Parameter Estimation: A Glimpse of Backing Out, Sensitivity Analysis & Meta-Analysis

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CMPT 858

Sources for Parameter Estimates

- Surveillance data
- Controlled trials
- Outbreak data
- Clinical reports data
- Intervention outcomes studies
- Calibration to historic data
- Expert judgement
- Systematic reviews

Introduction of Parameter Estimates

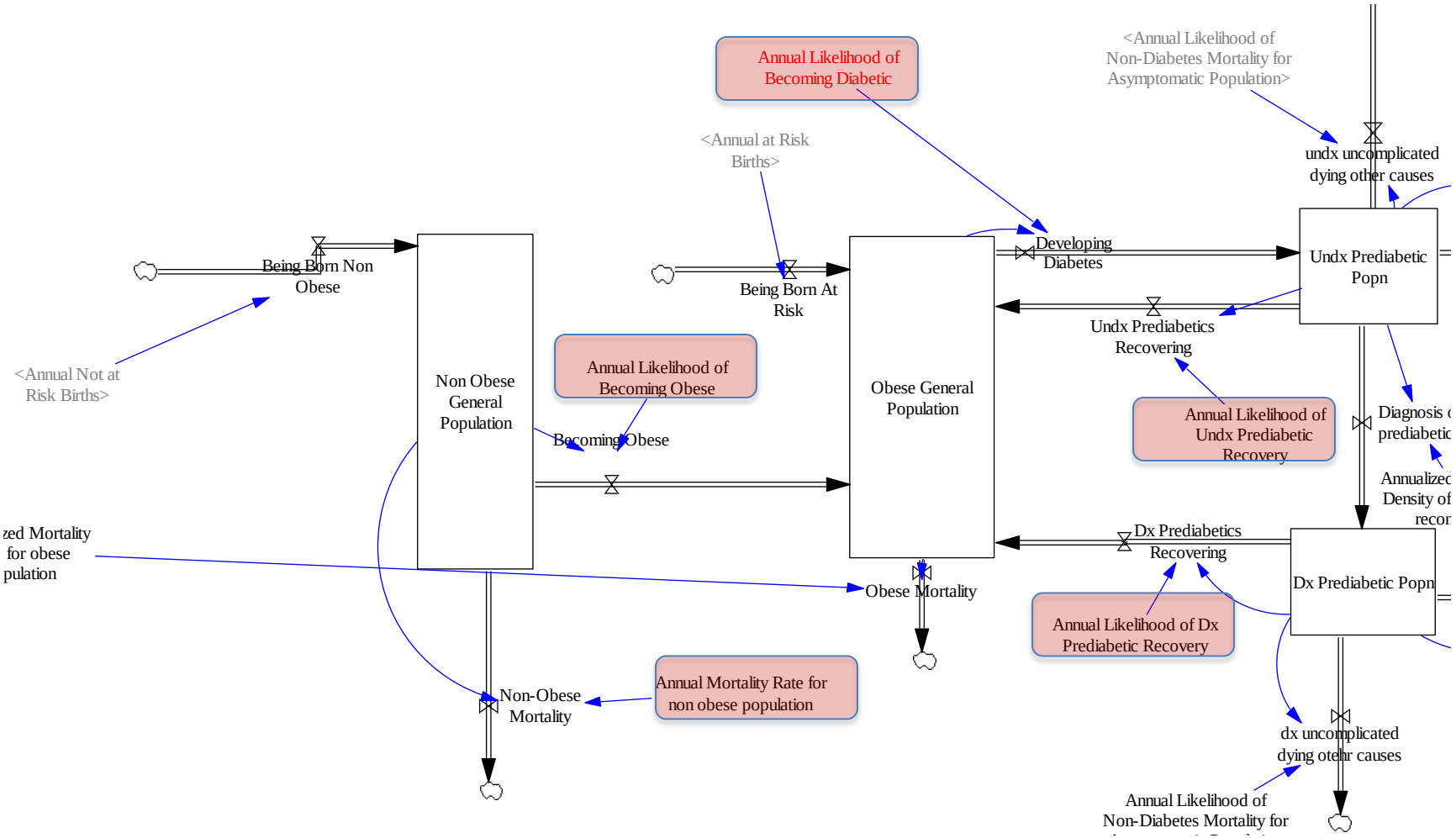

Table II.2.1 Smoking and mortality from tuberculosis
(Notes: Unless otherwise stated, numbers in parentheses are 95% confidence intervals; OR=odds ratio and RR=relative risk.)

Reference	Population	Methodology	Results
(Gajalakshmi et al., 2003)	Urban and rural populations in Tamil Nadu, India	Large case-control study looking at impact of smoking (cigarette and bidis) on mortality due to medical causes in men age 25-69; ever (current and former) smokers are compared to never smokers	RR for ever smokers compared to never-smokers of death from TB, standardized for age, education level and tobacco chewing: Urban / Rural Cigarette 4.5 (4.0-5.0) / 2.1 (1.6-2.9) Bidi 3.7 (2.9-4.6) / 4.2 (3.7-4.8)
(Gupta et al., 2005)	Mumbai, India	Large cohort study (initial cohort includes 99,570, 97.7% follow-up 5.5 years later) investigating tobacco-attributable mortality among men and women age 35 and over; ever (current and former) tobacco users are compared to never users	RR for ever- compared to never tobacco users (smokeless and smoked) by gender, unadjusted: Men / Women Smokeless (>=35) 1.5 (1.1-2.0) / 1.4 (1.0- 2.0) Smoked (>=35) 2.3 (1.7-3.2) / 5.9 (2.3-15.2) Smokeless (35-69) 1.6 (1.1-2.2) Smoked (35-69) 2.5 (1.8-3.5)
(Lam et al., 2001)	Hong Kong	Large case-control study looking at the impact of cigarette smoking (proxy or self-reported current or former versus never-smoking status 10 years prior to death) on mortality due to medical causes in men over age 35	RR for smokers compared to non-smokers of death from TB, controlling for age and education: 35-69 2.5 (1.2-5.2) over 70 1.6 (1.0-2.6) Dose response: RR for smokers compared to non-smokers, controlling for age and education: Avg # cigs/day: 1-14 / 15-24 / 25+ / Test for trend 35-69: 1.0 / 2.9 / 6.6 / p<0.001 over 70: 1.3 / 1.4 / 3.3 / p<0.01
(Liu et al., 1998)	Urban and rural populations in China	Large case-control study looking at impact of smoking (defined as current or former smoking 6-8 years prior to death) on mortality due to neoplastic, respiratory, or vascular causes in men and women 35-69	RR (standard error) for smokers compared to non-smokers of death from TB, adjusting for age at death and study area: Urban men 1.4 (0.05) Rural men 1.2 (0.04) Urban women 1.6 (0.09) Rural women 1.3 (0.09) Dose response: RR (standard error) for smokers compared to non-smokers, adjusting for age at death and study area: Avg # cigs/day: 1-19 / 20 / >20 Urban men 1.2 (0.06) / 1.5 (0.07) / 2.0 (0.14) Rural men 1.0 (0.06) / 1.2 (0.07) / 1.6 (0.14) Age initiate: <20 / 20-24 / >24 Urban men 1.9 (0.08) / 1.4 (0.06) / 1.2 (0.06) Rural men 1.3 (0.06) / 1.2 (0.05) / 1.1 (0.06)
(Sitas et al., 2004)	All of South Africa	Case-control study investigating impact of smoking (defined as reported smoking five years prior to death) on mortality due to medical causes known to be associated with smoking in men and women over age 25	OR for smokers compared to nonsmokers of death from TB, controlling for age, sex, education, ethnicity, and disease: Men 1.7 Women 1.5 Overall 1.6 (1.2-2.1)

Hassmiller, K. M. (2006). *The Impact of Smoking on Population-Level Tuberculosis Outcomes.* Unpublished PhD, University of Michigan, Ann Arbor, Ann Arbor.

Preparation for Pooling

TB Disease: Active exposure

study	RR	95% CI CI-l	CI-u	subgroup	%	TB Outcome	expnot	expnothi	evnev	evnevhi	currnot	currnoth	currnevhi	exnevhi	n
Adelstein	4.55	2.40	8.64	curr		PTB	0	0	0	0	0	0	1	0	73287
Adelstein	2.34	0.95	5.76	ex		PTB	0	0	0	0	0	0	0	1	73287
Adelstein	4.13	2.18	7.82	evNev		PTB	1	1	1	1	0	0	0	0	73287
Adelstein	3.40	2.06	5.63	currNot		PTB	0	0	0	0	1	1	0	0	73287
Alcaide	3.60	1.50	2.20	evNev		PTB	1	1	1	1	0	0	0	0	92
Ariyothai	2.70	1.04	6.97	current	78%	PTB	1	1	1	1	0	0	1	0	128
Ariyothai	2.88	0.85	9.78	ex	22%	PTB	0	0	0	0	0	0	0	1	128
Buskin	1.30	0.80	2.10	current	69%	AllTB	0	0	0	0	0	0	0	0	696
Buskin	1.40	0.80	2.50	ex	31%	AllTB	0	0	0	0	0	0	0	0	696
Crampin	0.90	0.50	1.70	cig/dayLight	37%	PTB	0	0	0	0	0	0	0	0	606
Crampin	1.30	0.70	2.40	cig/dayHeavy	37%	PTB	1	1	1	1	0	0	1	0	606
Crampin	1.60	0.70	3.20	ex	25%	PTB	0	0	0	0	0	0	0	1	606
Gajalakshmi	2.90	2.60	3.30	currNot		SRTB	0	0	0	0	0	0	0	0	235101
Kolappan	2.24	1.27	3.94	unclear		PTB	1	1	0	0	0	0	0	0	544
Leung2004	2.87	2.00	4.11	current	31%	PTB	1	1	1	1	0	0	1	0	42659
Leung2004	1.39	0.98	1.97	ex	69%	PTB	0	0	0	0	0	0	0	1	42659
Leung2003	2.13	1.46	3.11	youngEver		PTB	1	0	1	0	0	0	0	0	8686
Leung2003	1.90	1.35	2.66	OlderEver		PTB	0	0	0	0	0	0	0	0	8686
Lienhardt	2.03	1.22	3.39	current	79%	PTB	1	0	1	0	0	0	0	0	1376
Lienhardt	1.53	1.11	2.10	ex	21%	PTB	0	0	0	0	0	0	0	0	1376
Perez-Padilla	1.50	1.00	2.30	evNev		PTB	1	0	1	0	0	0	0	0	833
Shah	1.59	0.44	5.37	unclear		PTB	1	0	0	0	0	0	0	0	75
Tekkel	4.62	2.44	8.73	current	80%	PTB	1	0	1	0	0	0	0	0	492
Tekkel	2.27	1.00	5.14	ex	20%	PTB	0	0	0	0	0	0	0	0	492
Tocque	2.33	1.40	3.88	currNot		PTB	1	1	0	0	1	1	0	0	310
Toledo	1.30	1.00	1.60	evNev		PTB	1	0	1	0	0	0	0	0	477
Yu	2.17	1.29	3.63	currNot		PTB	1	1	0	0	1	1	0	0	30289

Abbreviations: expnot exposed versus not exposed; expnothi exposed versus not exposed, high quality studies; evnev ever versus never smokers; evnevhi ever versus never smokers, high quality studies; currnot current versus not current smokers; currnothi current versus not current smokers, high quality studies; currnev current versus never smokers; exnev ex versus never smokers; currnevhi current versus never smokers, high quality studies; exnevhi ex versus never smokers, high quality studies; PTB pulmonary TB; AllTB all types of TB (pulmonary and extrapulmonary); SRTB self-reported TB disease (any type)

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TB Mortality

study	RR	95% CI CI-l	CI-u	subgroup	TB Outcome	expnot	expnothi	evnev	evnevhi	currnot	n
Gajalakshmi	4.50	4.00	5.00	urbanPop	Mortality	1	0	1	0	0	33,220
Gajalakshmi	4.20	3.70	4.80	ruralPop	Mortality	1	0	1	0	0	33,220
Lam	2.54	1.24	5.22		Mortality	1	1	1	1	0	13,251
Liu	1.42	1.33	1.52	urbanMalePop	Mortality	1	1	1	1	0	18,331
Liu	1.17	1.09	1.25	ruralMalePop	Mortality	1	1	1	1	0	18,331
Sitas	1.61	1.23	2.11		Mortality	1	0	0	0	1	2,366

Abbreviations: expnot exposed versus not exposed; expnothi exposed versus not exposed, high quality studies; evnev ever versus never-smokers; evnevhi ever versus never-smokers, high quality studies; currnot current versus not current smokers

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Example of Other Pooling

Treatment Default

	Quality Score	Exposure	RR	95% CI CI-l	CI-u	n
Al-Hajjaj	NR	U	1.85	1.33	2.58	154
Balbay	NR	CNot	3.99	1.90	8.35	628
Chang	70.59	EN	2.90	1.73	4.85	408
Davidson	NR	CNot	1.34	0.87	2.07	354
Salami	63.16	U	1.61	1.31	1.98	1530
Santha	NR	U	2.10	1.30	3.40	581

Abbreviations: NR not rated; U unclear; Cnot current versus not current smoker; EN ever versus never smoker

Smear Conversion

	Quality Score	Exposure	RR	95% CI CI-l	CI-u	n
Abal	63.64	EN	0.47	0.21	1.06	339
Durban	66.67	U	0.58	0.40	0.84	347
Leung2003	61.11	EN	0.89	0.21	3.77	404

Abbreviations: EN ever versus never smoker; U unclear

Severity of TB: Risk of smear-positive (versus smear-negative)

	Quality Score	Exposure	RR	95% CI CI-l	CI-u	n
Altet-Gomez	70.59	CNot	1.40	1.30	1.60	13038
Leung2003	61.11	EN	1.30	1.00	1.80	851

Abbreviations: Cnot current versus not current smoker; EN ever versus never smoker

Severity of TB: Risk of pulmonary (versus extra-pulmonary only)

	Quality Score	Exposure	RR	95% CI CI-l	CI-u	n	n
Altet-Gomez	70.59	CNot	PTB	1.50	1.30	1.60	13038
Altet-Gomez	**70.59**	**Cnot**	**ETB only**	**0.67**	**0.77**	**0.63**	**13038**
Leung2004	**80.95**	**CEN-curr**	**ETB only**	**0.73**	**0.16**	**3.46**	**286**
Leung2004	80.95	CEN-ex	ETB only	1.77	0.72	4.35	286
Leung2003	**61.11**	**EN**	**ETB only**	**0.31**	**0.13**	**0.71**	**851**
Musellim	NR	EN	ETB only	0.54	0.32	0.93	375

Note: Values **in bold** were used in the metaanalysis

Abbreviations: NR not rated; Cnot current versus not current smoker; CEN-curr current versus never smoker; CEN-ex ex versus never smoker; EN ever versus never smoker

Severity of TB: Risk of cavitary (versus not cavitary)

	Quality Score	Exposure	RR	95% CI CI-l	CI-u	n
Altet-Gomez	70.59	CNot	1.90	1.60	2.30	13038
Leung2003	61.11	EN	1.76	1.18	2.63	851

Abbreviations: Cnot current versus not current smoker; EN ever versus never smoker

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Pooled Results

	Pooled estimate	95% CI Lower	95% CI Upper	Method	Test for hetero-geneity (p-value)	#Populations included	#Individuals included
Pooled estimate for odds ratio of being infected for smokers compared to non-smokers							
All definitions of active exposure included							
Exposed v. non-exposed							
High quality only	1.76	1.46	2.12	Fixed	0.36	4	4,460
Overall	1.76	1.47	2.12	Fixed	0.53	5	4,729
By study-specified definition of exposure							
Ever v. never-smoker							
High quality only	1.66	1.34	2.04	Fixed	0.50	2	3,742
Overall	1.66	1.36	2.04	Fixed	0.77	3	4,011
Current v. not-current							
High quality only	2.24	1.47	3.40	Fixed	0.29	2	718
Overall	2.24	1.47	3.40	Fixed	0.29	2	718
Pooled estimate for odds ratio of developing pulmonary TB disease for smokers compared to non-smokers							
All definitions of active exposure included							
Exposed v. non-exposed							
High quality only	2.64	2.07	3.38	Random	0.04	8	147,915
Overall	2.28	1.77	2.95	Random	<0.001	14	159,854
By study-specified definition of exposure							
Ever v. never-smokers							
High quality only	2.86	2.04	4.01	Random	0.03	5	116,772
Overall	2.34	1.68	3.24	Random	<0.001	10	128,636
Current v. not current							
High quality only	2.59	1.93	3.48	Fixed	0.42	3	103,886
Overall	2.59	1.93	3.48	Fixed	0.42	3	103,886
Current v. never							
High quality only	2.61	1.59	4.27	Random	0.05	4	116,680
Overall	2.72	1.88	3.93	Random	0.04	6	118,548
Ex v. never							
High quality only	1.56	1.17	2.09	Fixed	0.54	4	116,680
Overall	1.59	1.29	1.95	Fixed	0.71	6	118,548
Passive v. never (all TB)							
Overall	3.35	2.03	5.54	Fixed	0.32	3	480
Pooled estimate for odds ratio of mortality from TB for smokers compared to non-smokers							
All definitions of active exposure included							
Exposed v. non-exposed							
High quality only	1.35	1.11	1.64	Random	<0.001	3	31,582
Overall	2.24	1.34	3.73	Random	<0.001	6	67,168
By study-specified definition of exposure							
Ever v. never-smokers							
High quality only	1.35	1.11	1.64	Random	<0.001	3	31,582
Overall	2.39	1.35	4.24	Random	<0.001	5	64,802
Current v. not-current							
Overall	1.61	1.23	2.11	Reported		1	2,366
Pooled estimate for other relative risk estimates for smokers compared to non-smokers							
Treatement default	1.95	1.53	2.50	Random	0.05	6	3,655
Smear conversion	0.57	0.41	0.80	Fixed	0.74	3	1,090
Severity of TB: Risk of smear+ TB	1.39	1.26	1.53	Fixed	0.64	2	13,889
Severity of TB: Risk of ETB only	0.66	0.60	0.73	Fixed	0.21	3	14,175
Severity of TB: Risk of cavitary TB	1.88	1.59	2.21	Fixed	0.73	2	13,889

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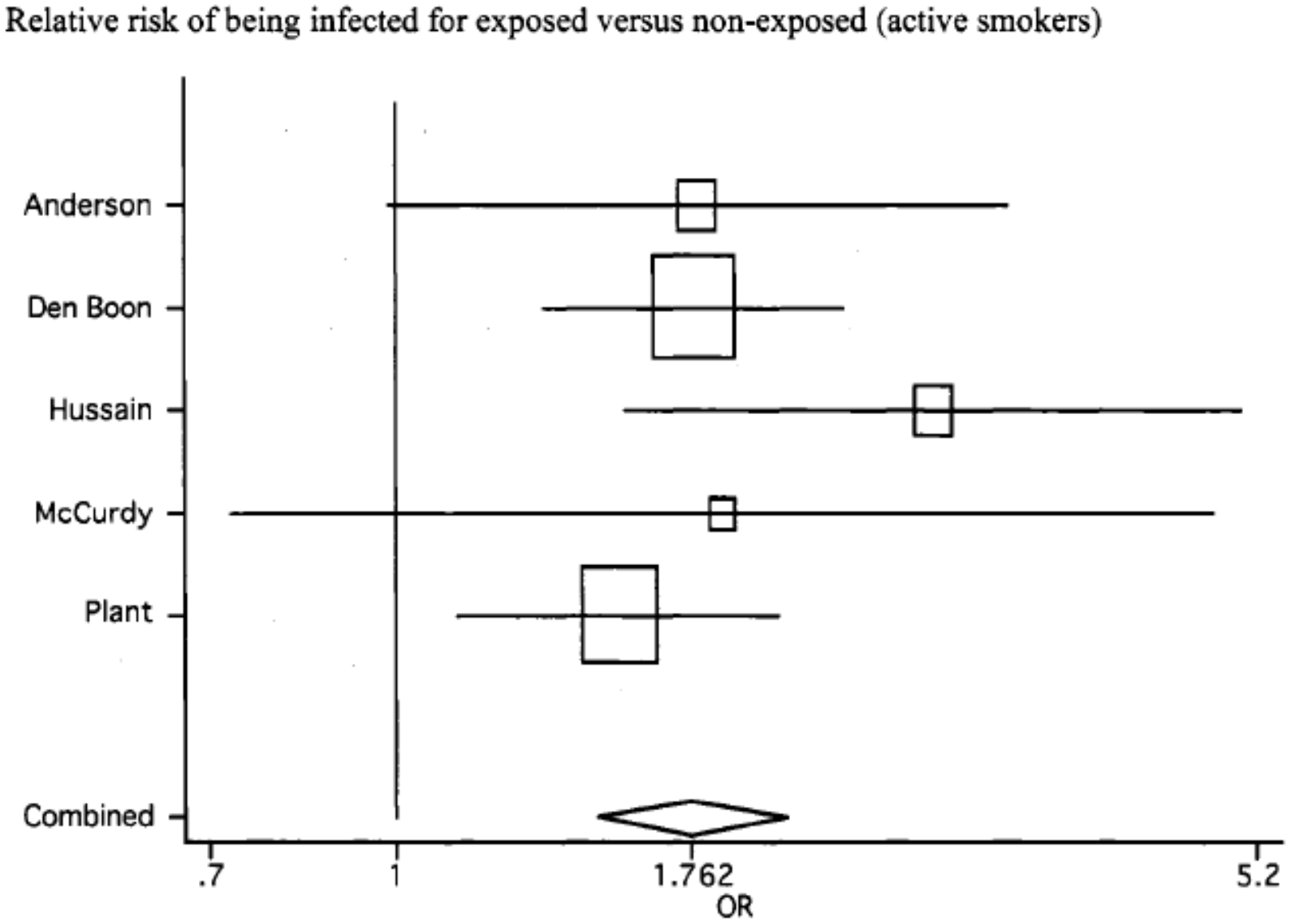
Forest Plot



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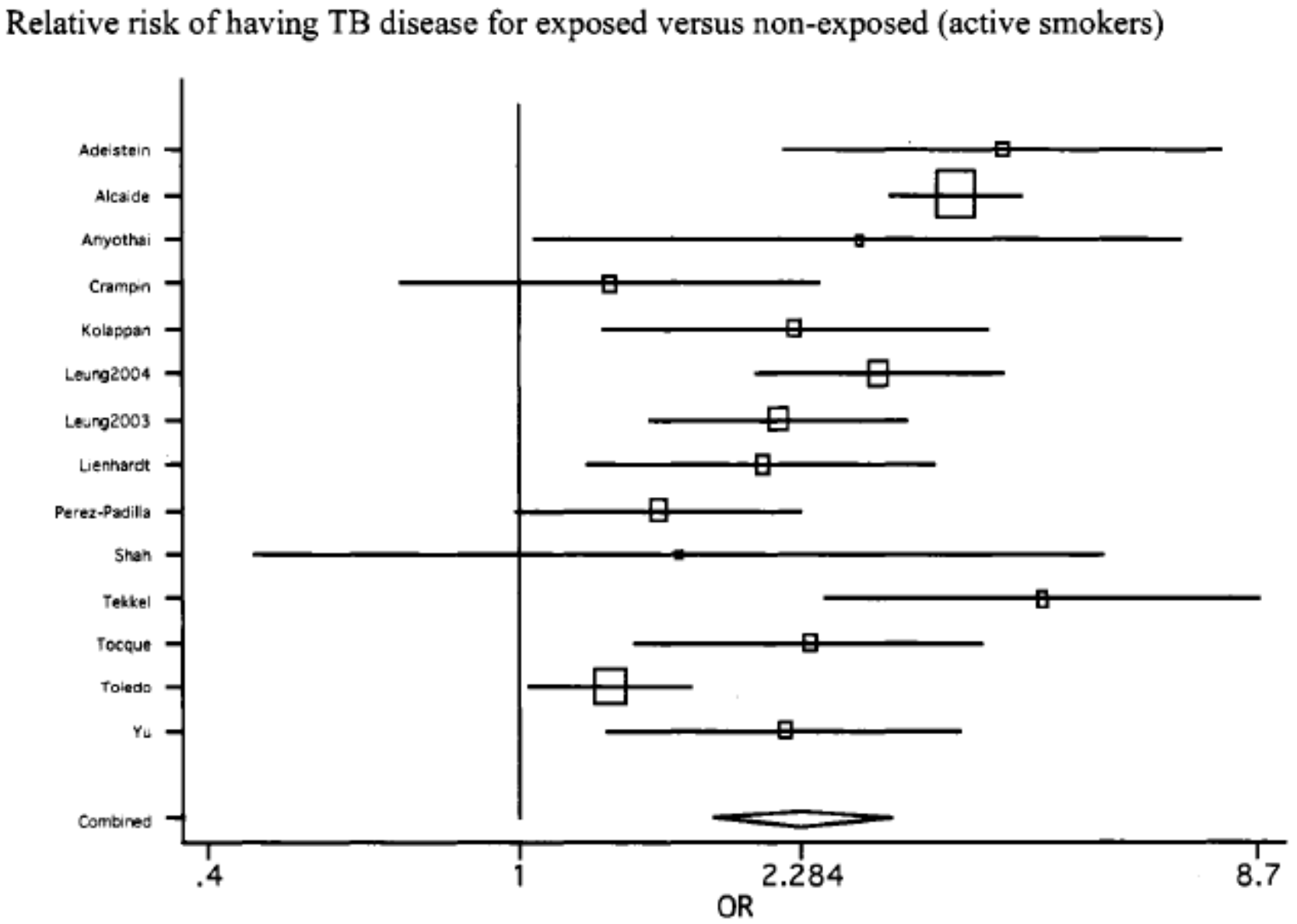
Forest Plot 2



Hassmiller, K. M. (2006). *The Impact of Smoking on Population-Level Tuberculosis Outcomes.* Unpublished PhD, University of Michigan, Ann Arbor, Ann Arbor.

Sensitivity Analyses

- Same relative or absolute uncertainty in different parameters may have hugely different effect on outcomes or decisions
- Help identify parameters that strongly affect
  - Key model results
  - Choice between policies
- We place more emphasis in parameter estimation into parameters exhibiting high sensitivity

Types of Sensitivity Analyses

- Variables involved
  - One-way
  - Multi-way
- Type of component being varied
  - Parameter sensitivity analysis: Parameter values
  - Structural sensitivity analysis: Examine effects of Model structure on results
- Type of variation
  - Single alternative values
  - Monte Carlo analyses: Draws from probability distributions (many types of variations)
- Frequency of variation
  - Static (parameter retains value all through simulation)
  - Ongoing change: Stochastic process
    - Accomplished via Monte-Carlo analyses

Example Spider Diagram

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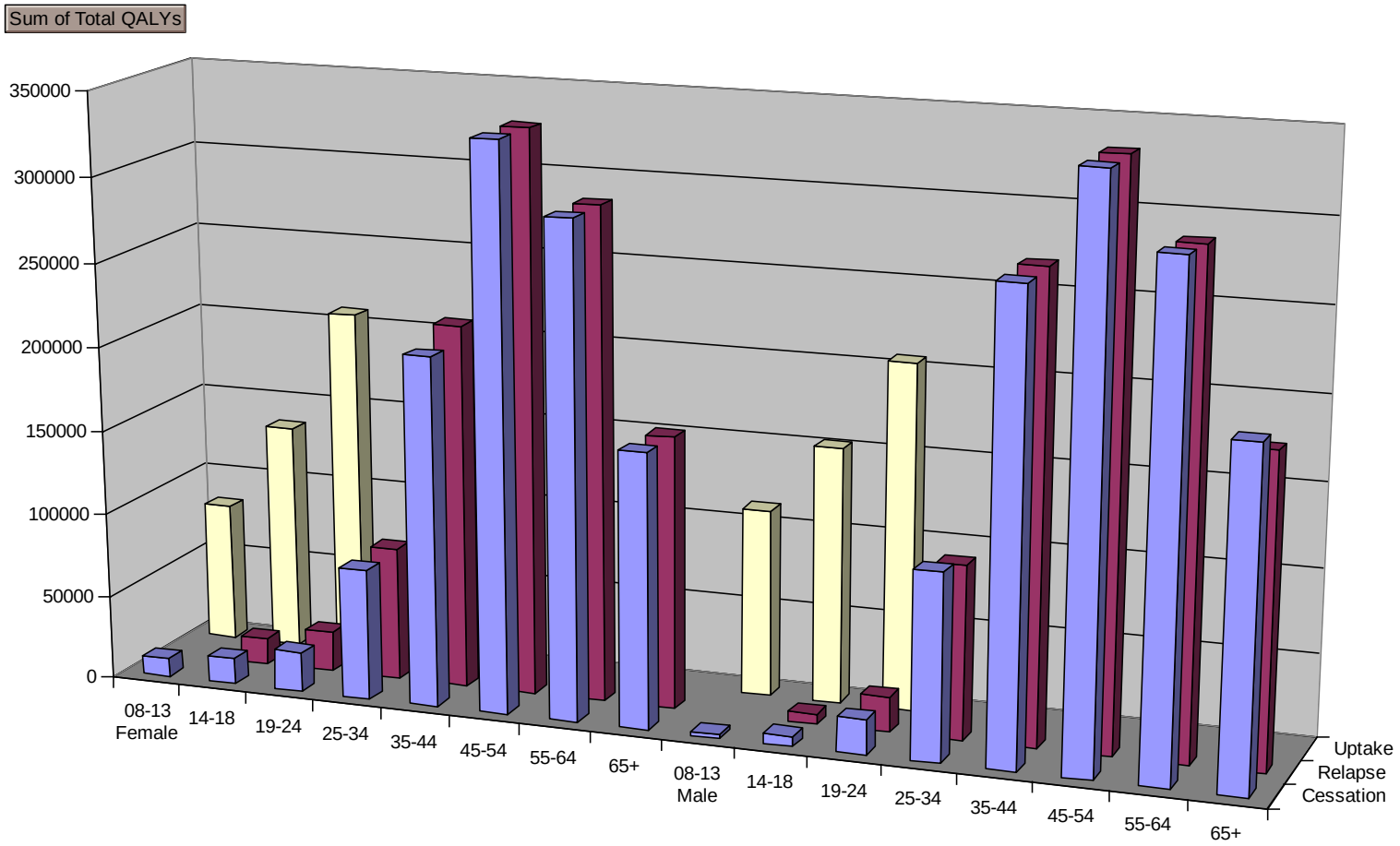
- Each axis represents a % change in a particular parameter
  - This proportional change is identical for the different parameters
- The distance assumed by the curve along that axis represents the magnitude of response to that change
  - Note that these sensitivities will depend on the state of system!

http://www.niwotridge.com/images/BLOGImages/SpiderDiagram.jpg

Systematic Examination of Policies



Tengs, T., Osgood, N., & Lin, T. (2001). Public health impact of changes in smoking behavior: results from the Tobacco Policy Model. *Medical Care, 39*(10), 1131-1141.

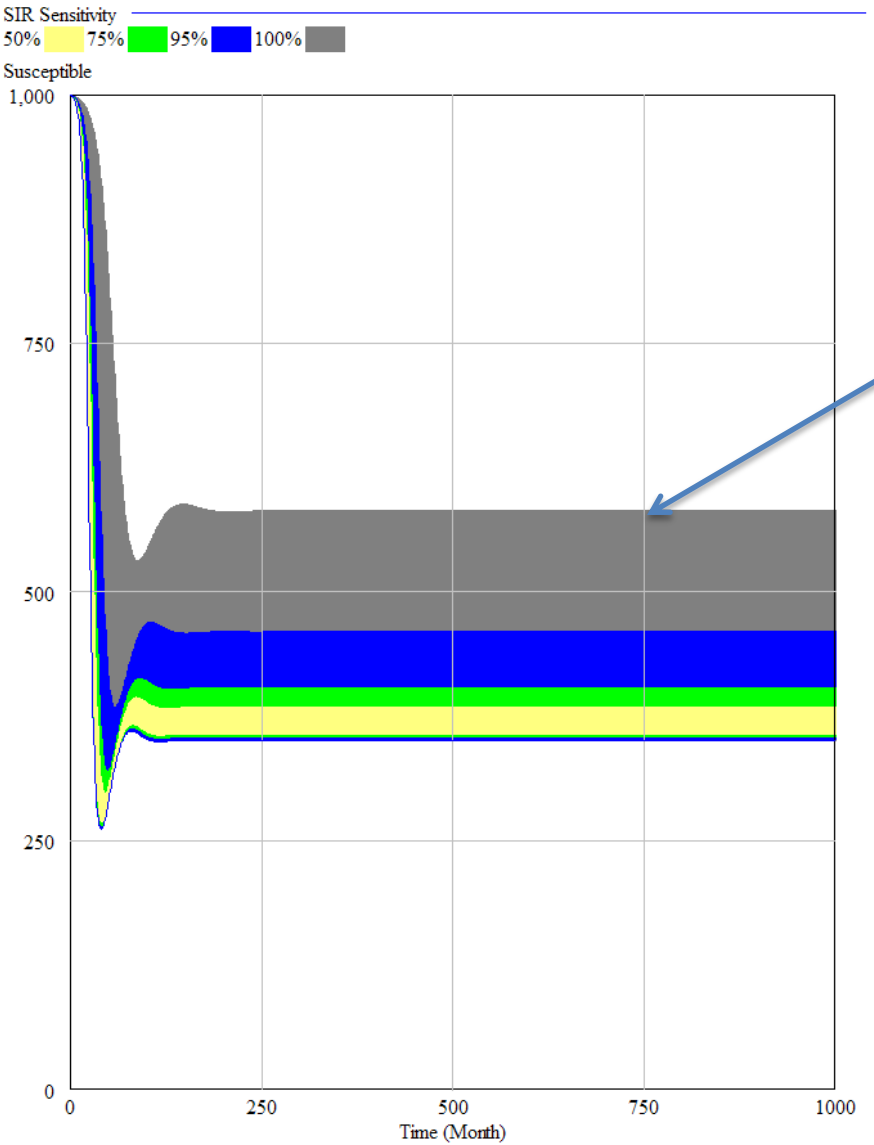
Sensitivity in Initial Value

- Frequently we don't know the exact state of the system at a certain point in time
- A very useful type of sensitivity analysis is to vary the initial value of model stocks
- In Vensim, this can be accomplished by
  - Indicating a parameter name within the "initial value" area for a stock
  - Varying the parameter value

Imposing a Probability Distribution Monte Carlo Analysis

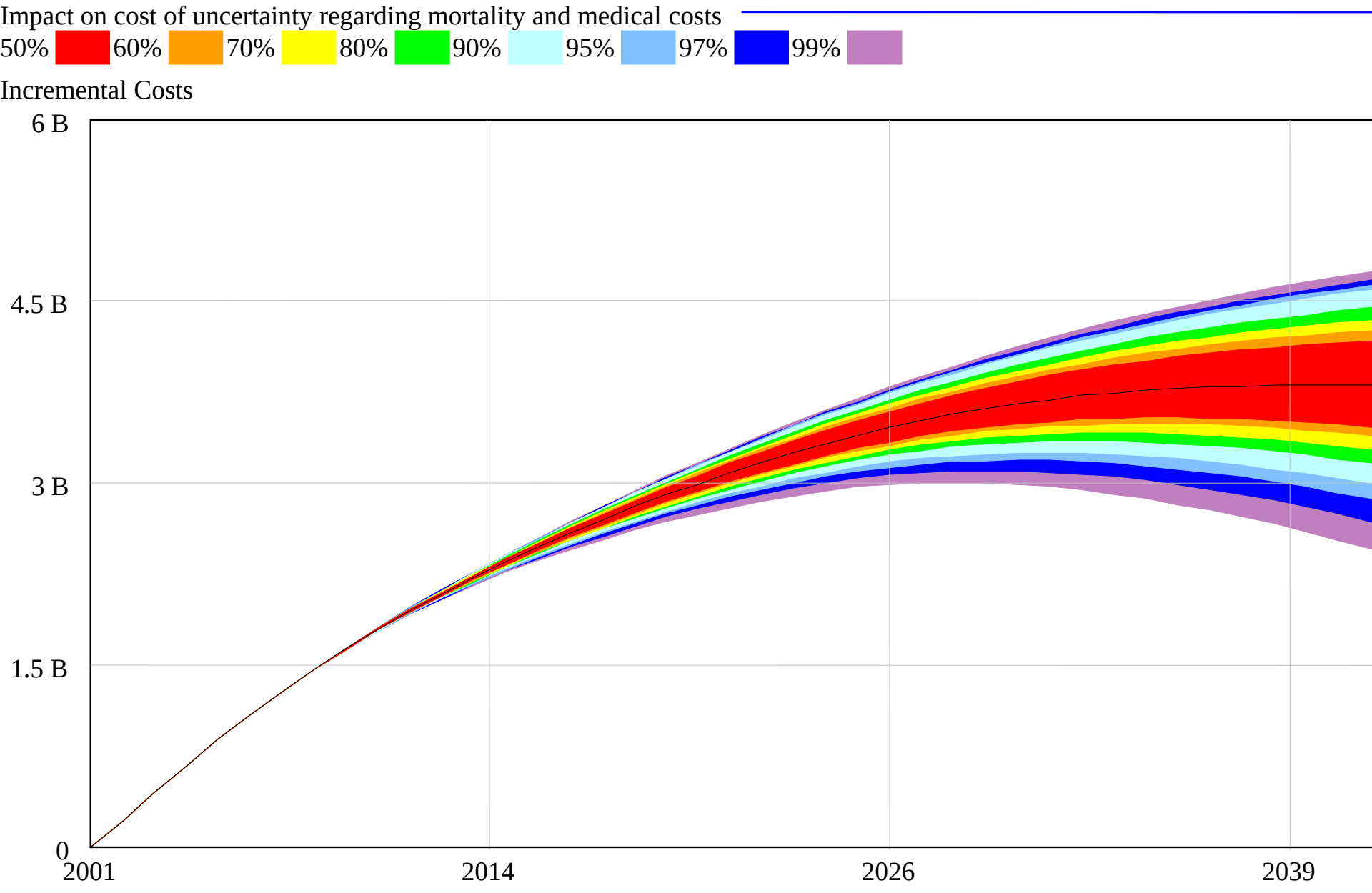
- We feed in probability distributions to reflect our uncertainty about one or more parameters
- The model is run many, many times (realizations)
  - For each realization, the model uses a different draw from those probability distribution
- What emerges is resulting probability distribution for model outputs

Example Resulting Distribution



Empirical Fractiles

Static Uncertainty



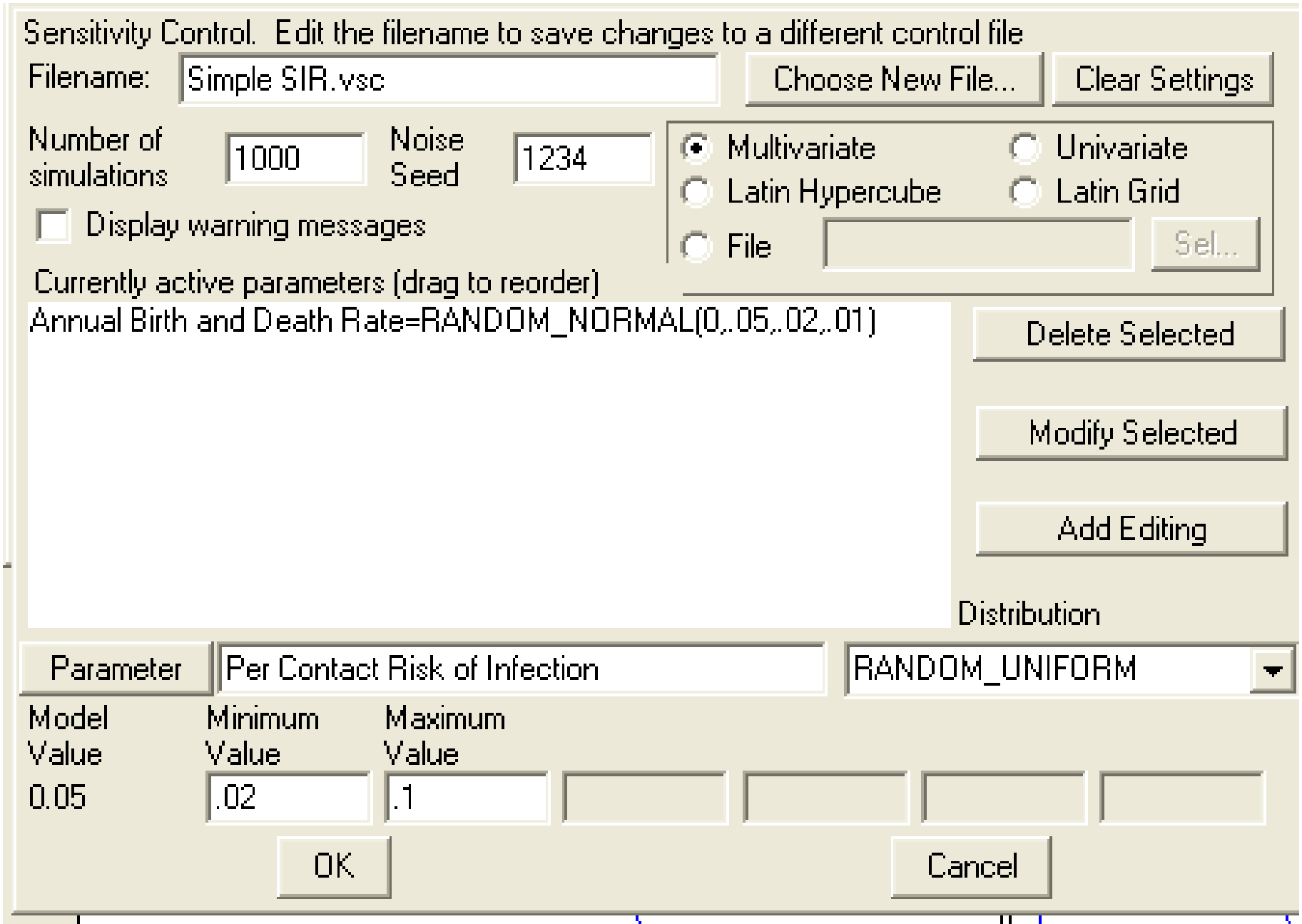
Multi-Way Sensitivity Analyses

- When examining the results of changing multiple variables, need to consider how multiple variables vary together
- If this covariation reflects dependence on some underlying factor, may be able to simulate uncertainty in underlying factor

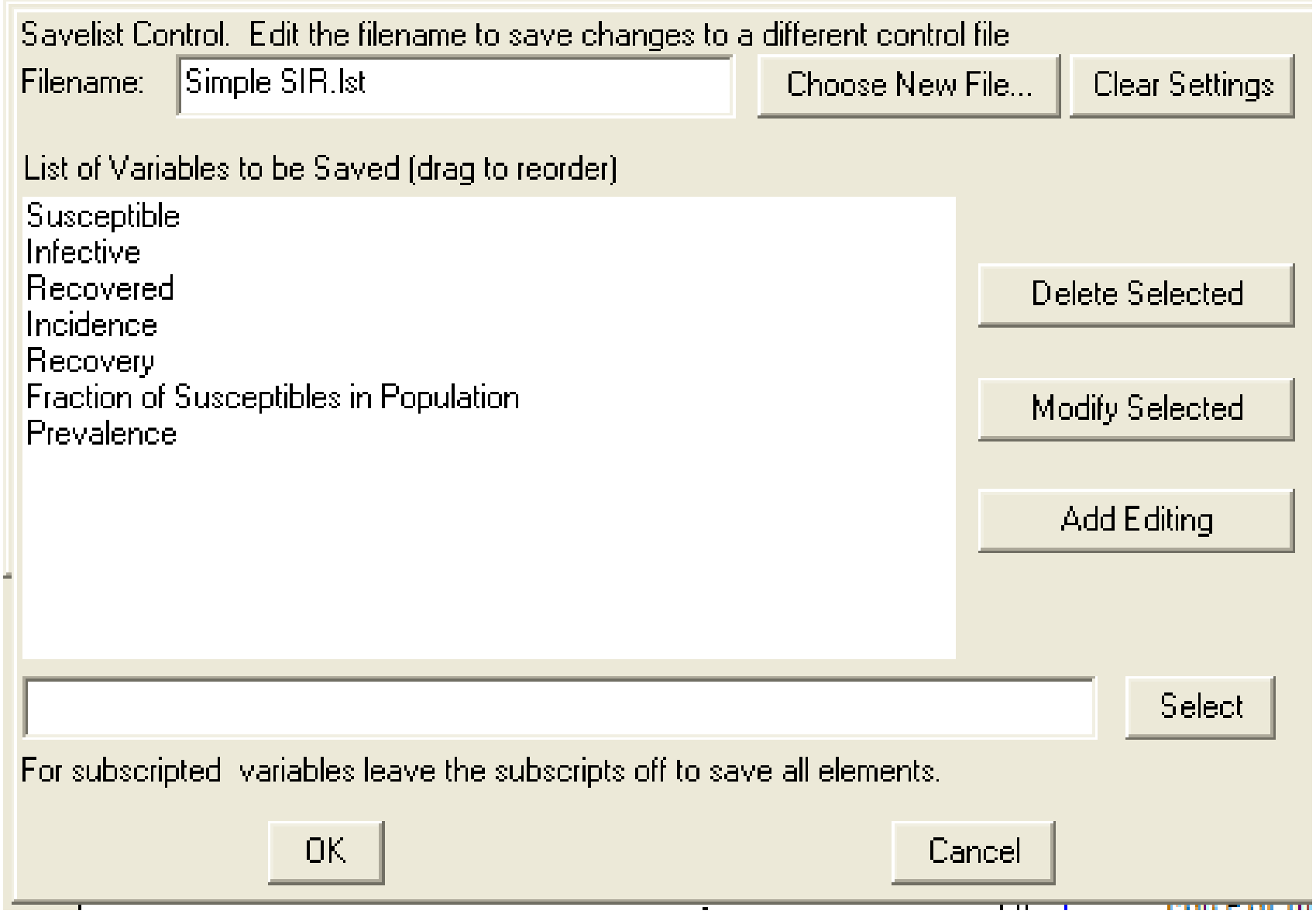
Performing Monte Carlo Sensitivity Analyses in Vensim

- Need to specify three things
  - The parameters to vary
  - How to vary those parameters
  - Which model variables to save away

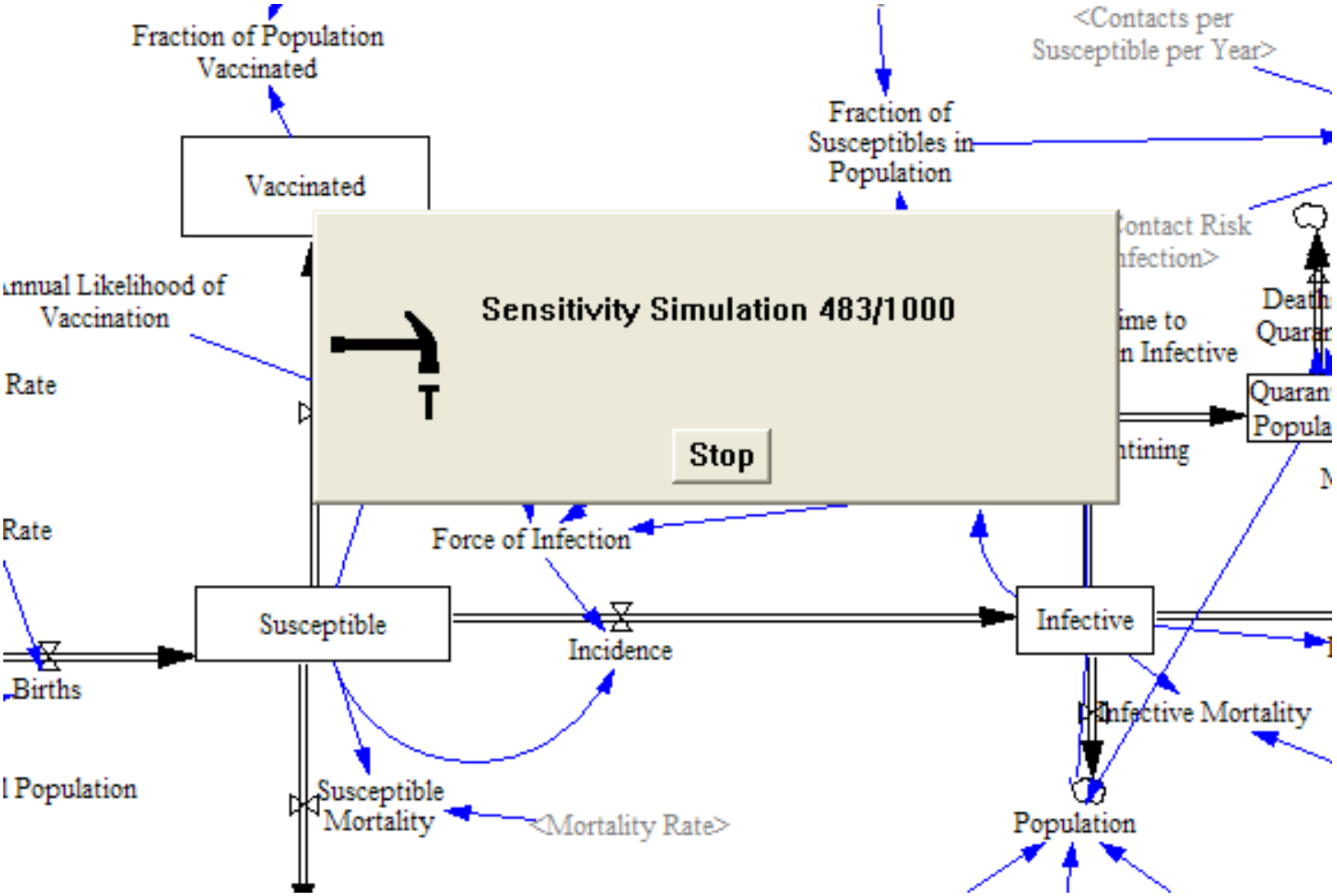
How & What Parameters to Vary



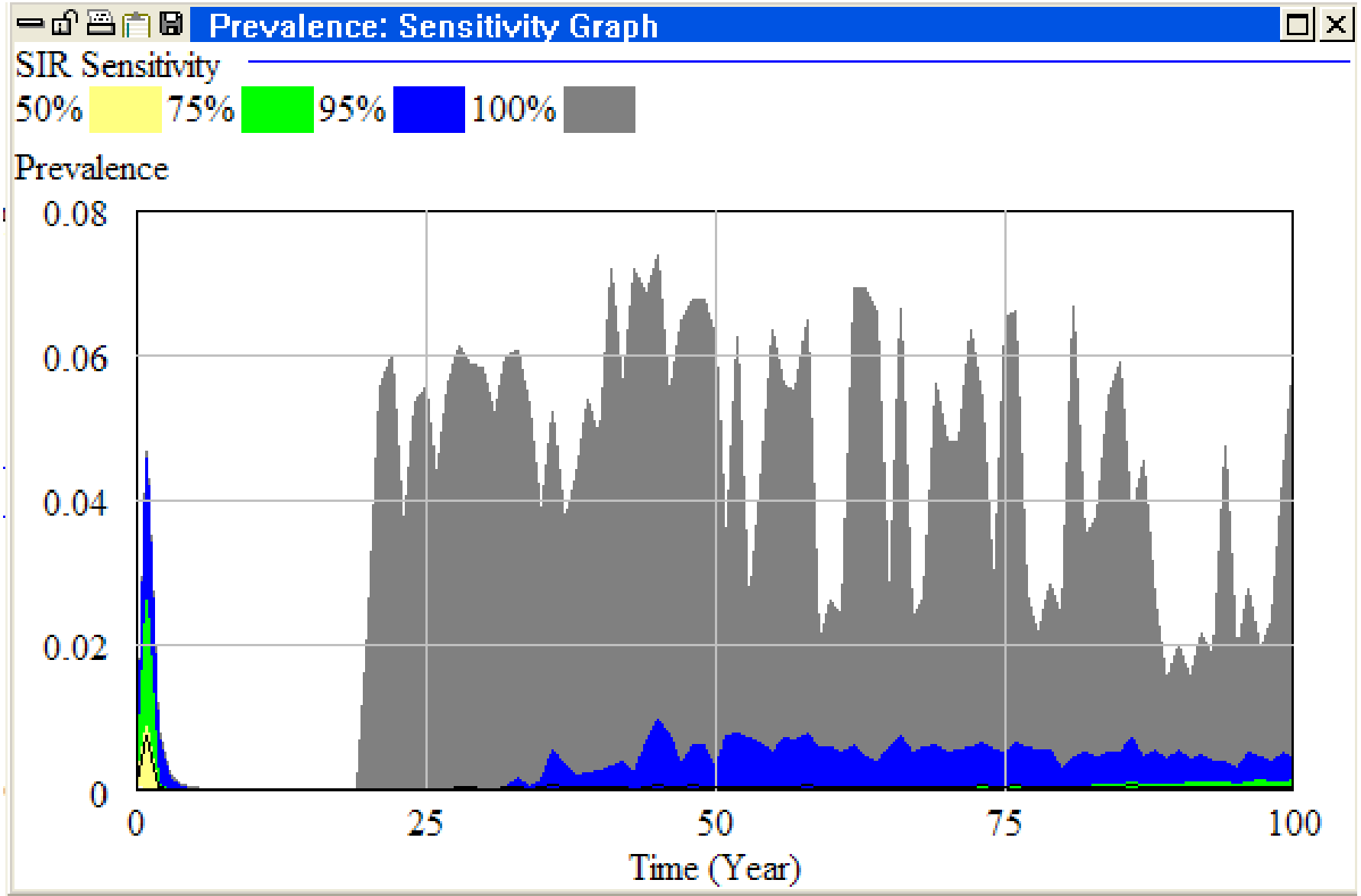
Model Values to Save Away



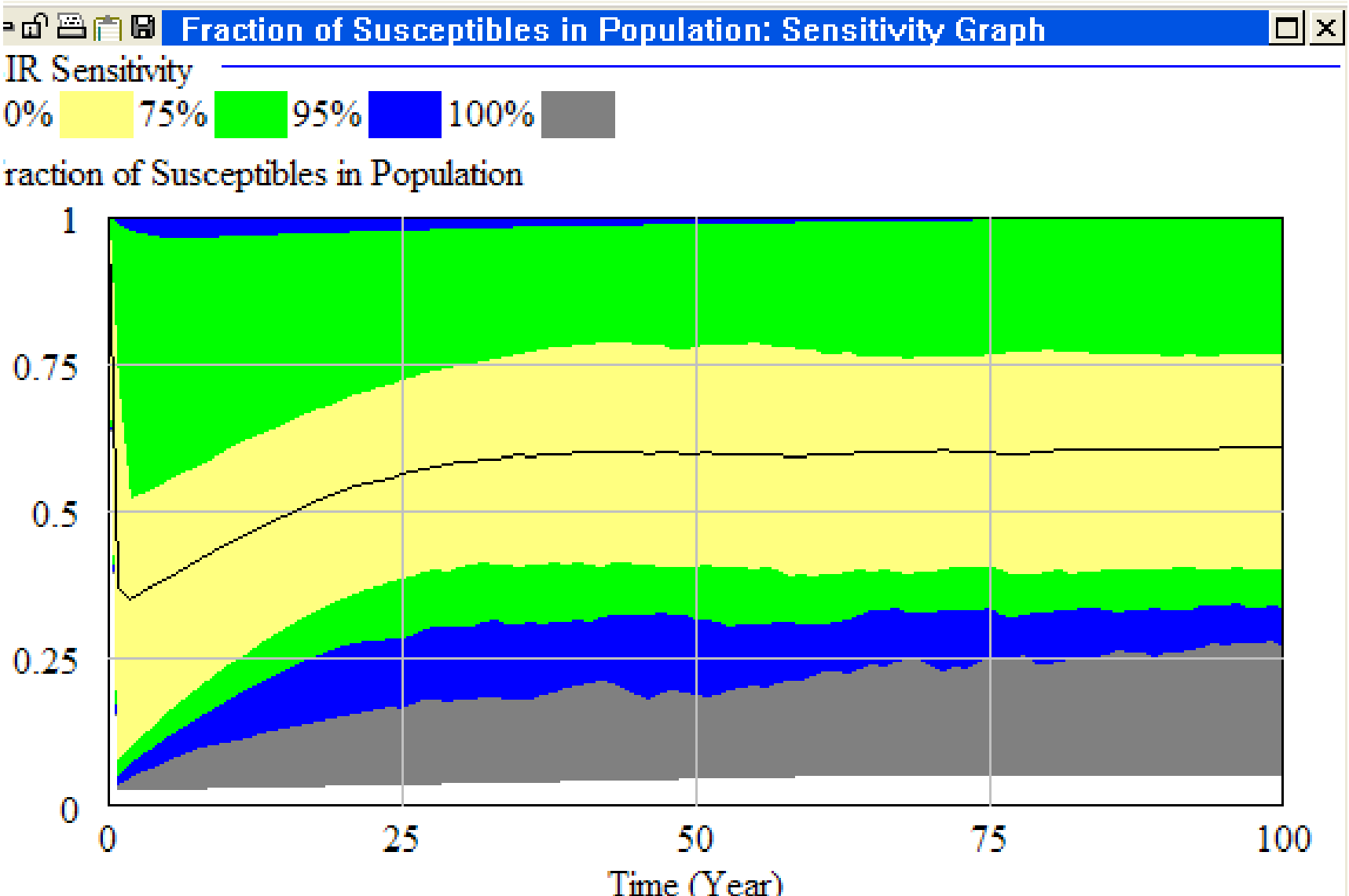
Monte Carlo Analyses



Sensitivity Results (Prevalence)



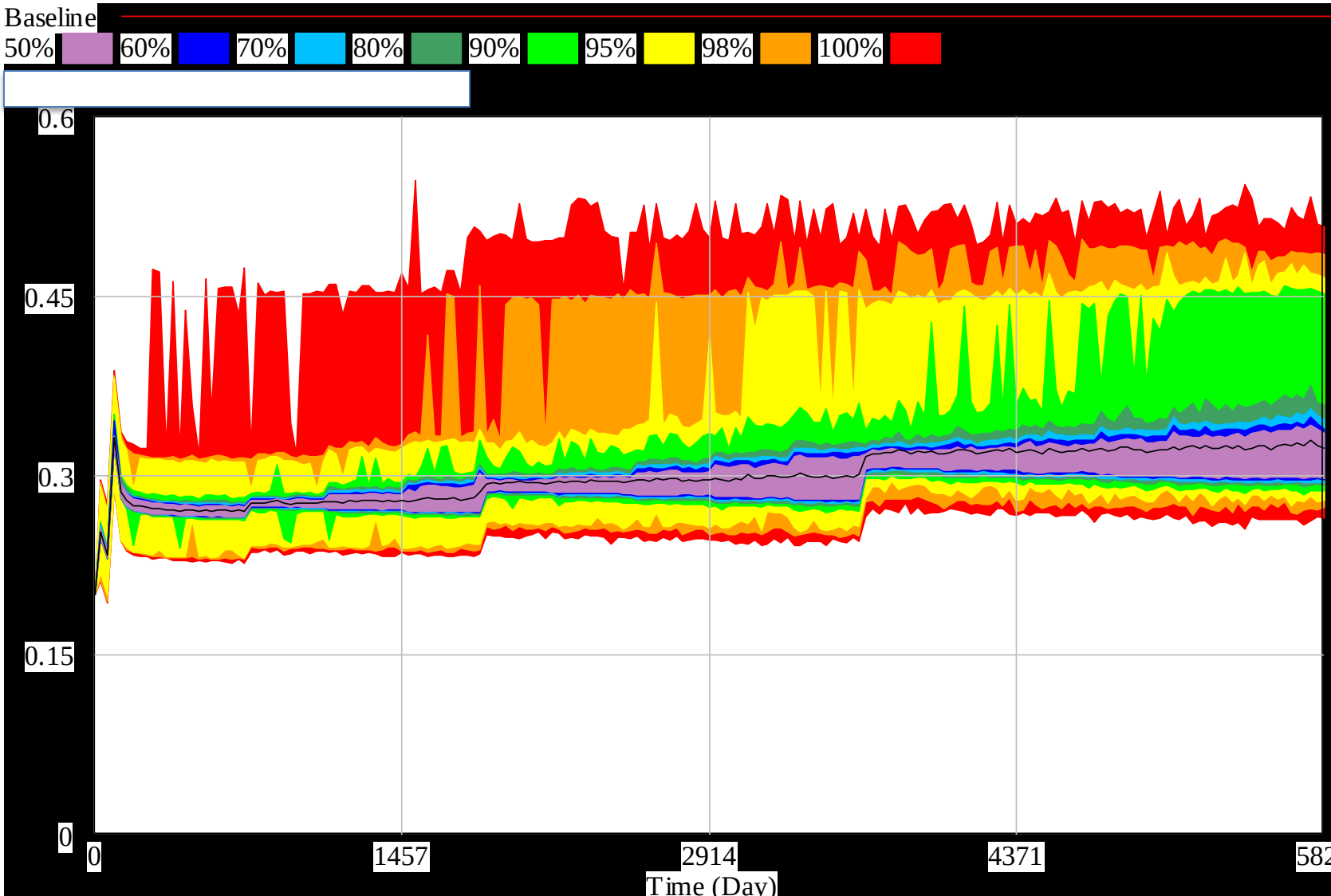
Sensitivity Results (Fraction of Susceptibles)



Stochastic Processes

- Examples of things stochastically approximated
  - Stock market
  - Rainfall
  - Oil prices
  - Economic growth
- What considered “stochastic” will depend on the scope of the model
  - Detailed model: Individual behaviour, transmission, etc.
  - A meteorological model may not consider rainfall stochastic

Stochastic Processes



Dealing with Data Gradients

- Often we don't have reliable information on *some* parameters, but do have other data
  - Some parameters may not be observable, but some closely related observable data is available
  - Sometimes the data doesn't have the detailed breakdown needed to specifically address one parameter
    - Available data could specify sum of a bunch of flows or stocks
    - Available data could specify some function of several quantities in the model (e.g. prevalence)
- Some parameters may implicitly capture a large set of factors not explicitly represented in model
- There are two big ways of dealing with this: manually "backing out", and automated calibration

“Backing Out”

- Sometimes we can manually take several aggregate pieces of data, and use them to collectively figure out what more detailed data might be
- Frequently this process involves imposing some (sometimes quite strong) assumptions
  - Combining data from different epidemiological contexts (national data used for provincial study)
  - Equilibrium assumptions (e.g. assumes stock is in equilibrium. Cf deriving prevalence from incidence)
  - Independence of factors (e.g. two different risk factors convey independent risks)

Example

- Suppose we seek to find out the sex-specific prevalence of diabetes in some population
- Suppose we know from published sources
  - The breakdown of the population by sex (c_M, c_F)
  - The population-wide prevalence of diabetes (p_T)
  - The prevalence rate ratio of diabetes in women when compared to men (rr_F)
- We can "back out" the sex-specific prevalence from these aggregate data (p_F, p_M)
- Here we can do this "backing out" without imposing assumptions

Backing Out

male diabetics + # female diabetics = # diabetics

$(p_M * c_M) + (p_F * c_F) = p_T*(c_M+c_F)$

- Further, we know that $p_F / p_M = rr_F \Rightarrow p_F = p_M * rr_F$
- Thus

$(p_M * c_M) + ((p_M * rr_F) * c_F) = p_T*(c_M+c_F)$

$p_M*(c_M + rr_F * c_F) = p_T*(c_M+c_F)$

- Thus
  - $p_M = p_T*(c_M+c_F) / (c_M + rr_F * c_F)$
  - $p_F = p_M * rr_F = rr_F * p_T*(c_M+c_F) / (c_M + rr_F * c_F)$

Disadvantages of “Backing Out”

- Backing out often involves questionable assumptions (independence, equilibrium, etc.)
- Sometimes a model is complex, with several related known pieces
  - Even thought we may know a lot of pieces of information, it would be extremely complex (or involve too many assumptions) to try to back out several pieces simultaneously

Another Example: Joint & Marginal Prevalence

	Rural	Urban	
Male	p_{MR}	p_{MU}	p_M
Female	p_{FR}	p_{MU}	p_F
	p_R	p_U	

Perhaps we know

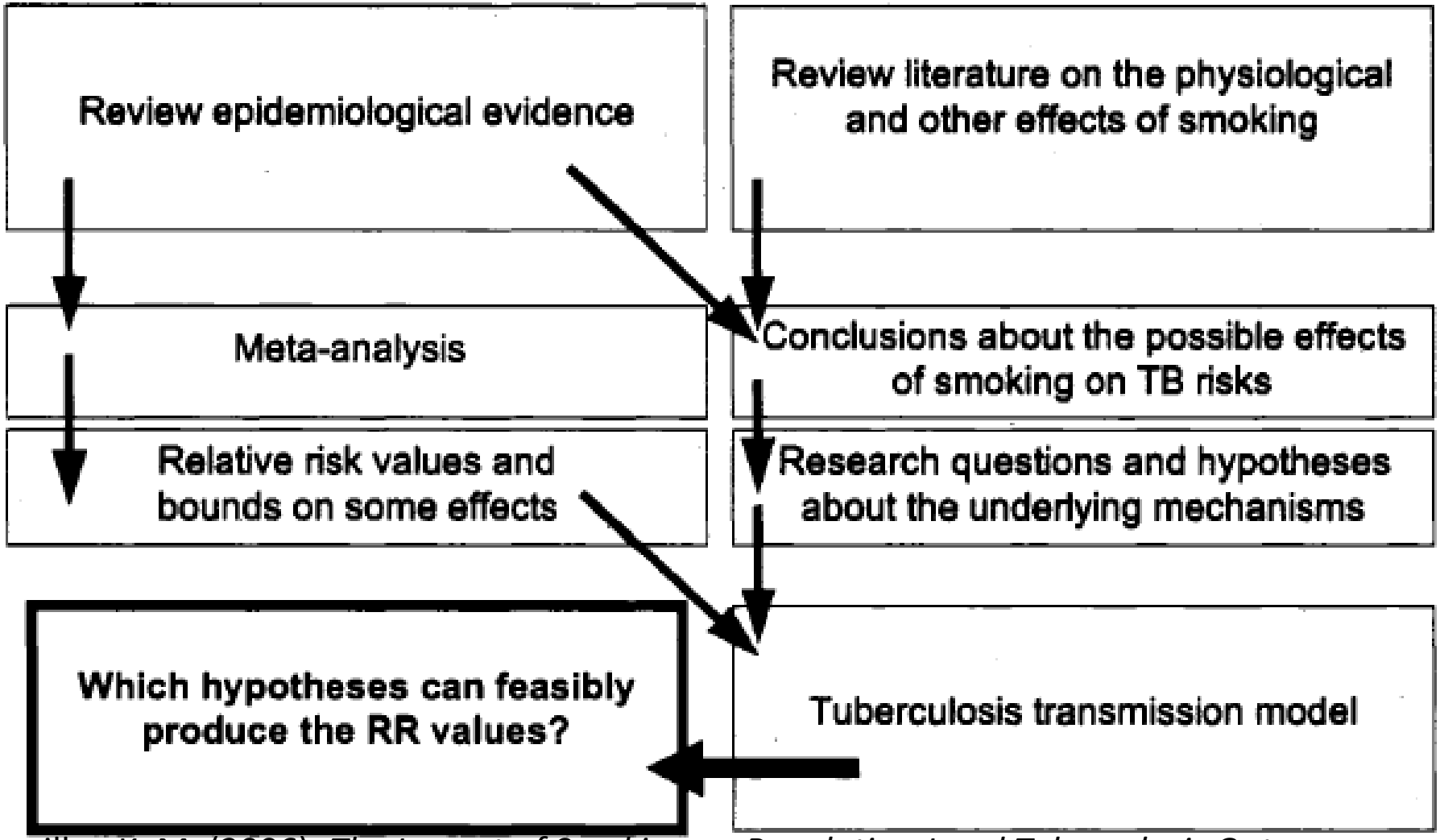
- The count of people in each { Sex, Geographic } category
- The marginal prevalences (p_R, p_U , p_M , p_F)

We need at least one more constraint

- One possibility: assume $p_{MR} / p_{MU} = p_R / p_U$

We can then derive the prevalences in each { Sex, Geographic } category

Example Tying Together Meta-analysis & Calibration



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