Risk-Risk Tradeoff Methods: Carcinogenicity/Sterilization with Ethylene Oxide (EtO) as an Example

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Ethylene Oxide Sterilization

- EtO is used to sterilize more than 50% of medical devices in U.S. (more than 20 billion annually)
  - Only method that effectively sterilizes without damaging many devices
- Preferred sterilization method in recent years because of its advantages over other technologies
  - Compatibility with wide range of materials and penetration properties
  - Particularly important since growth of single-use medical device market and with customized kits for specific medical and surgical procedures
  - Sterilization of multiple medical instruments/devices simultaneously in customized kits with multiple layers of packaging not easily penetrated by other sterilizing agents

Ethylene Oxide Regulatory Background

- EPA health assessment for ethylene oxide (EtO) in 1985

- EPA updated EtO IRIS assessment in December 2016
  - 30-fold increase in Inhalation Unit Risk Factor (IURF)

- New IURF used in the National Air Toxics Assessment (NATA)
  - Identified EtO emissions as a potential concern in areas across U.S.
    - Due to the 30-fold increase in IURF
    - EPA to identified commercial sterilization facilities using EtO as primary source category contributing these risks

- Led to EtO monitoring (24-hour) near sterilization plants
  - Use of 24-hour results and EPA's updated IURF to estimate theoretical cancer risks associated with long-term EtO exposure resulted in risks outside acceptable risk range of 1-in-1,000,000 to 1-in-10,000

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Problem Formulation

- Regulators and local communities focused on the direct benefit, decreased cancer risk, of decreased use/ban of EtO as sterilant
  - Countervailing risk of increased healthcare-associated infections (HAIs) has not been adequately considered

- Ban of EtO not entirely unlikely

- If EtO banned as sterilant, increased HAIs expected
  - Prepackaged procedure/surgical kits may become unavailable
    - Lack of a suitable alternative sterilizing agent that does not damage device materials and can penetrate multiple layers of packaging in kits
  - Sterilization of individual instruments/devices separately
    - Opening individually wrapped/enclosed medical supplies/instruments introduces source of contamination and repeated opening compounds potential for device contamination

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Preliminary Case Study – Risk-Risk Tradeoff

Theoretical Cancer Risk from EtO Emitted from Sterilization Plants

Vs

Increased Risk of Health Care-Associated Infection if EtO is Banned as Sterilant

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Preliminary Case Study – Risk-Risk Tradeoff (Continued)

- Estimate Cancer Risk

    Exposure Concentration ($\mu g/m^3$) ÷ Risk-Specific Concentration ($\mu g/m^3$)

    - Risk-Specific Concentrations (RSC) – 1-in-100,000 Cancer Risk

        - EPA IURF = 5E-03 $(\mu g/m^3)^{-1}$ EPA RSC = 0.002 $\mu g/m^3$
        - TCEQ IURF = 1.4E-06 $(\mu g/m^3)^{-1}$ TCEQ RSC = 7 $\mu g/m^3$

    - Exposure Concentrations

        - 24-hour ambient air samples in proximity to sterilization plants

        - Only EPA and local health/air pollution control department samples used

        - All EtO data used together as a single dataset for overall 95% Confidence Limit (UCL)

            - Estimated UCL = 1.2 $\mu g/m^3$

Preliminary Case Study – Risk-Risk Tradeoff (Continued)

- Estimate Tradeoff Risk – Increase in HAIs
  - Transformation Risk
    - Different type of risk – infection <u>not</u> cancer
    - Affects different population – U.S. population undergoing medical procedure vs those living/working near sterilization plants
  - Infection Requires a Chain of Events
    - Each step is independent, but required
    - Independent probability of each event is multiplied to estimate compound probability of developing an infection

$$P_{Total} = P_{event\ 1} \times P_{event\ 2} \times P_{event\ 3}$$

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HAI – Hazard Identification

- ID Microbe and Spectrum of Effects
  - 2018 National Healthcare Safety Network (NHSN) HAIs
    - Central line-associated bloodstream infections (CLABSIs)
    - Surgical site infections (SSIs)
  - Pathogens addressed for CLABSIs and SSIs
    - *Acinetobacter*
    - Coagulase Negative Staphylococcus (CoNS, *S. epidermis)*
    - *Enterococcus*
   - *Klebsiella*
    - *S. aureus*

HAI – Toxicity Assessment

- Relationship between inoculum size (i.e., dose) and probability of infection is unclear for most microorganisms
  - Assumed that any microbial contamination of medical supplies/devices poses some risk of infection
    - No type of inserted or implanted foreign body has ever failed to be colonized w/CoNS
    - Broken skin/respiratory/urinary tract can become asymptomatically colonized
  - Colonized patients may develop clinical infection, but this does not always occur
    - Humans naturally carry many of the bacteria associated with device-related HAIs on their skin and mucous membranes
- Probability of progression from colonization to CLABSI/SSI for bacteria responsible for HAIs were used where available

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Chain of Exposure
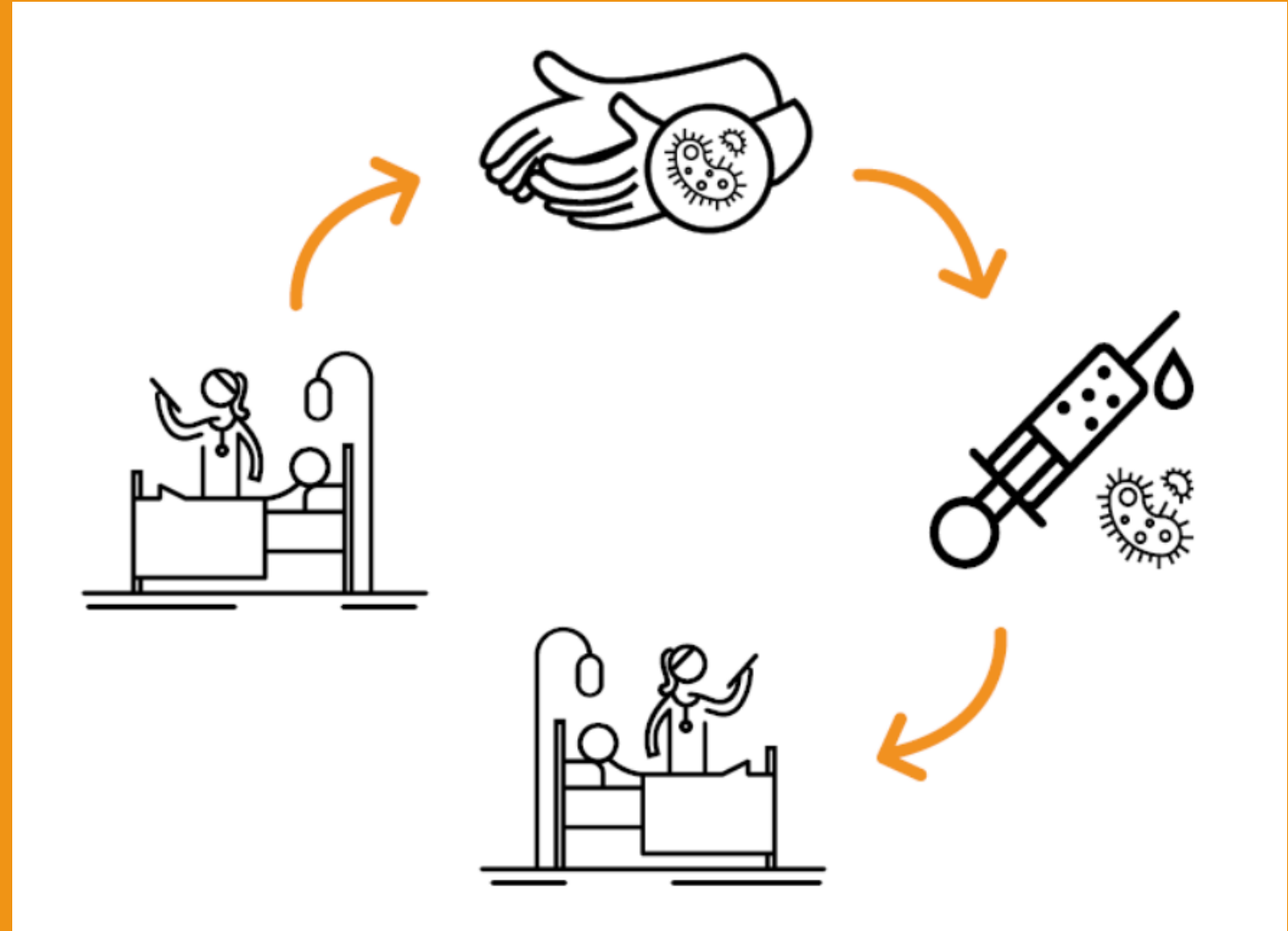
HAI – Exposure Assessment

- Pathogen Occurrence/Distribution
  - Common Sources of pathogens associated with HAIs:
    - Patients themselves
    - Medical equipment or devices
    - Hospital environment
   - Health care personnel

  - Wearing gloves during patient care is associated with decrease in hand contamination
    - Gloved hands of healthcare workers also showed significant bacterial colonization
    - Contamination of gloved and ungloved hands with low levels of pathogenic microorganisms occurs more than 50% of the time
    - Healthcare workers have also been observed to change gloves only 16% of the time between patient interactions

HAI – Exposure Assessment (Continued)

- Pathogen Transmission from Medical Devices to Patients
  - Medical devices
    - Provide a portal of entry for microbial colonization or infection
    - Facilitate transfer of pathogens from one part of the patient's body to another
    - Facilitate transfer of pathogens from Healthcare worker-to-patient
    - Facilitate transfer of pathogens from Patient-to-healthcare worker-to-patient

Contamination at the insertion site

Catheter

Vein   Fibrin Sheath   © NYSDOH
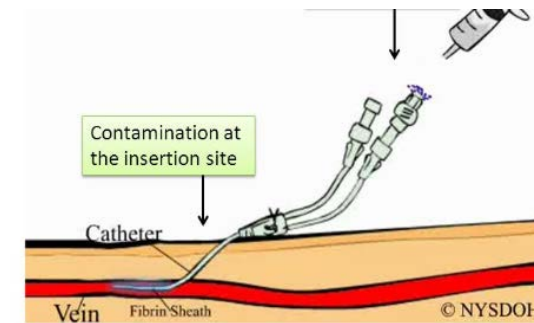
HAI – Exposure Assessment (Continued)

- Risk of Infection with Individually Packaged/Opened Packages
  - Two studies
    - Smith (2009) reported that the act of opening the packets yielded bacterial growth in 7/50 cases (14%)
    - Crick (2008) reported a 1% chance of contaminating medical devices/supplies with each individual package opened
  - Neither assessed health implications of the contamination
    - Microorganisms were not cultured from the devices themselves but rather from the packet opening process
  - Confirmed occult contamination of medical device packaging

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HAI – Exposure Assessment (Continued)

Central Line Kits Contain ~ 10 Items

- Mask
- Cap
- Gloves
- Drape
- Disinfectants
- Lines
- Needles
- Syringes
- Guidelines or a checklist

Surgical Kits Contain 20 – 50 Items

- Cutting/dissecting instruments
  - Scalpels, scissors
- Grasping/holding instruments
  - Forceps, clamps
- Hemostatic instruments
  - Sutures, cautery instruments
- Retractors
- Tissue unifying instruments
  - Needle holders or staple applicators

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HAI – Exposure Assessment (Continued)

- ## Assumptions Made about Exposure
  - All healthcare workers wear gloves
  - Probability that gloves are contaminated = 50%
  - Probability that contaminated gloves are <u>not</u> changed between activities = 85%
  - Probability of contaminating a medical device is 1% per individual package opened
  - 10 individual packages opened during central line insertion
  - 20 individual packages opened during surgery

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Estimating Risk of CLABSIs and SSIs

$$Risk = IR \times P_{microorg\ x,y,z...} \times P_{inf} \times P_{glove\ contam} \times P_{glove\ change} \times P_{MD/pkg} \times \#\ pgks$$

Where:

Risk	=	Risk of contracting a device-related HAI
IR	=	Annual NHSN CLABSIs or SSIs from ACHs + CAHs + IRFs
$P_{microorg}$	=	Probability infection caused by specific microorganism
P_{inf}	=	Probability that microbe colonization progresses to infection
$P_{glove\ contam}$	=	Probability that healthcare workers' gloves are contaminated
$P_{glove\ change}$	=	Probability healthcare workers' gloves are <u>not</u> changed
$P_{MD\ contam/pkg}$	=	Probability of contaminating medical device with each package opened
# pkgs	=	Number of medical supply/device packages opened

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HAI - Risk Characterization (Continued)

HAI Risk (EtO is Banned as Sterilizing Agent)			Cancer Risk (EtO in air near sterilization plants)	
CLABSI	SSI	TOTAL	EPA IURF	TCEQ IURF
5×10^{-6}	8×10^{-5}	8×10^{-5}	6×10^{-3}	2×10^{-6}

One risk is substituted for another

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HAI – Risk Characterization (Continued)

- Estimating Risk and Number of CLABSI/SSI Deaths
  - CLABSI
    - Risk of CLABSI Death = risk of CLABSIs x mortality ratio for CLABSIs
    - Number of CLABSI deaths (annually) = risk of CLABSI death x number of central line insertions each year
  - SSI
    - Risk of SSI Death = risk of SSIs x mortality ratio for SSIs
    - Number of SSI deaths = Risk of SSI death x annual number of surgeries each year

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Risk of Death from Infection and Total Deaths

Risk of HAI Deaths			Total Number of Deaths (Annually)		
CLABSI	SSI	TOTAL	CLABSI	SSI	TOTAL
6×10^{-7}	2×10^{-6}	3×10^{-6}	3	25	28

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Weaknesses in the Method

- Risk of HAI
  - Underestimated
    - Only 2 of 4 HAI categories included
    - NHSN data voluntarily reported for ½ U.S.
    - 50% of SSIs only evident after discharge
    - Low-end estimates for inputs
    - Progression from colonization to infection available for few microorganisms
      - Commensal colonization data used
    - Few studies on impact of handling on device contamination
      - Available studies involved experienced nurses not blind to study purpose
    - Microbial occurrence data gathered using insensitive analytical methods
  - Sub-acute risk associated with a single procedure
  - Infection may not be as serious but some result in death

- Theoretical Risk of Cancer
  - Overestimated
    - EPA IURF overly conservative
      - Supra-linear curve not biologically supported
      - High background exposure
    - Long-term exposure estimates based on 24-hour samples
  - Assumed to accrue over a lifetime of repeated exposures
  - Serious adverse effect
    - Estimated risk of dying from lymphoid/breast cancer likely to be misused

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Specific Input Requested

1. Suggested databases or resources for more current information on the annual number of central-line insertions, surgeries, urinary catheter insertions, and ventilator events?

2. Any need to include the probability that patients are young, of advanced age, or immunocompromised given that NHSN infection rates are risk-adjusted for patient characteristics?

3. Suggestions for additional resources for data on progression from colonization to infection for the microorganisms involved in HAIs?

4. Is it scientifically defensible to use the probability of infection in patients naturally colonized with a bacterium as a surrogate for the probability that colonization of a central-line insertion site or surgical site wound will progress to CLABSI or SSI?

5. Is there any reason not to use the most recent NHSN data?

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Thank You!

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