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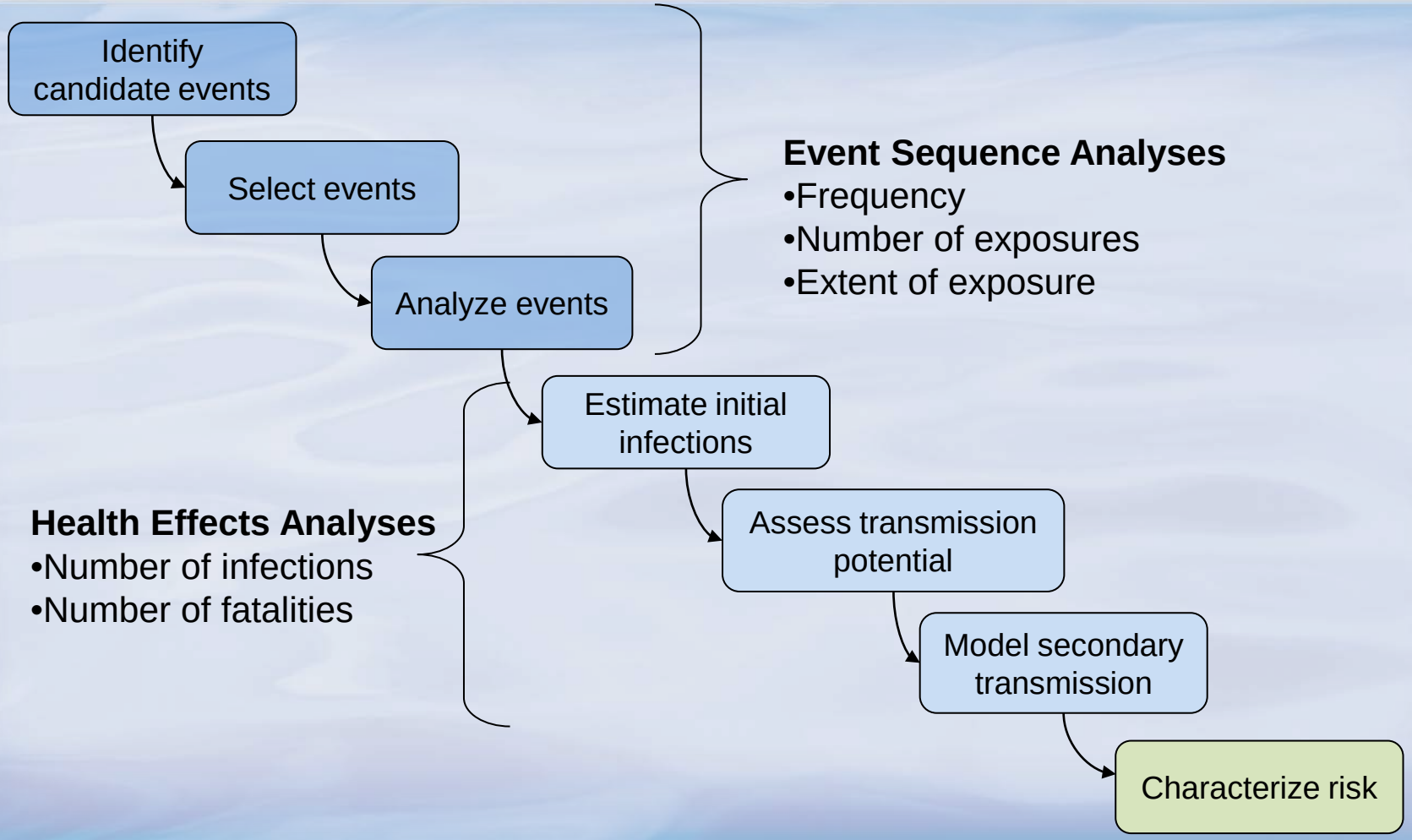
National Emerging Infectious Diseases Laboratories Risk Assessment

TETRA TECH

Process Overview



Health Effects Analyses

- Modeling team
- Adi Gundlapalli, MD, PhD, MS
  - University of Utah
  - Board certified infectious diseases physician
  - Epidemiology, immunology & informatics
- Damon Toth, PhD
  - University of Utah
  - PhD in applied mathematics
  - Mathematical biology and modeling

Health Effects

- Follow-on from event sequence analysis
- **Estimate initial infections**
- Assess transmission potential
- Model secondary transmission
- Summary

Estimate Initial Infections

- Translating exposure to infection
- Dose-response relationships
- Mathematical estimation of the probability of infection
- Uncertainty analysis
- Sensitivity analysis
- Summary

Translating exposure to infection

- Infection: establishment of an organism on or within a host
  - Could potentially lead to disease
- Not every exposure will lead to an infection
- Factors involved:
  - Dose received
  - Route of exposure
  - Human infectious dose
  - Status of the exposed
  - Dose-response relationships

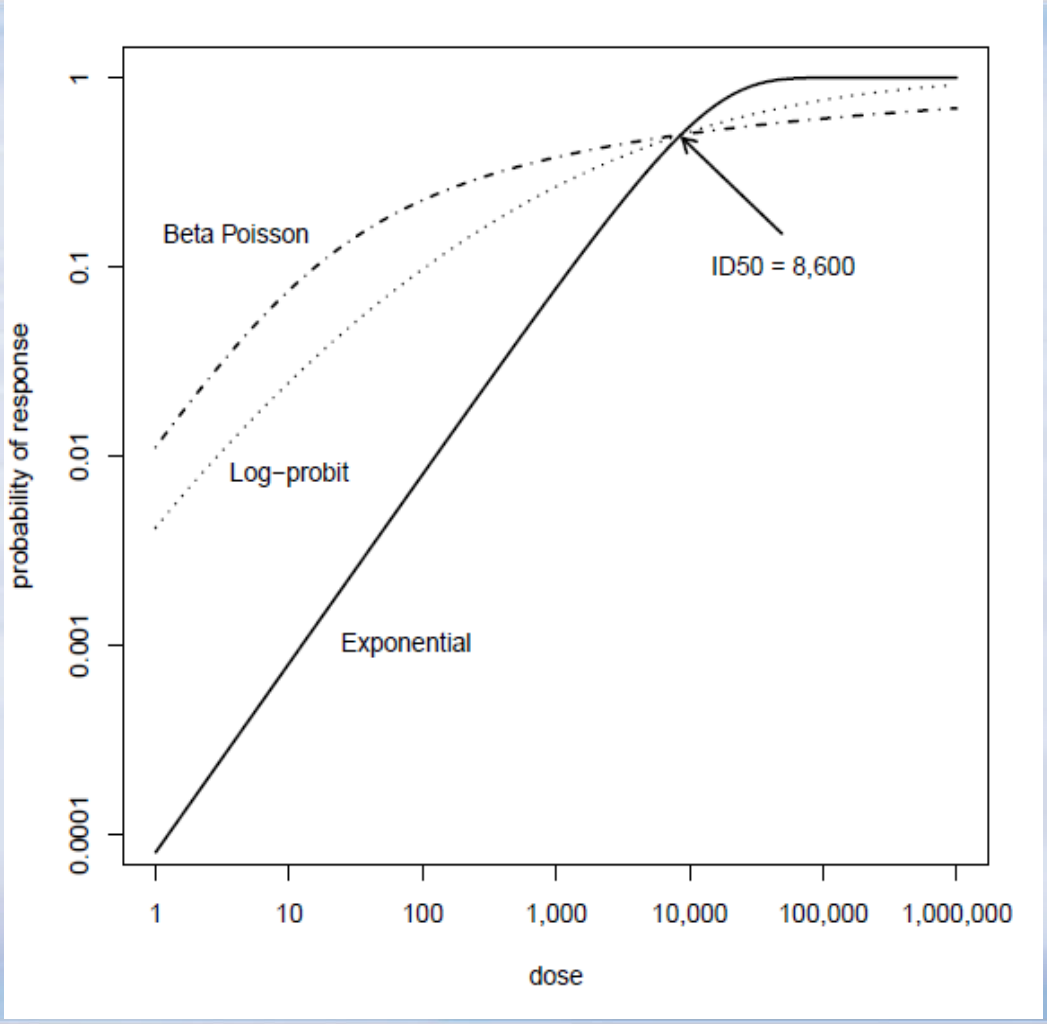
Factors for today's presentation

- Doses received are outputs from event sequence analyses
- Route of exposure is aerosol
- Human infectious doses (HID) are HID10, 50 and 90
  - Minimum dose required to cause infection in 10%, 50% and 90% of individuals exposed
- Categories of the exposed individuals
  - Healthy adults
  - Vulnerable sub-populations

Dose-response relationships

Model	Detail	Equation
Log-probit	• Traditional model in toxicology • 2-parameter model	$P(d)=\Phi(m \ln(d/ID_{50}))$ Φ is the c.d.f of the standard normal distribution
Exponential	• Based on single hit theory • Assumes one particle can cause infection • Constant single-hit probability • Single parameter model	$P(d) = 1 - \exp\{-r\, d\}$ Single parameter $r = \ln(2)/ID_{50}$
Beta Poisson	• Single hit framework • Variable single-hit probability (β distribution) • 2-parameter model	$p(d) = 1 - \left(1 + \frac{d}{\beta}\right)^{-\alpha}$

Dose-response relationships



Adapted from Wilkening, PNAS (2006)

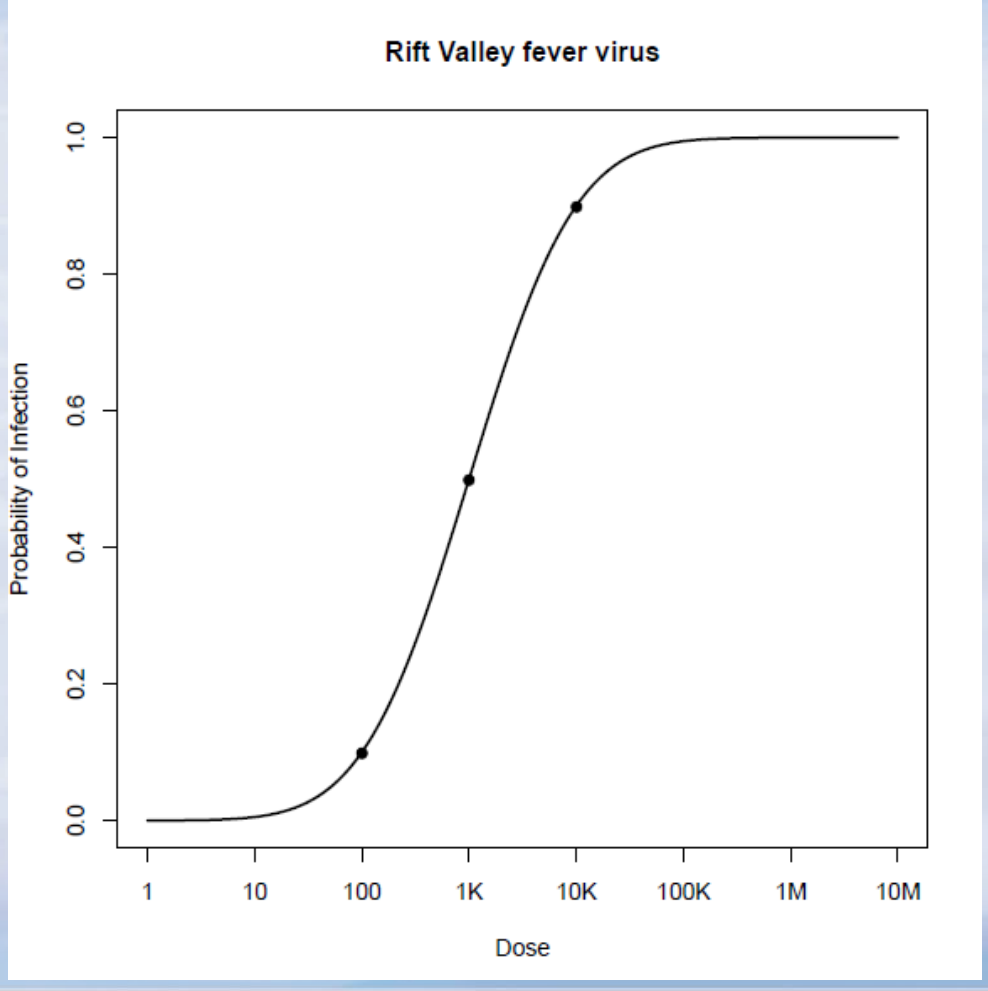
Generating dose response curves

- Human infectious dose
  - Limited data in the literature
  - Estimates available for only 4 of 13 pathogens
- Modified Delphi method
  - Convened an expert panel of bio-defense specialists, microbiologists and virologists
  - Solicited estimates of HID10, 50 and 90
  - Three rounds of voting for all 13 pathogens
- Use median values from experts for base case analysis
  - Determine best fit among the 3 models
- Use individual expert curves for uncertainty analysis

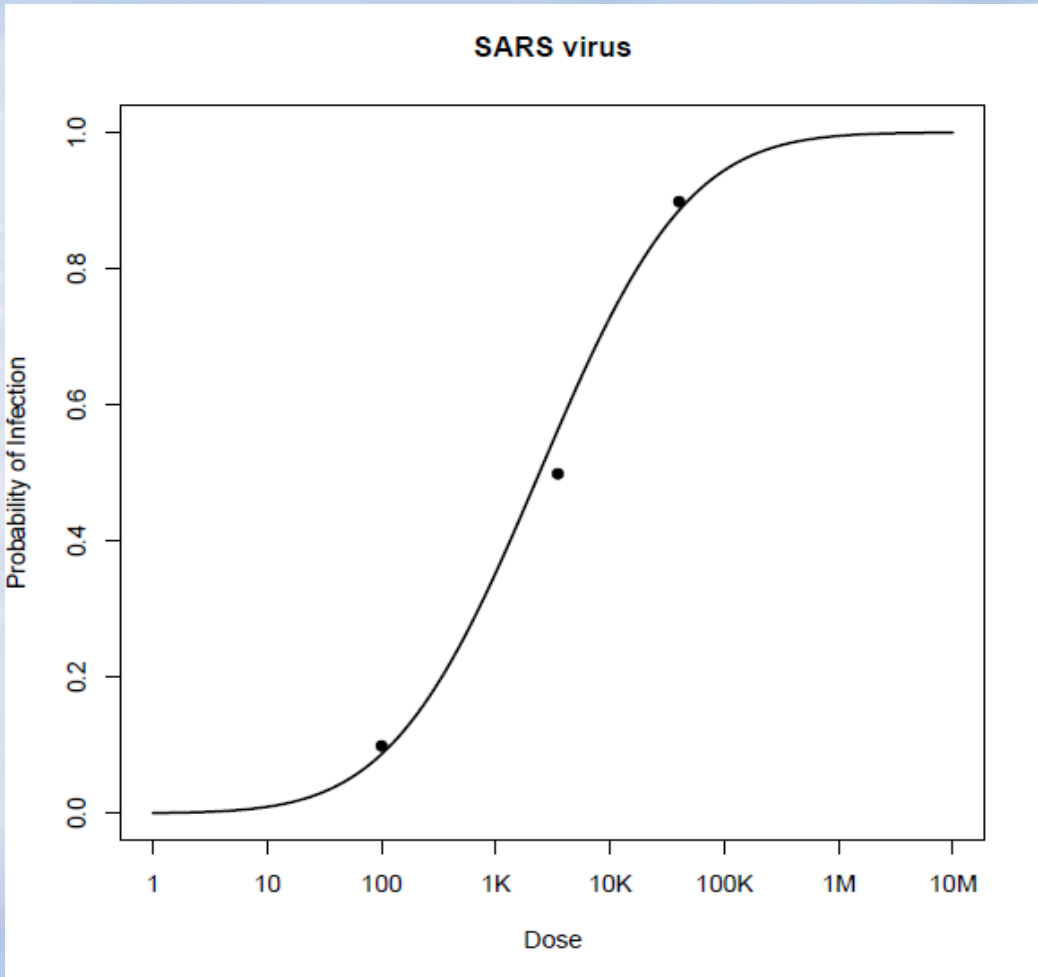
List of 13 Pathogens

- BSL-3
  - 1918 pandemic influenza virus
  - *Yersinia pestis*
  - *Francisella tularensis*
  - *Bacillus anthracis*
  - **SARS-associated coronavirus**
  - **Rift Valley fever virus**
- BSL-3 or 4
  - Andes hantavirus
- BSL-4
  - Junin haemorrhagic fever virus
  - Tick-borne encephalitis complex (Russian spring-summer encephalitis) virus
  - Lassa fever virus
  - Marburg virus
  - Ebola virus
  - Nipah

Rift Valley Fever Virus (RVFV)
Best fit curve: Log-probit



SARS Corona Virus (SARS-CoV)
Best fit curve: Log-probit



Mathematical estimation of probability of initial infection

- Initial infection
  - From direct exposure to a pathogen as a result of a release scenario
- Conditional probability of initial infection(s)
  - Number of individuals exposed
  - Amount of exposure per individual
  - Probability of infection given dose
- Frequency of the event

Operational Event: BSL-3 centrifuge aerosol release involving RVFV

- Frequency per event of initial infections for RVFV

	BSL-3 centrifuge aerosol release with RVFV	
	With PAPR	With Degraded PAPR
Number of particles inhaled	0-10	0-1000
Number of lab workers exposed	Average 3	1
Best dose-response curve	Log-probit	Log-probit
Event Frequency Category	High 0.5 to 50 per facility lifetime	Moderate 0.005 to 0.5 per facility lifetime
Rate of initial infection conditional on exposure	**1 in 200 events**	**1 in 4 events**

Operational Event: BSL-3 centrifuge aerosol release involving RVFV

- Frequency per time of initial infections for RVFV

	Number of Initial Infections	Infection Frequency (per facility lifetime of 50 years)	Return Period	Frequency Category
Centrifuge aerosol release with PAPR	≥1	0.003 to 0.3	200 to 20,000 yrs	Moderate
	≥2	7×10^{-4} to 7×10^{-6}	80,000 to 8 million yrs	Low
	≥3	7×10^{-7} to 7×10^{-9}	> 10 million years	Beyond Reasonably Foreseeable
Centrifuge aerosol release with degraded PAPR	≥1	0.001 to 0.1	400 to 40,000 yrs	Moderate
	≥2	Beyond Reasonably Foreseeable	Beyond Reasonably Foreseeable	Beyond Reasonably Foreseeable

Return period: estimate of the interval of time between events

Operational Event: BSL-3 centrifuge aerosol release involving SARS-CoV

- Frequency per event of initial infections for SARS-CoV

	BSL-3 centrifuge aerosol release with SARS-CoV	
	With PAPR	With Degraded PAPR
Number of particles inhaled	<1	0-10
Number of lab workers exposed	Average 3	1
Best dose-response curve	Log-probit	Log-probit
Event Frequency Category	High 0.5 to 50 per facility lifetime	Moderate 0.005 to 0.5 per facility lifetime
Rate of initial infection conditional on exposure	**0**	**1 in 300 events**

Operational Event: BSL-3 centrifuge aerosol release involving SARS-CoV

- Frequency per time of initial infections for SARS-CoV

Event	Number of Initial Infections	Infection Frequency (per facility lifetime of 50 years)	Return Period	Frequency Category
Centrifuge aerosol release with PAPR	≥1	Beyond Reasonably Foreseeable	Beyond Reasonably Foreseeable	Beyond Reasonably Foreseeable
Centrifuge aerosol release with degraded PAPR	≥1	2×10^{-5} to 0.002	30,000 to 3 million years	Low
	≥2	Beyond Reasonably Foreseeable	Beyond Reasonably Foreseeable	Beyond Reasonably Foreseeable

Return period: estimate of the interval of time between events

Uncertainty analyses: Latin Hypercube Sampling (LHS)

- Test all four sources of uncertainty at once
- Generate *n* combinations of input values from Latin Hypercube
  - Ensures full and efficient coverage of parameter space
  - Better analysis of "worst case" than choosing extremes
  - A form of "Monte Carlo" simulations
- Also provides data for sensitivity analyses

Parameter	Base Case Value	Range Tested
Exposed workers	Average of 3 workers, from a uniform distribution	From three distributions with skew toward higher and lower end
Dose	Uniform distribution from event sequence analysis results	Skew distribution to lower and higher end of range
Dose response curves	Log-probit	Range of response curves
Event frequency	From event sequence analysis	Select from uniform distribution

Results of uncertainty analysis

BSL3 centrifuge aerosol release with PAPR

- Rift Valley Fever Virus
- Outcomes of 10,000 combinations of LHS
- Representative base-case scenario
  - Rate of ≥1 initial infection: moderate category
  - Rate of ≥2 initial infections: low category
  - Rate of ≥3 initial infections: BRF

Number of Initial Infections	BEYOND REASONABLY FORESEEABLE	LOW	MODERATE	HIGH	ROUTINE
≥1	-	31%	**66%**	3%	-
≥2	57%	**29%**	14%	0.04%	-
≥3	**84%**	16%	0.4%		-

Results of uncertainty analysis

BSL3 centrifuge aerosol release <u>with degraded</u> PAPR

- Rift Valley Fever Virus
- Outcomes of 10,000 combinations of LHS
- Representative base-case scenario
  - Rate of ≥1 initial infection: moderate category
  - Rate of ≥2 initial infections: BRF

Number of Initial Infections	BEYOND REASONABLY FORESEEABLE	LOW	MODERATE	HIGH	ROUTINE
≥1	-	69%	**31%**	-	-
≥2	**100%**	-	-	-	-

Results of uncertainty analysis

BSL3 centrifuge aerosol release with degraded PAPR

- SARS-associated corona virus
- Outcomes of 10,000 combinations of LHS
- Representative base-case scenario
  - Rate of ≥1 initial infection: low category
  - Rate of ≥2 initial infections: BRF

Number of Initial Infections	BEYOND REASONABLY FORESEEABLE	LOW	MODERATE	HIGH	ROUTINE
≥1	77%	**23%**	-	-	-
≥2	**100%**	-	-	-	-

Sensitivity analysis

- Evaluates the variable to which the estimate is most sensitive
- Partial Rank Correlation Coefficients (PRCCs)
  - Measures the influence of uncertainty in estimating the values of the input parameter on the imprecision in predicting the value of the output variable
  - Higher PRCC = higher contribution to uncertainty
- Evaluate the four variables
  - Distribution of number exposed
  - Distribution of amount of exposure
  - Dose response curve
  - Frequency of incident

Sensitivity Analyses

- Partial Rank Correlation Coefficient values

Event	Pathogen	Distribution of number exposed	Distribution of amount of exposure	Dose response curve	Frequency of incident
Centrifuge aerosol release with PAPR	RVFV	0.30	0.59	**0.92**	0.80
Centrifuge aerosol release with degraded PAPR	RVFV	0.36	0.37	0.81	**0.84**
	SARS Co-V	0.31	0.58	**0.89**	0.81

Maximum Reasonably Foreseeable event: Earthquake

- Frequency per event of initial infections for RVFV/SARS-CoV

	Earthquake aerosol release	
	RVFV	SARS-coV
Number of particles inhaled	<1	<1
Number of individuals exposed	Urban daytime population	Urban daytime population
Best dose-response curve	Log-probit	Log-probit
Event Frequency Category	Low 0.005 to 0.00005 per facility lifetime	Low 0.005 to 0.00005 per facility lifetime
Rate of initial infection conditional on exposure	**1 in 1000 events**	**1 in 10,000 events**

Maximum Reasonably Foreseeable event: Earthquake

- Frequency per time of initial infections for RVFV or SARS-Co-V

Pathogen	Number of Initial Infections	Infection Frequency (per facility lifetime of 50 years)	Return Period	Frequency Category
RVFV	≥1	5×10^{-6} to 5×10^{-8}	≥ 10 million yrs	Beyond Reasonably Foreseeable
SARS-CoV	≥1	3×10^{-7} to 3×10^{-9}	> 10 million yrs	Beyond Reasonably Foreseeable

Uncertainty Analysis for Earthquake

- Similar to uncertainty for centrifuge incidents
- Test all four sources of uncertainty at once
- Generate *n* combinations of input values from Latin Hypercube

Parameter	Base Case Value	Range Tested
Exposed members of the public	Site specific population estimates	Higher, lower population per sector
Dose	Uniform distribution from event sequence analysis results	Higher, lower average exposure per sector
Dose response curves	Log-probit	Range of response curves
Event frequency	From event sequence analysis	Select from uniform distribution

Results of uncertainty analysis

Earthquake, urban daytime population

- Rift Valley Fever Virus
- Outcomes of 10,000 combinations of LHS
- Representative base-case scenario
  - Rate of 1 initial infection: BRF category

Number of Initial Infections	BEYOND REASONABLY FORESEEABLE	LOW	MODERATE	HIGH	ROUTINE
≥1	**97%**	3%	-	-	-

Sensitivity analysis not necessary as uncertainty is low

Results of uncertainty analysis

Earthquake, urban daytime population

- SARS-associated corona virus
- Outcomes of 10,000 combinations of LHS
- Representative base-case scenario
  - Rate of 1 initial infection: BRF category

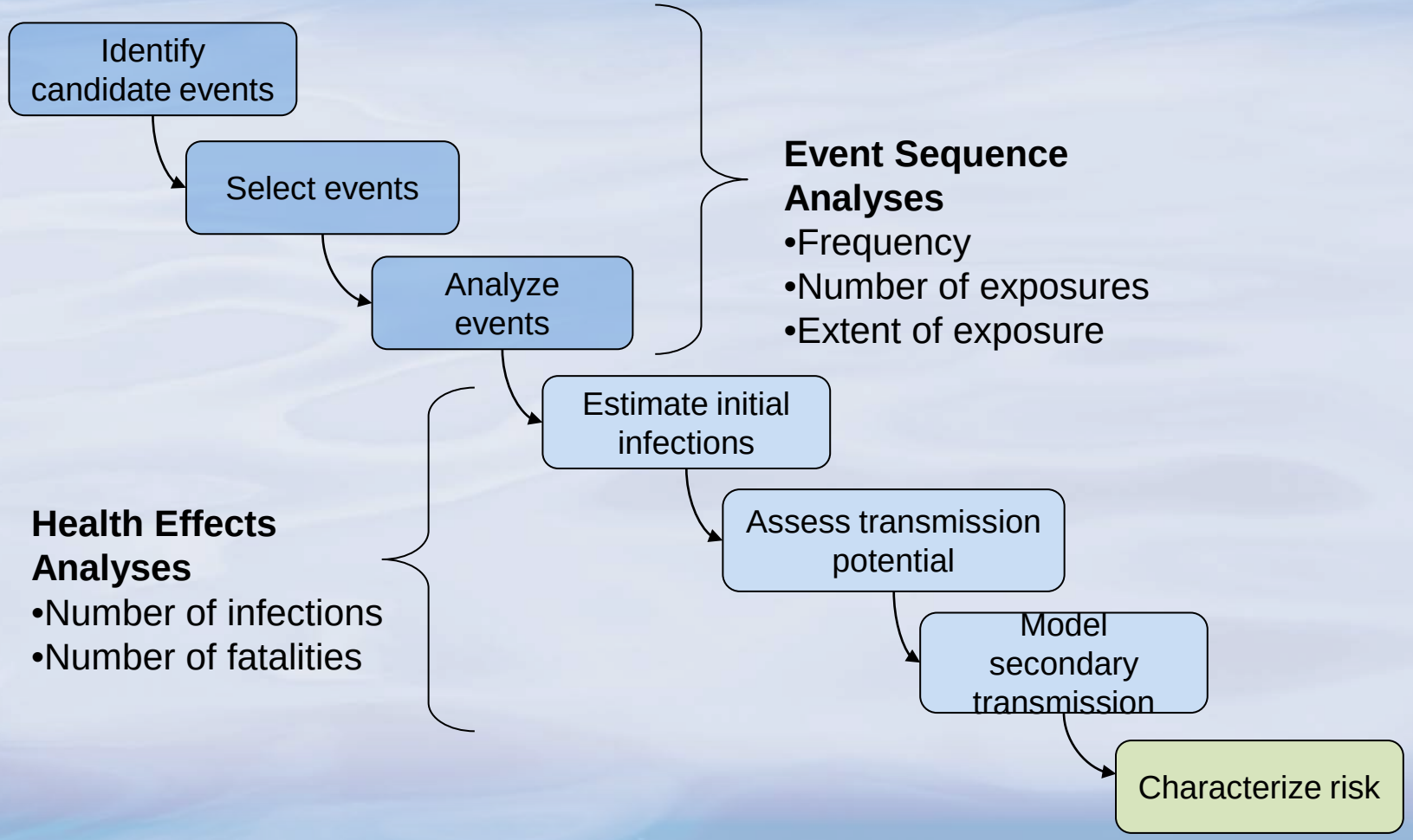
Number of Initial Infections	BEYOND REASONABLY FORESEEABLE	LOW	MODERATE	HIGH	ROUTINE
≥1	**100%**	-	-	-	-

Sensitivity analysis not necessary as uncertainty is low

Summary

- Approach to estimating initial infections
- For centrifuge events
  - With effective PAPR
    - ≥1 RVFV infection expected with moderate frequency
      1 in 2000 years
    - ≥1 SARS-CoV infection beyond reasonably foreseeable
      <1 in 1 million years
  - With degraded PAPR
    - ≥1 RVFV infection expected with moderate frequency
    - ≥1 SARS-CoV infections expected with low frequency
      I in 300,000 years
- For an earthquake
  - ≥1 RVFV or SARS-CoV infections are beyond reasonably foreseeable

Process Overview



Health Effects

- Follow-on from Event Sequence
- Estimate initial infections
- **Assess transmission potential**
- Model secondary transmission
- Summary

Assess transmission potential

- Potential event sequences leading to transmission
- Transmission potential of pathogens
- Example event-pathogen pairs considered

Event sequences leading to secondary transmission

- Operational Events
  - Event leads to exposure of lab/facility worker(s)
  - Exposure results in infection
  - Exposure/infection is undetected or unreported
  - Infectious worker interacts with contacts
- Maximum Reasonably Foreseeable Event
  - Event leads to direct exposure of the public
  - Exposure results in infection(s)
  - Infectious individuals interact with contacts

Secondary Transmission Potential of Pathogens

- Rift Valley Fever Virus (RVFV)
  - No direct human-human transmission described
- SARS-associated Coronavirus (SARS-CoV)
  - Direct human-human transmission possible

Example Event-Pathogen Pairs Considered

Event	Pathogen	Frequency Category for ≥1 Initial Infection	Potential for Secondary Transmission?
Centrifuge aerosol release with PAPR	RVFV	Moderate	NO
	SARS-CoV	Beyond Reasonably Foreseeable	NO
Centrifuge aerosol release with degraded PAPR	RVFV	Moderate	NO
	SARS-CoV	**Low**	**YES**
Earthquake	RVFV	Beyond Reasonably Foreseeable	NO
	SARS-CoV	Beyond Reasonably Foreseeable	NO

Health Effects

- Follow-on from Event Sequence
- Estimate initial infections
- Assess transmission potential
- **Model secondary transmission**
- Summary

Model Secondary Transmission

- Recap of transmission modeling approach
- Modeling SARS-CoV transmission
  - Base case assumptions and results
  - Uncertainty and sensitivity analysis
- Site differences in vulnerable sub-populations

Recap of Transmission Modeling Approach

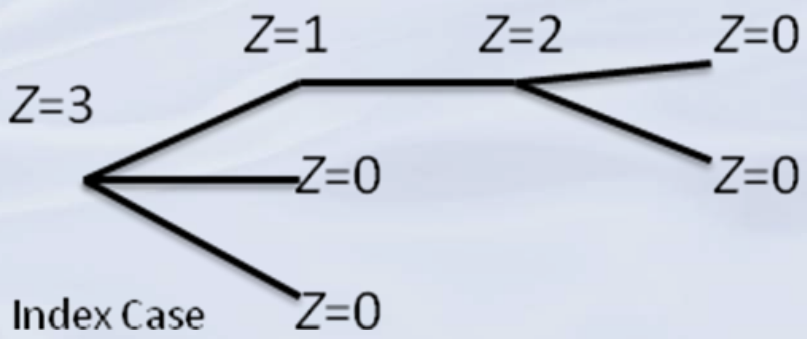
- Use branching process modeling
  - Probabilistic and individual-based
  - Well-suited to modeling small outbreaks
  - Impose variability in individual transmission
  - Incorporate mitigation and demographics
- Transition to compartmental modeling as needed
  - For handling large outbreaks

Basic Reproduction Number (R_0)

- Key parameter for transmission modeling
- Definition of R_0
  - *The average number of transmissions per infected individual in a fully susceptible population, in the absence of interventions to control transmission*
- Apply to early generations of transmission in simulations
- Use values derived from outbreak data and ratified by panel of experts

Recap of branching process modeling

- Infected individuals given reproductive number
  - Expected number of transmissions
  - Mean R_0, with distribution around R_0
  - k_0 constant determines shape of distribution
- Example simulation result:



Z = number of transmissions (based on reproductive number)

Lloyd-Smith *et al.*, Nature (2005)

Control Measures in Branching Process

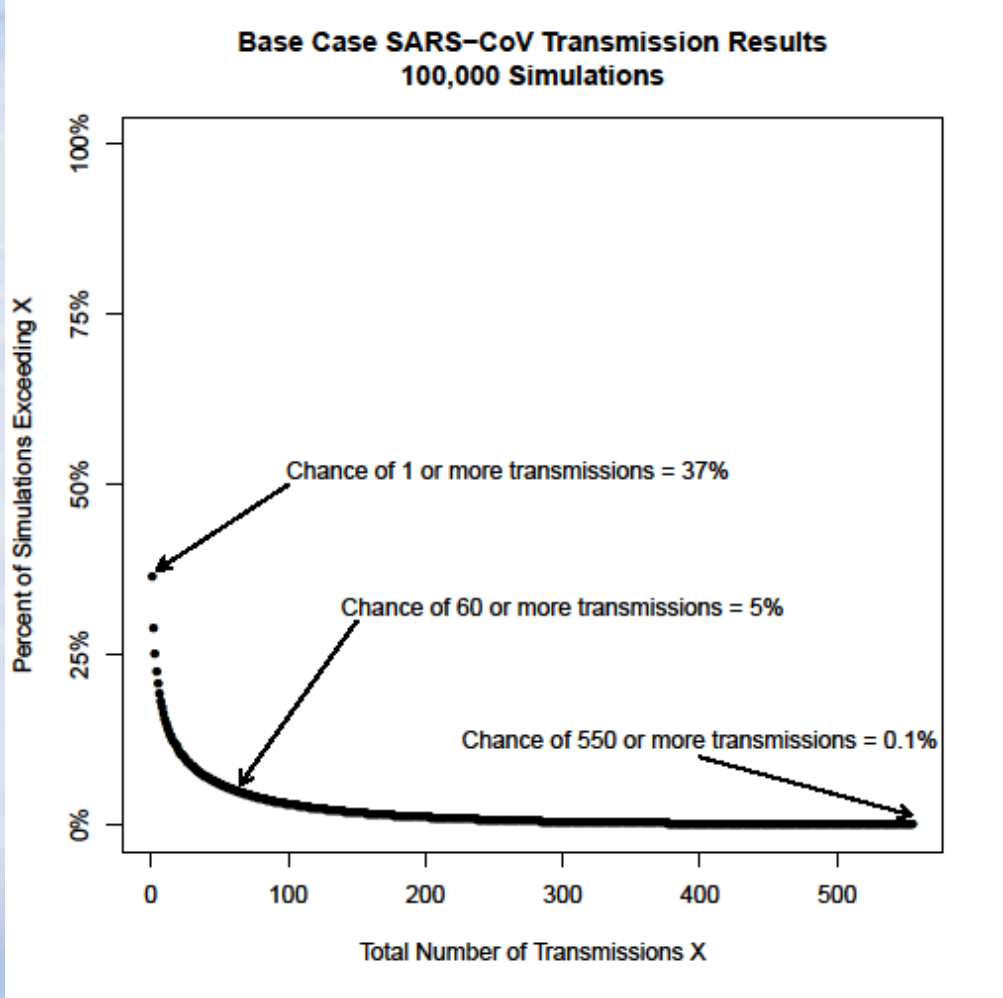
- Modeling effect of public health intervention
  - Quarantine, isolation in hospitals
- Switch reproductive number parameters post-implementation of control
  - R_0 changed to R_c – the control reproductive number
  - k_0 changed to k_c
- Incorporate control time in simulations
  - Choose time delay after first case onset
  - Switch to new parameters after control time

Modeling SARS-CoV Base Case Parameter Values

Parameter		Distribution of Values
Individual reproductive number	Pre-control	Gamma distribution R_0 = 3.0 (mean), k_0 = 0.15 (shape)
	Post-control	Gamma distribution R_c = 0.7 (mean), k_c = 0.07 (shape)
Generation time* (in days)		Weibull distribution mean = 8.4, shape = 2.35
Delay in implementation of control measures		3 days

*Generation time = time between onset of symptoms of primary case and onset of symptoms of secondary case

Base Case SARS-CoV Secondary Transmission Results



Uncertainty Analysis Procedure

- Construct a distribution for each parameter using
  - Base case as most likely (mode)
  - Range extremes as minimum, maximum
- Give lower weight to values near extremes
- Randomly sample values from each distribution using Latin Hypercube Sampling

Parameter Uncertainty (SARS-CoV)

Parameter	Base Case Value	Range Tested
R_0	3.0	(2.0, 4.0)
k_0	0.15	(0.05, 0.64)
R_c	0.7	(0.3, 1.0)
k_c	0.07	(0.01, 0.41)
T_G mean	8.4 days	(5, 12)
T_G shape	2.35 days	(1.35, 3.35)
T_C	3 days	(1, 10)

T_G = Generation time; T_C = Delay in control

Uncertainty Results (SARS-CoV)

Output	Base Case	90% Uncertainty Interval*
Probability of at least one transmission	0.37	(0.25, 0.58)
95th percentile number of transmissions	60	(40, 200)

*90% of input combinations result in output values in interval

Sensitivity Analysis (SARS-CoV)

- Output: *Probability of one or more transmissions*
  - Relevant input parameters: R_0 and k_0
  - Output strongly positively correlated with both inputs
- Output: *95th percentile number of transmissions*
  - All input parameters relevant
  - Output most influenced by parameters R_c and R_0

Frequency of Full Sequence
(Laboratory Release to Public Transmission)

- Pathogen: SARS-CoV
- Event: Centrifuge Aerosol Release With Degraded PAPR (assume undetected/unreported)

3 Steps: Exposure to Initial Infection to Public Transmission

Frequency of Lab Worker Exposure (per time) × **Frequency of Worker Infection (per exposure)** × **Frequency of Transmissions (per worker infection)**

= **Frequency of Full Event Sequence (per time)**

Frequency of Full Sequence – Base Case (Laboratory Release to Public Transmission)

- Pathogen: SARS Co-V
- Event: Centrifuge Aerosol Release With Degraded PAPR

Frequency of 1 Worker Exposure	Frequency of 1 Worker Infection (Given Exposure)	Frequency of Transmissions (Given Worker Infection)		Frequency of Full Sequence*	Frequency Category
1 in 1000 yrs (1/100 to 1/10000)	1 in 300	≥1	1 in 3	1 in 900,000 yrs (1/90k to 1/9m)	Low
		≥5	1 in 5	1 in 1.5 million yrs (1/150k to 1/15m)	Beyond Reasonably Foreseeable

*Product of frequencies in 1st three columns

Frequency of Full Sequence – Uncertainty (Laboratory Release to Public Transmission)

- Pathogen: SARS-CoV
- Event: Centrifuge aerosol release with degraded PAPR

Number of Secondary Infections	BEYOND REASONABLY FORESEEABLE	LOW	MODERATE	HIGH	ROUTINE
≥1	90%	**10%**	-	-	-
≥5	**95%**	5%	-	-	-

Site Differences in Vulnerable Sub-populations

- Vulnerable sub-populations and susceptibility
- Vulnerable sub-populations near the three sites
- Accounting for vulnerable sub-populations in site-specific secondary transmission

Vulnerable Sub-populations and Susceptibility

- Increased susceptibility of sub-populations could affect value of reproductive numbers (R_0 and R_c)
- Median values from expert solicitation (viruses)

Sub-population	Increased Susceptibility*
Children under 5	20%
People over 65	22.5%
Diabetic	15%
HIV-infected	30%
Pregnant women	5%

*compared to a healthy adult

Vulnerable Sub-populations Near 3 Sites

- Estimated proportion of populations containing sub-groups

Sub-population	U.S. (%)	Boston City (%)	Urban Site (%)	Suburban Site (%)	Rural Site (%)
Children under 5	7	6	4	9	5
People over 65	13	10	8	7	20
Diabetic	6	9	13	8	7
HIV-infected	0.5	0.9	1.6	0.2	0.1
Pregnant	1	1	1	1	1

Accounting for Vulnerable Sub-populations

Assumptions for adjusting *R* values for site-specific transmission

- Baseline *R* value relevant for U.S. population
- Site-specific adjusted values assume
  - Probability that a random contact is from a sub-group = proportion of local population in that group
  - Probability of transmission per contact changes by increased susceptibility

Accounting for Vulnerable Sub-populations

- Adjusted, site-specific transmission values

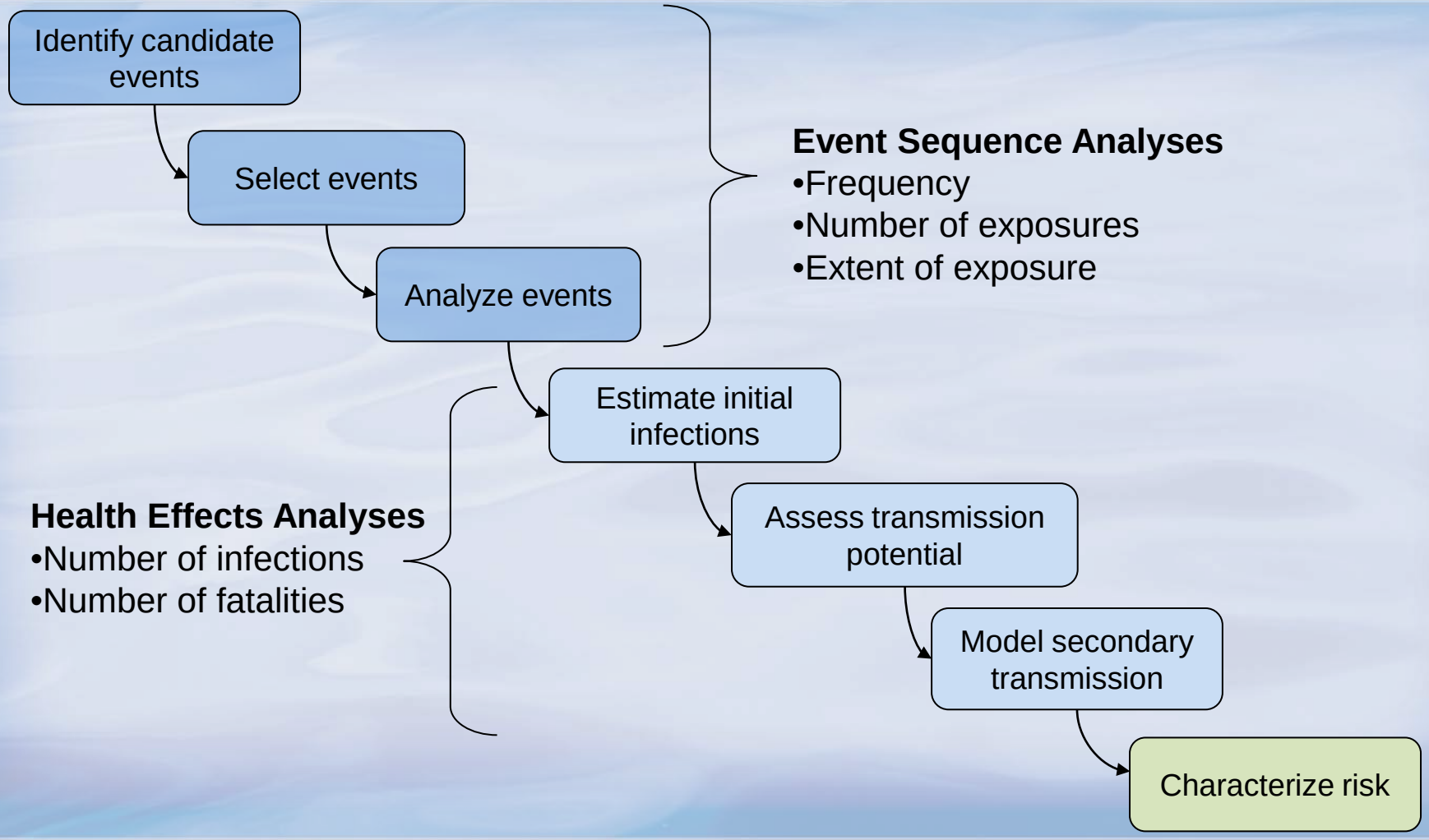
	U.S.	Boston city	Urban site	Suburban site	Rural site
R_0	3.000	2.999	2.993	2.980	3.039
Prob. of > 0 transmissions	36.7%	36.7%	36.6%	36.6%	36.8%

- Higher HIV-infected, diabetic urban population offset by higher elderly rural population
- Overall – R_0 differences too small to cause significant difference in transmissions
  - Overwhelmed by R_0 uncertainty range (2-4)

Summary

- One event – pathogen pairing could lead to transmissions
  - Centrifuge aerosol release with degraded PAPR
  - SARS-associated coronavirus
- Given an undetected / unreported worker infection
  - About 2/3 chance of no transmissions occurring
  - About 1/3 chance of at least one transmission
- Frequency of full sequence (lab release to transmission)
  - ≥1 transmission frequency is LOW (1 in 900,000 years)
  - Larger outbreaks beyond reasonably foreseeable
  - (<1 in 1 million years)
- Differences in vulnerable sub-populations across sites do not cause significant site differences in estimated transmissions

Process Overview



Approach to Risk Characterization

- Risk is a function of frequency and consequence
  - Three NRC questions
- General methodology
  - Hazard identification
  - Exposure and dose-response assessment
  - Synthesis of findings to characterize risk
- Approach includes
  - Risk to public from operational & max reasonably foreseeable events
  - Differential risk among alternative sites

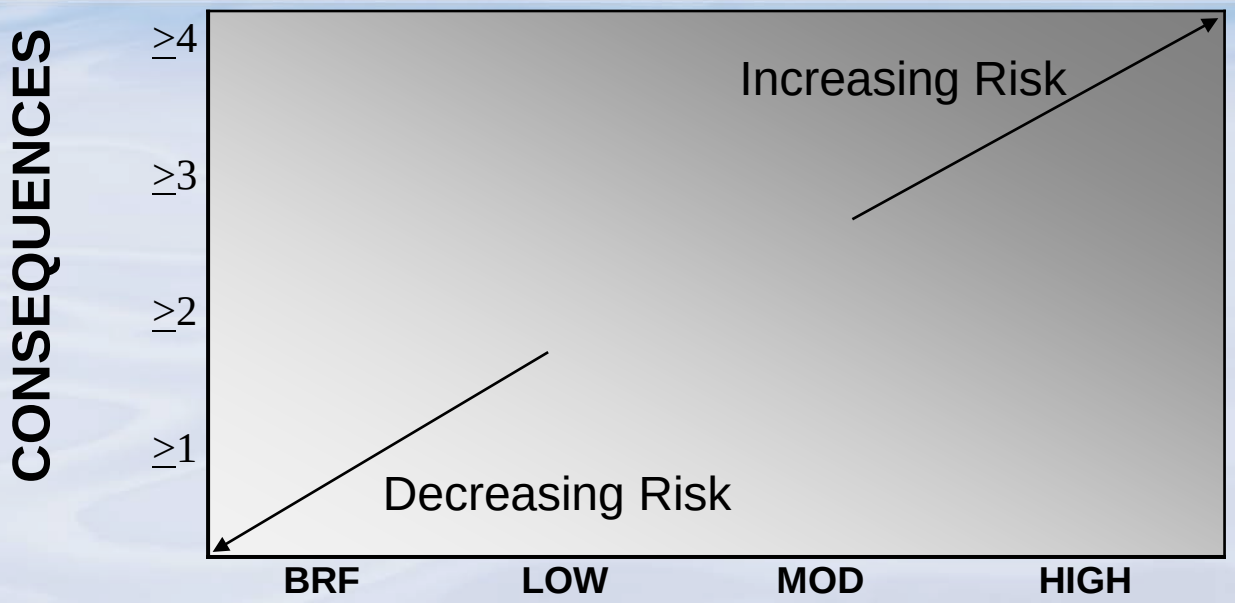
Framework

Risk	Analysis	Frequency	Consequences
Stage 1	**Event sequence:** What is the risk of exposure from an event?	Of event	Number and extent of exposures
Stage 2	**Initial Infections:** What is the risk of initial infection given an exposure event?	Of initial infections	Initial infections
Stage 3	**Secondary Transmission:** What is the risk of secondary transmission given an initial infection?	Of secondary transmissions	Secondary infections

Summary of Operational Events

BSL3 Centrifuge Event	Pathogen	Number of Events Expected Per Facility Lifetime of 50 years	Rate of Initial Infections Given Event	Rate of Secondary Transmissions Given Initial Infection
Centrifuge aerosol release with PAPR	RVFV	0.5 to 50	1 in 200 events	0
	SARS-CoV	0.5 to 50	0	0
Centrifuge aerosol release with degraded PAPR	RVFV	0.005 to 0.5	1 in 4 events	0
	SARS-CoV	0.005 to 0.5	1 in 300 events	1 in 3 initial infections

Risk Matrix Display



FREQUENCY

Product of frequencies of event, initial infections and secondary transmissions

Return period (yrs):	>1 million yrs	>10,000 to ≤1,000,000 yrs	>100 to ≤10,000 yrs	>1 to ≤100 yrs

Centrifuge Event Risk Matrices

RVFV With PAPR

	BRF	Low	Mod.	High
≥4	I S			E
≥3	I S			E
≥2	S	I		E
≥1	S		I	E

RVFV With Degraded PAPR

	BRF	Low	Mod.	High
≥4	E I S			
≥3	E I S			
≥2	E I S			
≥1	S		E I	

SARS-CoV With PAPR

	BRF	Low	Mod.	High
≥4	I S			E
≥3	I S			E
≥2	I S			E
≥1	I S			E

SARS-CoV With Degraded PAPR

	BRF	Low	Mod.	High
≥4	E I S			
≥3	E I S			
≥2	E I S			
≥1		I S	E	

E= Exposures in lab workers; I= Initial infections in lab workers; S= Secondary infections in the public

Summary of Max. Reasonably Foreseeable Event

Max. Reasonably Foreseeable Event	Pathogen	Number of Events Expected Per Facility Lifetime of 50 years	Rate of Initial Infections Given Event	Rate of Secondary Transmissions Given Initial Infection
Earthquake	RVFV	0.005 to 0.00005	1 in 1000 events	0
	SARS Co-V	0.005 to 0.00005	1 in 10,000 events	1 in 3 initial infections

Urban population

- Daytime and resident

	Urban daytime population	Urban residents
People within 0.5 km	25,333	2,904
People inhaling 1 particle (RVFV)	16	2
People inhaling 1 particle (SARS-CoV)	<1	<1

Earthquake Event Risk Matrices

RVFV – Urban daytime population

	BRF	Low	Mod.	High
≥22	E I S			
≥21	I S	E		
≥5	I S	E		
≥4	I S	E		
≥2	I S	E		
≥1	I S	E		

SARS-CoV – Urban daytime population

	BRF	Low	Mod.	High
≥22	E I S			
≥21	E I S			
≥5	E I S			
≥4	E I S			
≥2	E I S			
≥1	I S	E		

RVFV - Urban resident population

	BRF	Low	Mod.	High
≥22	E I S			
≥21	E I S			
≥5	E I S			
≥4	I S	E		
≥2	I S	E		
≥1	I S	E		

SARS-CoV - Urban resident population

	BRF	Low	Mod.	High
≥22	E I S			
≥21	E I S			
≥5	E I S			
≥4	E I S			
≥2	E I S			
≥1	E I S			

E= Exposure to the public ; I= Initial infections in the public;
S= Secondary infections in the public

Potential site differences

- Operational events and initial infections
  - No difference between sites as NEIDL operations are assumed to be identical at alternative sites
- Max Reasonably Foreseeable event
  - No difference in earthquake event frequency as all sites are in relatively low hazard area
  - Potential site differences
    - Number of expected exposures to RVFV and SARS-CoV based on meteorology and population density

Site differences: Population

	Urban (daytime population)	Urban (residents)	Suburban (residents)	Rural (residents)
People within 0.5 km	25,333	2,904	225	12
People inhaling 1 particle (RVFV)	16	2	<1	<1
People inhaling 1 particle (SARS-CoV)	<1	<1	<1	<1

Risk Comparison of RVFV at 3 sites

Urban daytime population

	BRF	Low	Mod.	High
≥22	E I S			
≥21	I S	E		
≥5	I S	E		
≥4	I S	E		
≥2	I S	E		
≥1	I S	E		

Urban resident population

	BRF	Low	Mod.	High
≥22	E I S			
≥21	E I S			
≥5	E I S			
≥4	I S	E		
≥2	I S	E		
≥1	I S	E		

Suburban Site

	BRF	Low	Mod.	High
≥22	E I S			
≥21	E I S			
≥5	E I S			
≥4	E I S			
≥2	E I S			
≥1	I S	E		

Rural Site

	BRF	Low	Mod.	High
≥22	E I S			
≥21	E I S			
≥5	E I S			
≥4	E I S			
≥2	E I S			
≥1	E I S			

E= Exposure to the public ; I= Initial infections in the public;
S= Secondary infections in the public

Risk Comparison of SARS Co-V at 3 sites

Urban daytime population

	BRF	Low	Mod.	High
≥22	E I S			
≥21	E I S			
≥5	E I S			
≥4	E I S			
≥2	E I S			
≥1	I S	E		

Urban resident population

	BRF	Low	Mod.	High
≥22	E I S			
≥21	E I S			
≥5	E I S			
≥4	E I S			
≥2	E I S			
≥1	E I S			

Suburban Site

	BRF	Low	Mod.	High
≥22	E I S			
≥21	E I S			
≥5	E I S			
≥4	E I S			
≥2	E I S			
≥1	E I S			

Rural Site

	BRF	Low	Mod.	High
≥22	E I S			
≥21	E I S			
≥5	E I S			
≥4	E I S			
≥2	E I S			
≥1	E I S			

E= Exposure to the public ; I= Initial infections in the public;
S= Secondary infections in the public

Potential Site Differences

- Secondary transmission
  - Number of secondary transmissions small relative to size of local populations
  - No significant site differences expected
- Differences in vulnerable sub-populations
  - No significant difference in R_0 adjusted for vulnerable sub-populations at the three sites
    - Offset by vulnerable sub-population variation
  - Overall no significant site differences expected

Summary

- Discussed three examples of operational and max. reasonably foreseeable events
- Preliminary results
  - BSL-3 centrifuge event with degraded PAPR/SARS-CoV
    - Risk of ≥1 infection in the public is low (1 in 900,000 yrs)
    - Risk of ≥2 infections in the public is BRF (1 in >1 million yrs)
  - For all other analyzed event-pathogen pairs
    - Risk of ≥1 infection in the public is BRF (1 in >1 million yrs)
- Analyses of remaining events and pathogens in progress