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# National Emerging Infectious Diseases Laboratories Risk Assessment

**NIH Blue Ribbon Panel**
**Boston Community Meeting**
**April 28, 2010**

TETRA TECH

# Presentations

## Selection and Analysis of Pathogen Release Events

**Ken Bulmahn, P.E.**

## Modeling of Pathogen Transmission and Health Effects

**Adi Gundlapalli, M.D., Ph.D., M.S.**

# Introduction: Risk Assessment in General

As defined by the U.S. Environmental Protection Agency (EPA)

- **Risk** is “the chance of harmful effects occurring to human health or to ecological systems”
- **Risk assessment** is the process used “to characterize the nature and magnitude of health risks to humans” and ecological systems

http://epa.gov/riskassessment/basicinformation.htm#risk

# Introduction: Risk Assessment for the NEIDL

- What could potentially go wrong?
  - Types and probabilities of events that could lead to a release
  - Number of workers and members of the public that may be exposed if a release occurs
  - Extent to which people may be exposed
- What are the consequences if there is a release?
  - Infections and fatalities in workers and the public

# Introduction: NEIDL Risk Assessment Scope

- Considers 13 pathogens that are representative of those anticipated to be studied at NEIDL
- Addresses risk of pathogen exposure
  - Directly to workers and the public
  - Indirectly through secondary transmission to the public
- Analyzes urban, suburban and rural sites
- Based on accepted scientific methodologies

# Introduction: Risk Assessment Process Overview

Step 1. Identify candidate events

Step 2. Select event-pathogen pairs

Step 3. Analyze events

**Release Event Analyses**

- Frequency of events
- Number of people exposed
- Extent of exposure

Step 4. Estimate initial infections

Step 5. Assess transmission potential

Step 6. Model secondary transmission

Step 7. **Characterize risk**

**Health Effects Analyses**

- Number of infections
- Number of fatalities

# *Selection and Analysis of Pathogen Release Events*

**Ken Bulmahn, P.E.**

Risk Assessment Team Lead, Tetra Tech

# Release Event Analyses

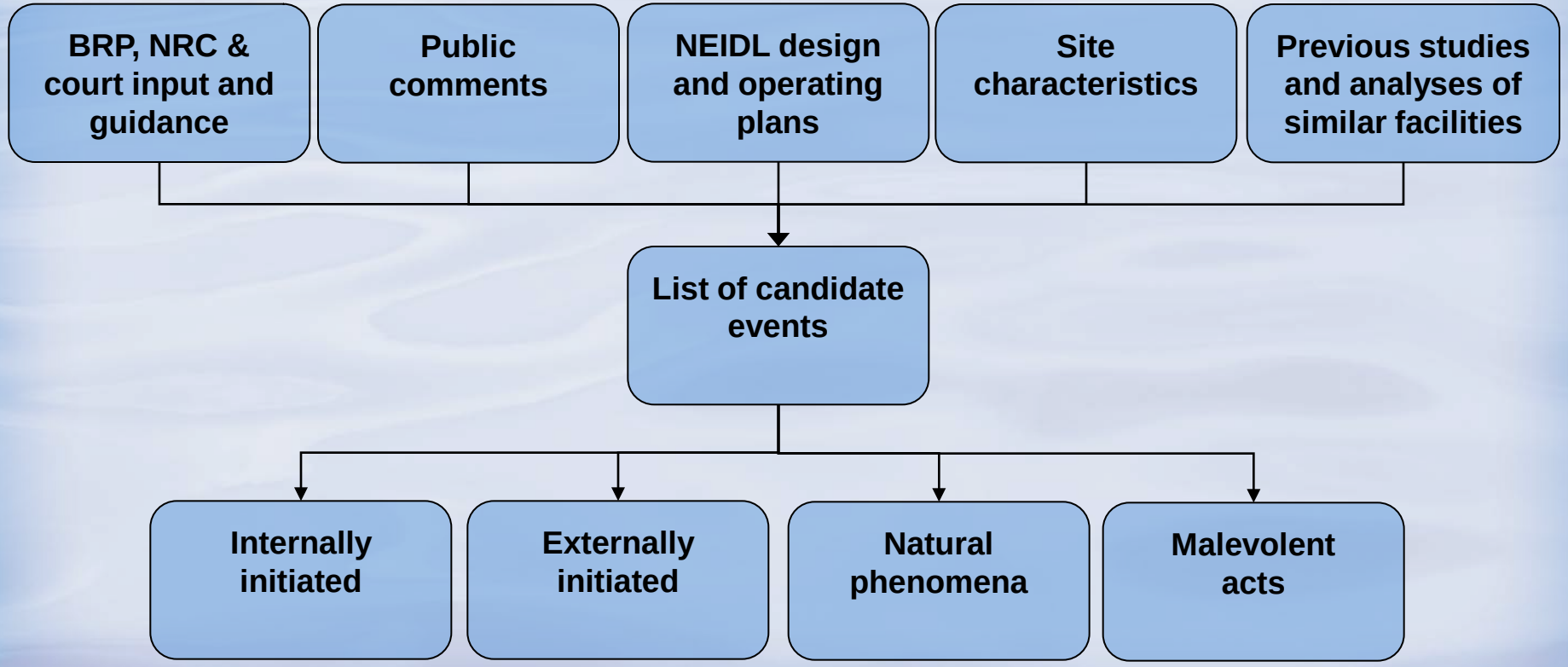
- Identify, select and analyze events
- Includes
  - Variety of plausible events
  - Highly unlikely but credible, high-consequence events (i.e., maximum reasonably foreseeable)

# Maximum Reasonably Foreseeable Events

- Includes potentially catastrophic events
- Includes low probability events that are
  - Supported by credible scientific evidence,
  - Not based on pure conjecture, and
  - Within the rule of reason

    (National Environmental Policy Act)
- Generally sufficient to consider events occurring more than once per million years

# Step 1. Identify Candidate Events



# Step 2: Select Event-Pathogen Pairs

- Step 2a: Define Event Sequence
- Step 2b: Assign Event Categories
- Step 2c: Estimate Event Frequencies
- Step 2d: Select Events for Detailed Analysis
- Step 2e: Select Relevant Pathogens

# Step 2a. Define Event Sequences

- Initiating event as well as subsequent events
- Effect of preventive and mitigative features
  - Administrative controls (e.g., training, procedures)
  - Safety equipment (e.g., respiratory protection)
  - Facility (e.g., ventilation)
- Identification of possible exposures

# Step 2b: Assign Event Categories

| | |
|---|---|
| Point of Release: | → **BSL-3**<br>→ **BSL-4**<br>→ **Other internal areas**<br>→ **External areas** |
| Potentially Exposed Groups: | → **Laboratory worker**<br>→ **Facility worker**<br>→ **Public** |
| Initial Route of Exposure: | → **Direct contact**<br>→ **Inhalation**<br>→ **Ingestion**<br>→ **Sharps/punctures**<br>→ **Animal related** |

# Step 2c: Estimate Event Frequencies

| Category | Frequency |
|---|---|
| Routine | Yearly |
| High | Once per 100 years |
| Moderate | Once per 10,000 years |
| Low | Once per million years |
| Not reasonably foreseeable | Less than once per million years |

# Step 2d: Select Events for Detailed Analysis

## Criteria for Event Selection

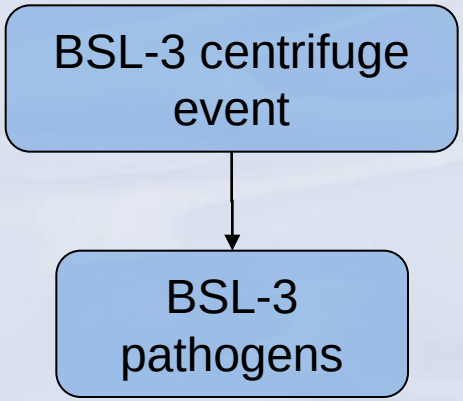
- Range of frequencies
- Events must address all
  - Points of release
  - Potentially exposed groups
  - Initial routes of exposure
- Address differences between
  - Pathogens
  - Sites

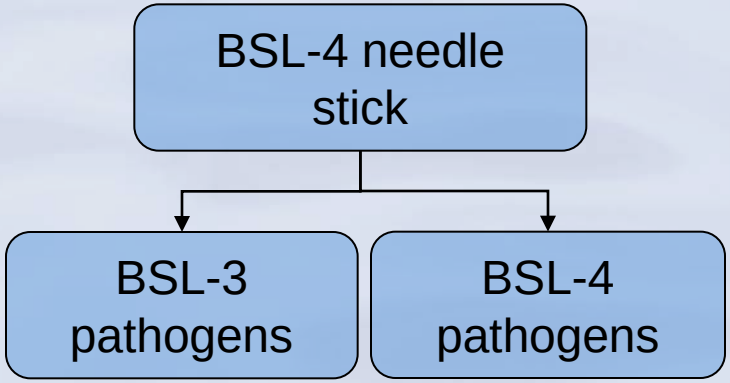
# Example Events

- Needle stick
  - Lab worker is exposed
  - Exposure is undetected or unreported
- Centrifuge release
  - Aerosol is released from centrifuge
  - Respiratory protection fails to protect workers
  - Exposure is undetected or unreported
- Earthquake
  - Event leads to direct exposure of members of public
  - Potential escape of animal

# Step 2e: Select Relevant Pathogens

- Consider all 13 pathogens for each event
- Select all pathogens that are relevant for the event



# Step 3: Analyze Events

Determine

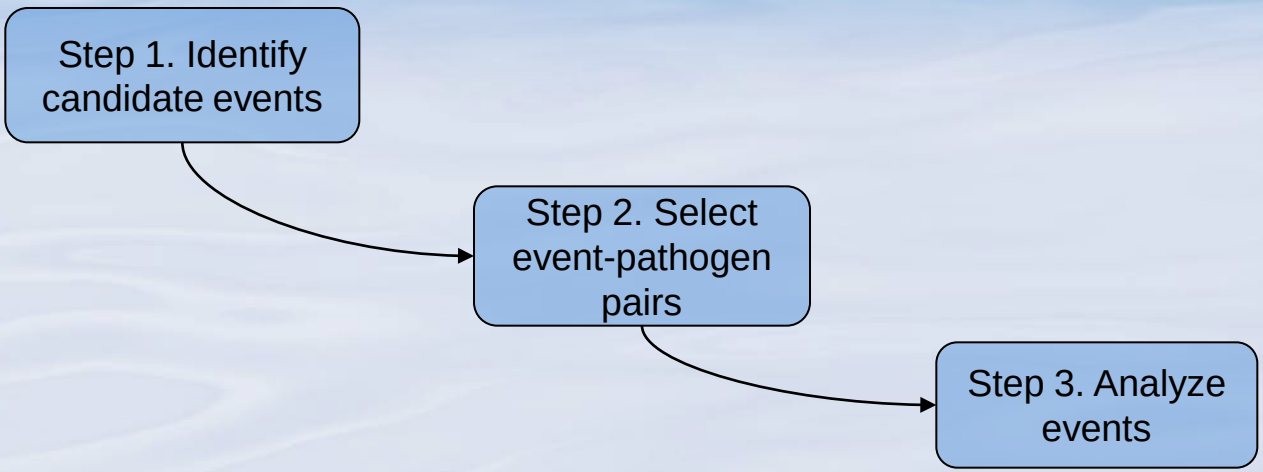
- Number of people potentially exposed, for example
  - 2 - 4 lab workers
  - Public within 200 meters of the facility
- Extent of exposure, for example
  - Potential exposure to 1 - 1,000 *Y. pestis* bacteria

# Release Event Analysis Results

*<u>Example</u>: BSL-3 Centrifuge event*

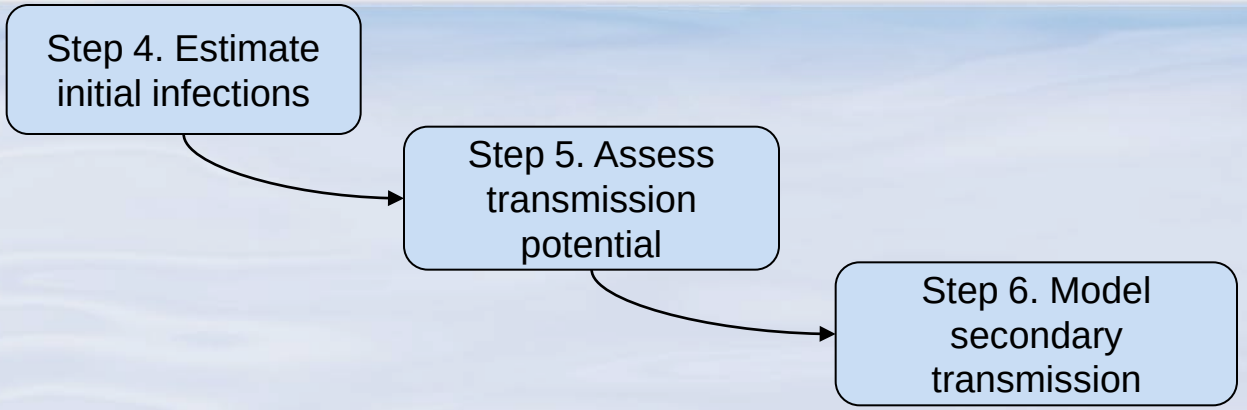
| | |
|---|---|
| Frequency: | High |
| Route of exposure: | Inhalation |
| Exposed group: | 1 - 4 Lab workers |
| Extent of exposure: | Pathogen specific |
| Pathogen 1: | 1 - 10 particles |
| Pathogen 2: | 1 - 1,000 particles |

# Summary: Release Event Analyses




- Summarize type of events that could occur
- Estimate probabilities of those events
- Estimate exposures to a pathogen

# Summary: Health Effects Analyses




- Generate estimates of initial infections
- Assess secondary transmission potential
- Select representative pathogens for transmission modeling
- Use established mathematical modeling approaches
- Present typical and high-consequence events
- Analyze differences between sites

# Summary: Risk Characterization

Step 7.
**Characterize risk**

- Present results
- Synthesize key findings
  - Summary of the event-specific risk to identified exposed groups
  - Potential differences between sites
  - Disproportionate impacts

# Discussion

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Step 7. **Characterize risk**

**Health Effects Analyses**

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- Number of fatalities

# Modeling of Pathogen Transmission and Health Effects

Adi Gundlapalli, M.D., Ph.D., M.S.
Modeling Lead, Tetra Tech

# Exposure *versus* Infection

An exposure *may* result in an infection based on

- Amount and route of exposure
  - Developed during the Release Event Analyses
- Pathogen characteristics
  - Human infectious dose
  - Particular strain of the pathogen
- Individuals exposed
  - Immune status of the individual
  - Increased susceptibility to disease

# Human Infectious Dose

- Knowledge of basic biology and diseases
- Estimating human infectious dose is challenging
  - The amount of pathogen required to cause infection
- From review of available scientific literature
  - Estimates for 4 of 13 pathogens
- Additional estimates to be generated by expert consultation
  - Formal process used in scientific research

# Step 4: Estimate Initial Infections

- Receive from Release Event Analysis
  - Probability of an event occurring
  - Quantity of pathogen released by event
- Estimate the probability that a given exposure will result in an infection
  - Relationship between the amount of exposure and the human infectious dose

# Step 4: Estimate Initial Infections (continued)

- Based on estimates of human infectious dose
- For a given number of exposed individuals
  - A fraction may become infected
  - A fraction of those infections may be fatal
- Uncertainty and sensitivity analyses
  - Assess the effect of changing the assumptions and input values on the outcomes

# Step 5: Assess Transmission Potential

- Secondary transmission
  - Process by which a pathogen would spread from the first infected person to another
  - Also refers to subsequent generations of transmissions
- Assess potential for secondary transmission
  - Qualitatively based on biology of pathogen
  - Quantitatively using mathematical modeling
- Assess Transmission Potential of all 13 pathogens

# Step 5: Assess Transmission Potential

- Possible scenario for secondary transmission
  - Direct human-to-human transmission
- Facility worker release event sequence

  *Example: centrifuge accident*
  - Event leads to exposure of a facility worker
  - Exposure results in infection
  - Exposure and/or subsequent infection is undetected or unreported
  - Infectious worker interacts with others

# Step 5: Assess Transmission Potential

- Possible scenario for secondary transmission
  - Direct human-to-human transmission
- Direct-to-community event sequence

  *Example: earthquake or transportation accident*
  - Event leads to exposure of members of the public
  - Exposure results in multiple infections
  - Exposure and/or subsequent infection is undetected or unreported
  - Infectious individuals interact with others

# Step 5: Assess Transmission Potential

- Qualitative discussion of secondary transmission
- Direct human-to-human transmission
  - SARS-associated coronavirus
  - 1918 pandemic influenza virus
  - *Yersinia pestis* (pneumonic plague)
  - Andes hantavirus
  - Junin virus
  - Lassa fever virus
  - Marburg virus
  - Ebola virus
  - Nipah virus

# Step 5: Assess Transmission Potential

- Possible scenario for transmission via animals
  - From direct contact with infected animal from facility
  - Transmission from human-to-human via animals
- Escape of infected animal from facility

  *Example: earthquake damage to biocontainment*
  - Infected animal
    - Transmits disease directly to human
    - Establishes "reservoir" of pathogens in local environment
      - Potential for spread of infection to humans

# Step 5: Assess Transmission Potential

- Potential for a pathogen to establish a reservoir
  - An animal or inanimate substance in which a pathogen normally lives and multiplies
  - Examples of reservoirs
    - Environmental (e.g., soil)
    - Arthropod (e.g., mosquitoes, fleas, ticks)
    - Animal (e.g., rodents, ruminants)
- Importance to human health
  - Potential for transmission of pathogen to humans
- Analyze all 13 pathogens

# Step 5: Assess Transmission Potential

- Qualitative discussion
- Transmission of pathogens via animals
  - Establish reservoir in local environment
- Pathogens
  - *Yersinia pestis* (bubonic plague)
  - *Francisella tularensis*
  - Rift Valley fever virus
  - Tick-borne encephalitis complex (Russian spring-summer encephalitis virus)

# Step 5: Assess Transmission Potential

- Qualitative discussion
- No known human-to-human transmission
  - *Bacillus anthracis*

# Step 6: Model Secondary Transmission

**Mathematical modeling of secondary transmission**

- An established method for estimating
  - the range of outcomes that could occur if an infected individual interacts with others in the community
  - the extent of disease spread in the community
- Can address “what if…” questions in the absence of real life experience

# Step 6: Model Secondary Transmission

- Step 6a: Pathogen Selection
- Step 6b: Model Selection Criteria
- Step 6c: Description of models selected

# Step 6a: Pathogen Selection

- Pathogen selection criteria
  - Evaluated all 13 pathogens for transmission modeling
  - Published models and epidemiologic data
- Five pathogens chosen for mathematical modeling of secondary transmission
  - SARS-associated coronavirus
  - 1918 pandemic influenza virus
  - *Yersinia pestis* (plague)
  - Rift Valley Fever virus
  - Ebola virus
- Qualitative analysis of the others

# Step 6b: Model Selection Criteria

- Published and peer reviewed
- Adequate data for model inputs
- Clearly defined assumptions and results
- Suitable for scenarios relevant to NEIDL
  - Small and large scale accidents
  - Possibility of high-consequence outcomes
  - Effects of public health intervention
  - Differences between urban / suburban / rural sites

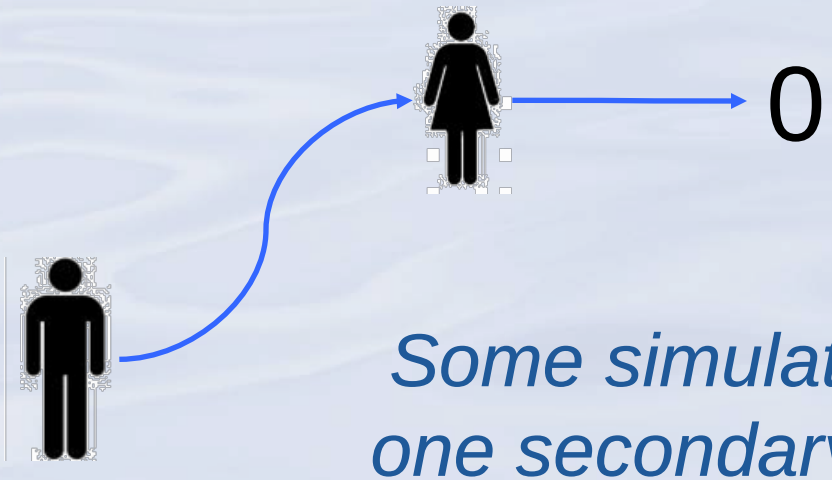
# Step 6c: Description of models selected

- Branching process modeling
  - Well-developed literature in epidemiology
  - Incorporates randomness
  - Accounts for individual differences in transmission
  - Suitable for <u>small</u> outbreaks
- Compartmental modeling
  - Widely published and well understood
  - Averages transmission rates over different groups
  - Suitable for <u>large</u> outbreaks

# Branching Process Modeling

*Most simulations result in no transmissions to others*

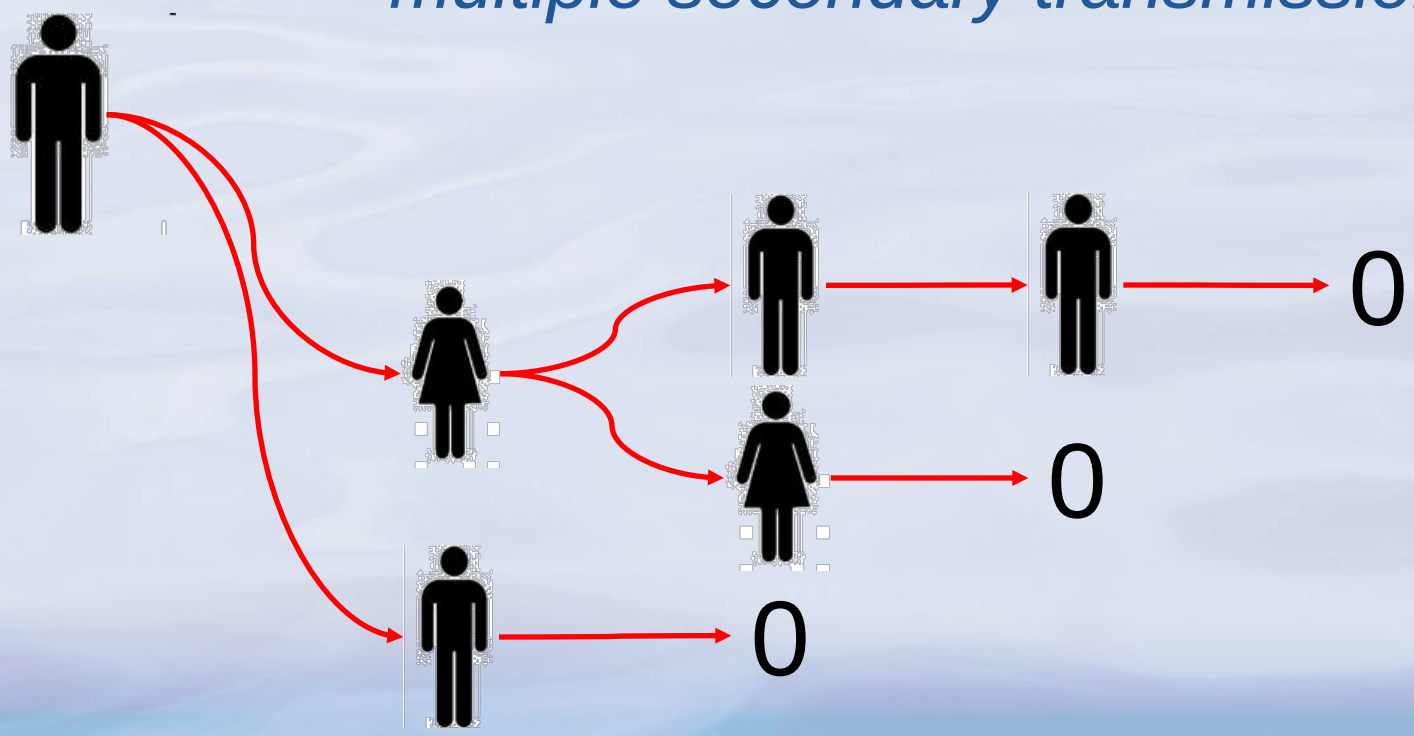
# Branching Process Model
## *Single Transmission*



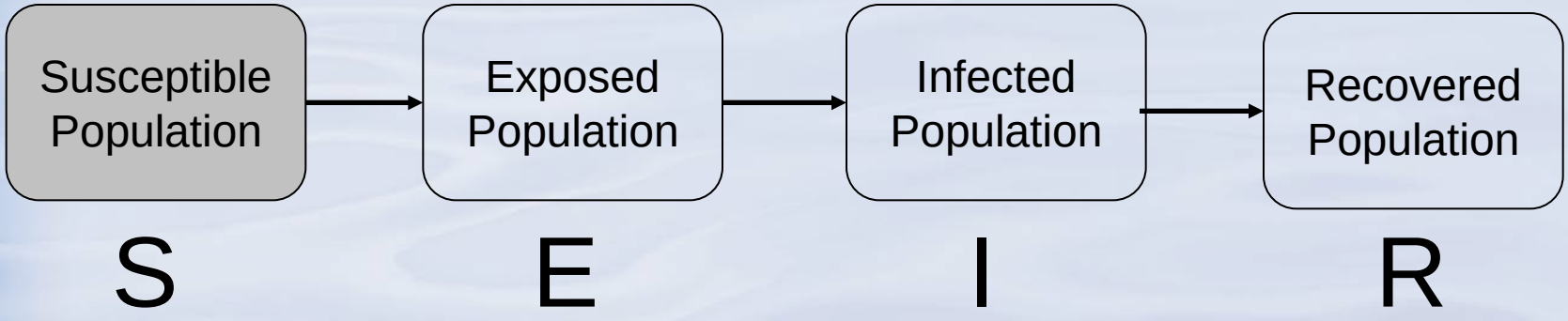

*Some simulations result in one secondary transmission*

# Branching Process Model
## *Multiple Transmissions*

*A few simulations result in multiple secondary transmissions*



# Compartmental Modeling

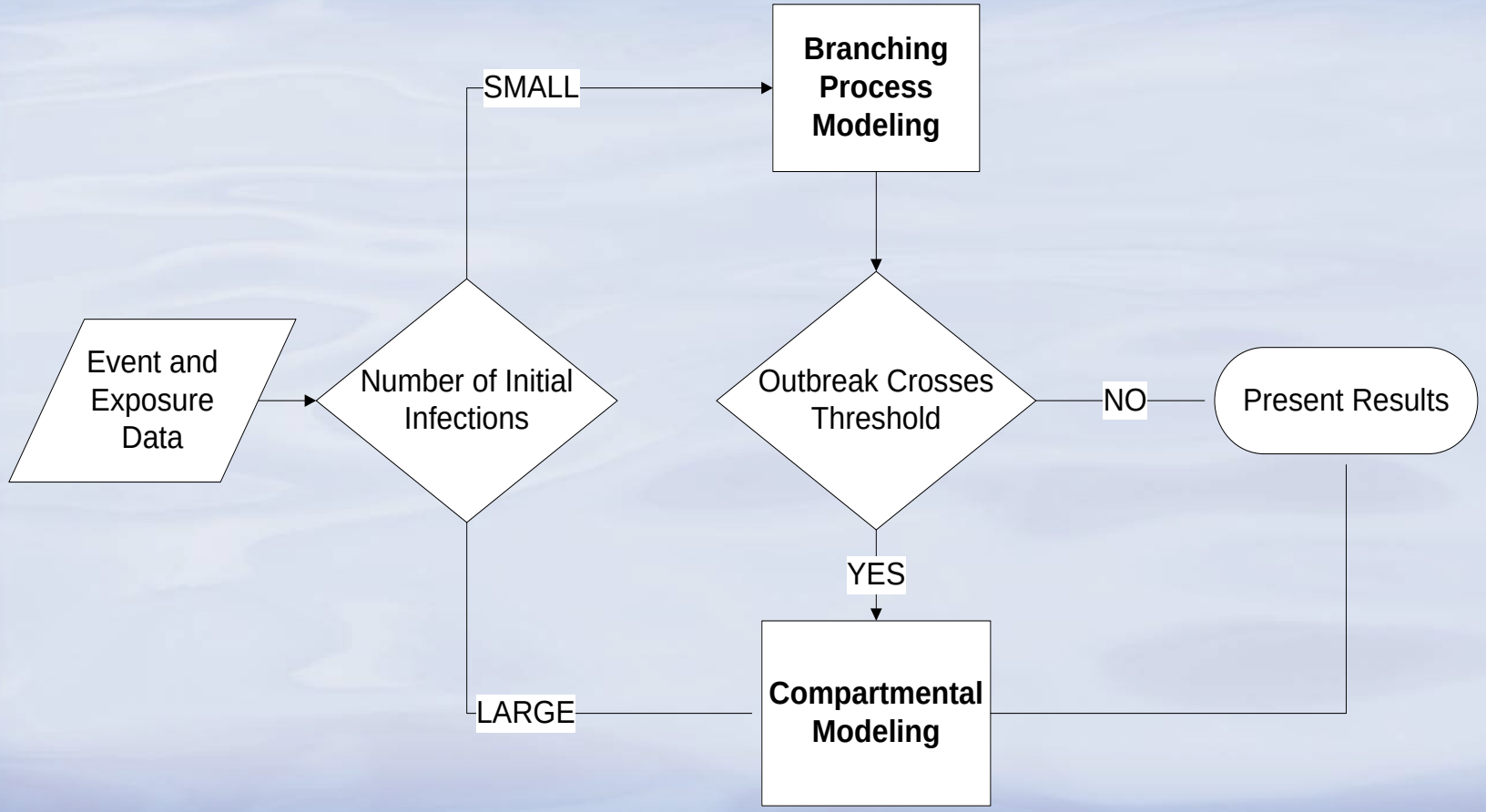



- Track changes in the number of individuals in each compartment
- Additional compartments are added as appropriate

# Hybrid Modeling Approach

- Uses both branching and compartmental models
  - Combines strengths of both models
  - Transitions from one to the other
- Criteria for transition
  - As number of infections exceeds a predefined threshold
  - When chance extinction of outbreak becomes unlikely
  - When large numbers of individuals are infected
- Potential scenarios
  - Modeling transmission in the absence of adequate control measures

# Hybrid Modeling Approach Overview



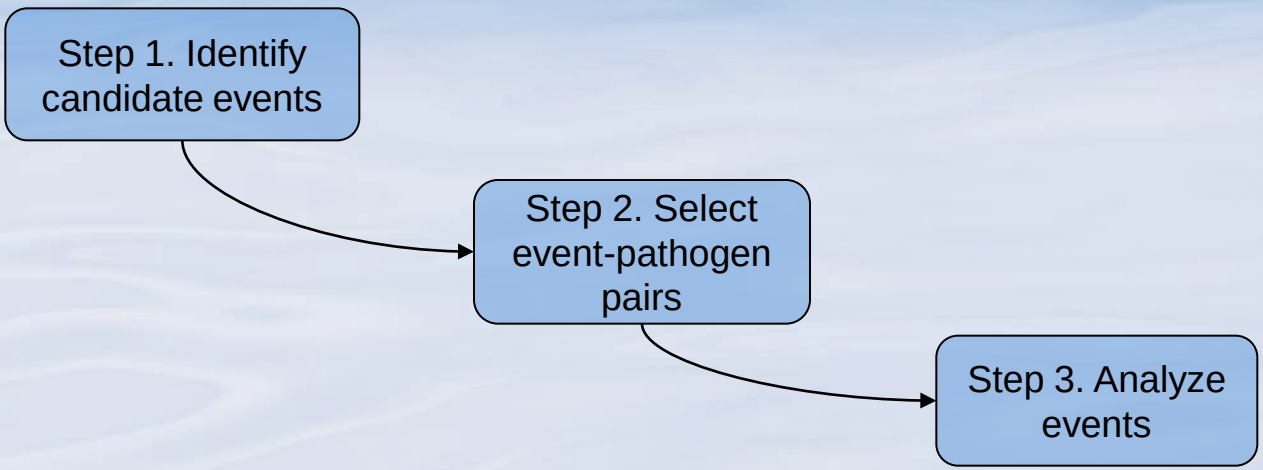
# Mathematical Modeling

- Tabulate results of simulations
- Statistical analyses of results
- Examine effect of mitigation strategies
- Apply demographic data
- High-consequence events
- Uncertainty and sensitivity analyses
  - Assess the effect of changing the assumptions and input values on the outcomes

# Secondary Transmission: Site Differences

- Size and density of surrounding population
- Facility worker commuting patterns
- Differences in social contact networks
  - Urban, suburban and rural settings
- Health status of local community
- Differential access to
  - Emergency and medical services
  - Public health services

# Summary: Release Event Analyses

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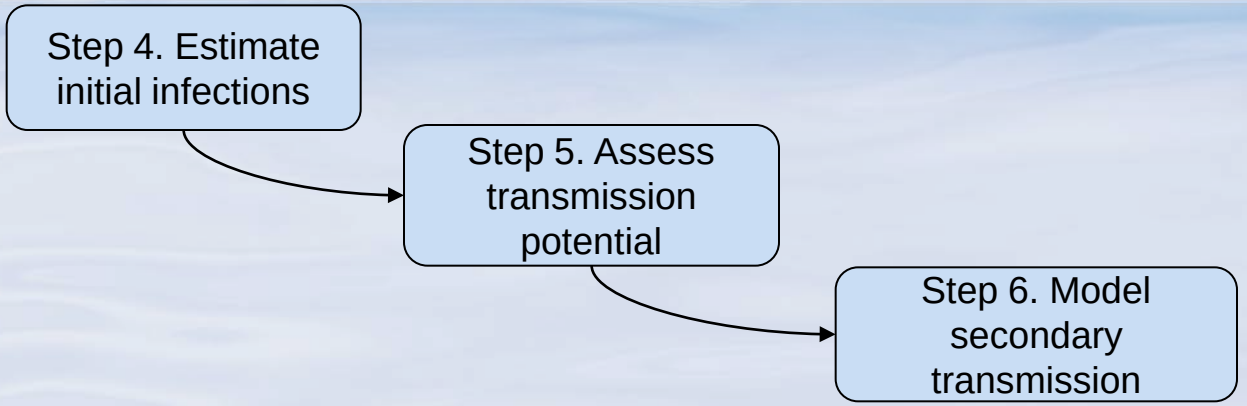


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