease, with
 - Efficacy of at least 30% (China), or 40% (India)
- Cost savings greater if:
 - Efficacy greater
 - Prevents early and late disease
 - Unit cost lower
 - Used in more countries

Summary and Conclusions (cont):

- Cost savings will be less if:
 - Can be given only in infancy
 - LONG lag before any epidemiologic impact.
 - Thus ‘payback’ delayed by more than 12-14 years
 - Unit costs higher – especially if given in infancy
- This analysis suggests that the greatest benefit will be from a vaccine that
 - Is safe in HIV infected
 - Is safe in already TB infected
 - Has (some) efficacy against “adult” pulmonary TB
 - So, can be given safely to adolescents and young adults

THANK - YOU

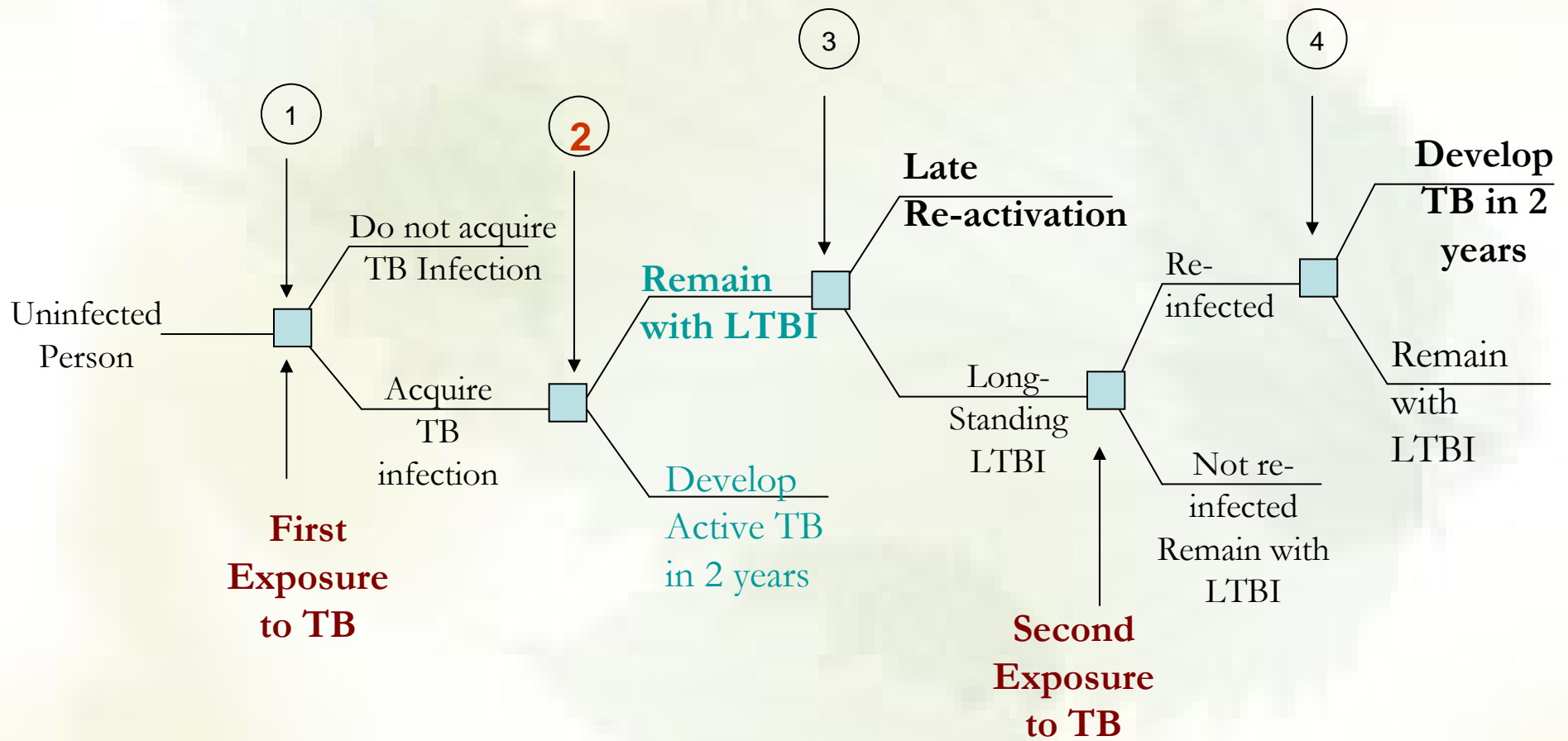
Acknowledgements

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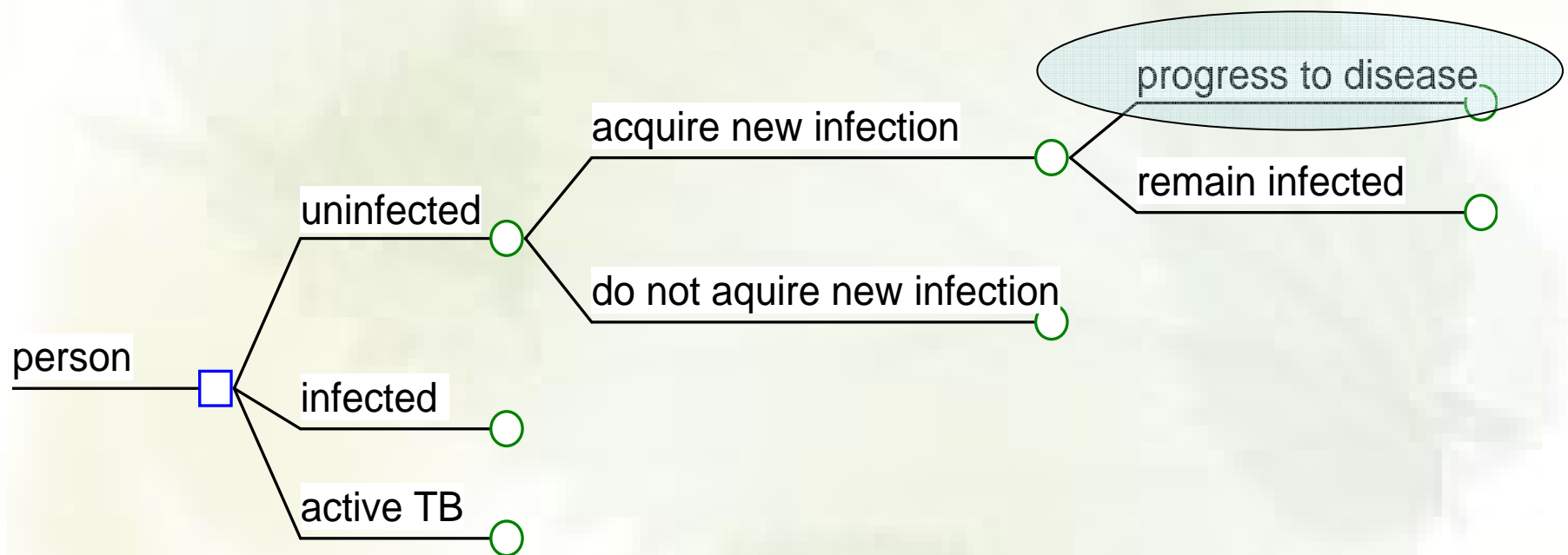
Sensitivity Analyses

- Allows examination of impact of any modeling parameter (singly or in combination) on predicted outcomes, and hence on ultimate decisions.
- Will address every parameter/assumption.
- Wide variation of key parameters:
 - Vaccine efficacy
 - Age when vaccinated
 - Mechanism of action
 - Costs – Initial development, and unit cost

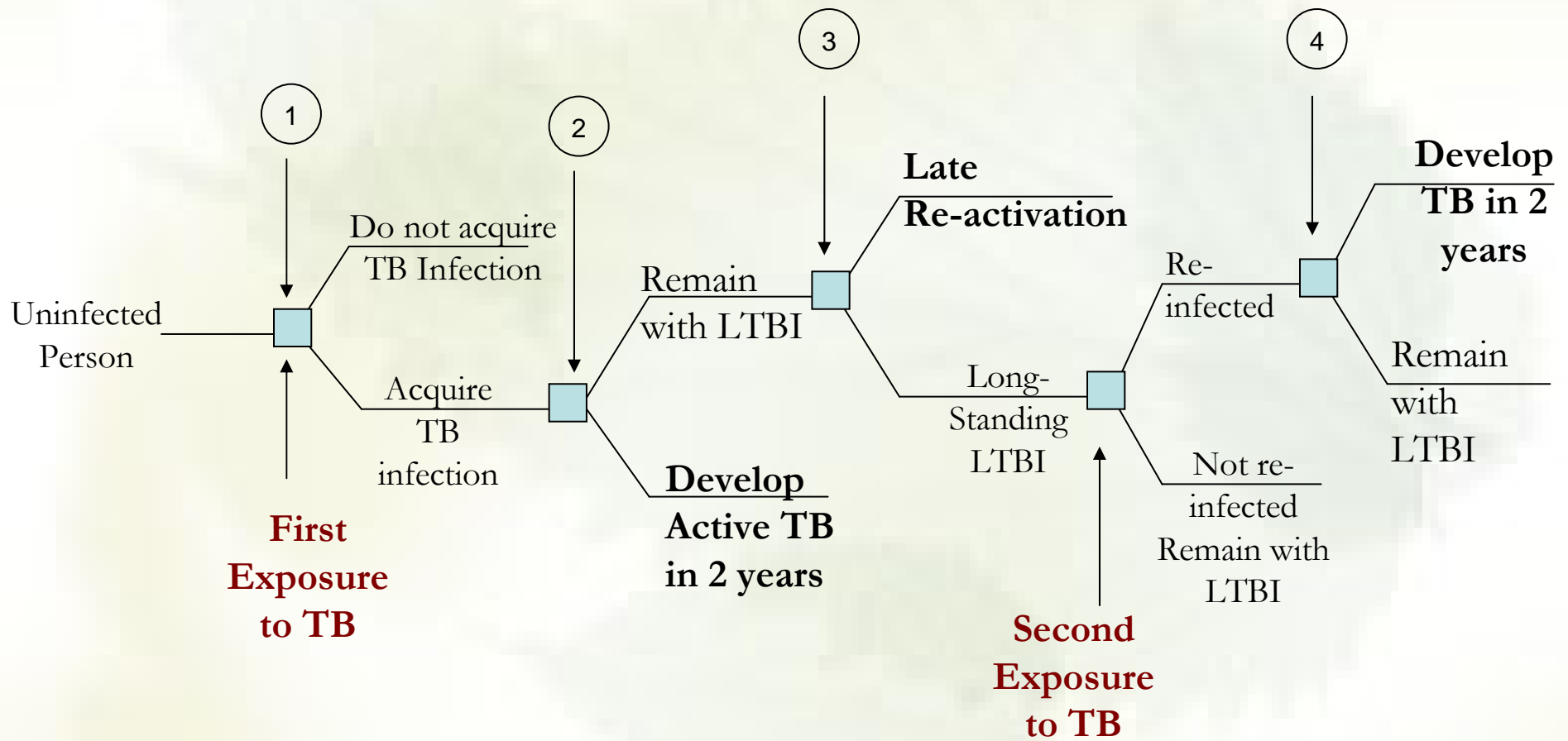
Modeling the new vaccine - reduces early disease after First infection (Step 2)



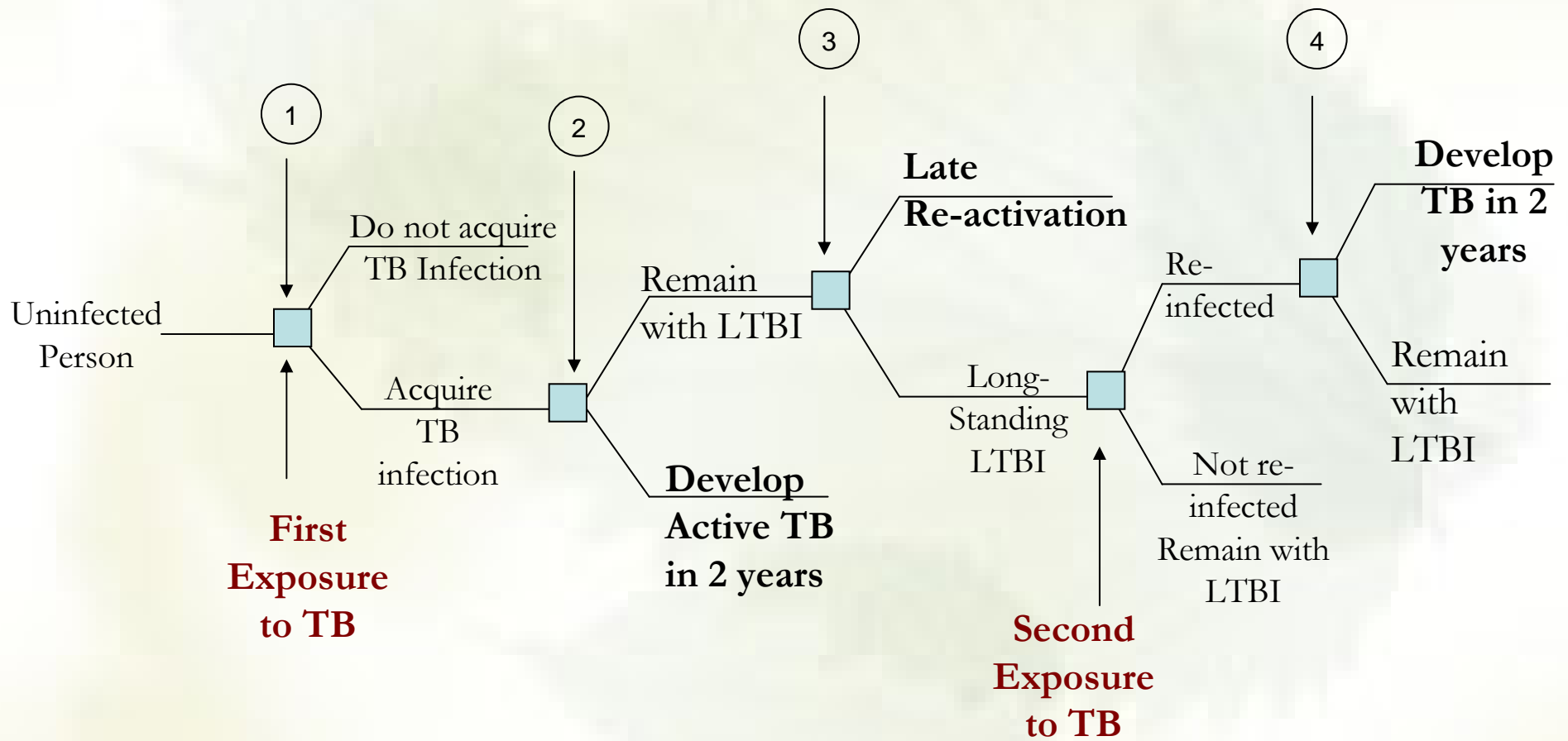
Impact of a new vaccine on progression to disease with new LTBI infection



Modeling the new vaccine - reduces risk of late reactivation (Step 3)



Modeling the new vaccine - reduces risk of early disease following first TB infection and reactivation of old TB infection (Steps 2 & 3)



Modeling the new vaccine - reduces risk of early diseases following RE-infection (Step 4)

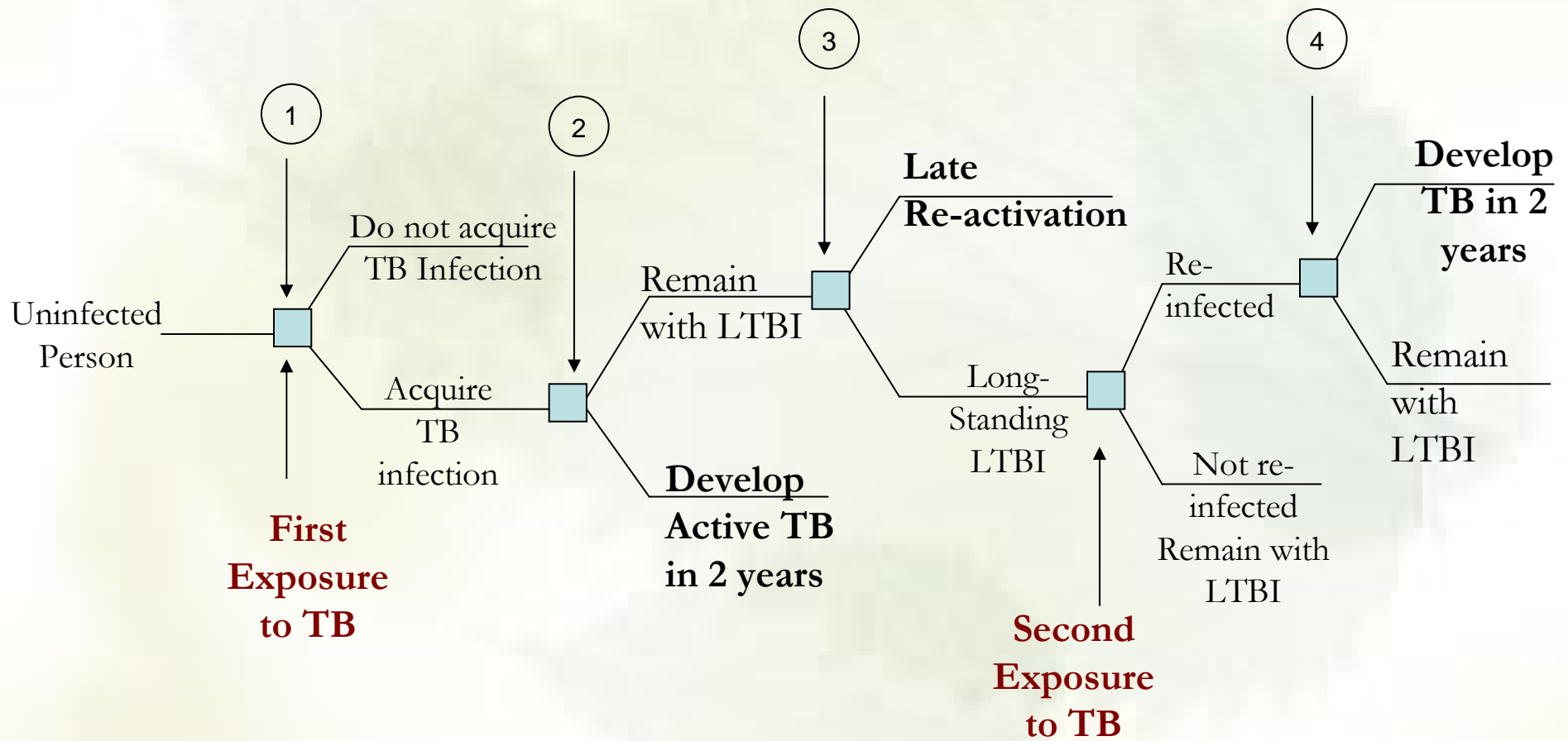


TABLE 4
COMPONENT COSTS

Item	Components	Cost
Initial evaluation	1 physician consultation, including clinic fee	\$85.75
	Baseline chemistry, blood count	\$30.00
	Total	\$115.75
Workup	0.38 special X-ray views per patient	\$28.08/view
	3 pooled sputa for mycobacteriology per patient	\$81.00
	0.035 bronchoscopies per patient	\$333/scope
	1 follow-up visit per patient, including clinic fee	\$50.50
	Total	\$153.83

Background

- Natural immunity – provides substantial protection from disease following re-infection
 - 80% protective efficacy in pre anti-biotic era
- BCG vaccine – introduced in 1923
 - Attenuated *M. Bovis* over seven years of serial cultures
 - Further attenuated over next 30 – 40 years of serial cultures
 - Efficacy – wide range from none to maximum 80%
 - More consistent evidence for BCG given in infancy
- New vaccines – None of proven efficacy,
 - Very active area of research