Basics of Outbreak Management
Dr. William R. Jarvis, Jason and Jarvis Associates
A Webber Training Teleclass

Basics of Outbreak Management

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Purpose

1. **Review the approach to investigating outbreaks in healthcare facilities.**
2. **Illustrate the value of combined epidemiologic and laboratory investigations.**
3. **Illustrate how you can impact on patient outcomes (locally and nationally) through outbreak investigations.**

Epidemic

- Increase in incidence beyond the expected in a defined geographic area, within a defined period of time.
- A significant increase ($p < 0.05$) in the rate of adverse events above that noted in the past.

Nosocomial Infections and Outbreaks

- Each year 2 million patients acquire a healthcare-associated infection*
- Outbreaks:
  - Among hospitals in the National Nosocomial Infections Surveillance (NNIS) System, 5% of healthcare-associated infections occur in epidemics/outbreaks**
  - Most are small clusters; many are unrecognized
  - Outbreaks can lead to morbidity, mortality, consume time, effort and resources

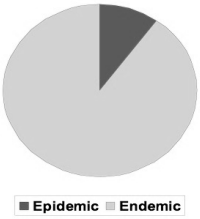
*Jarvis, Outbreak investigations in the healthcare setting, Seminars in infection control, 2001, 1:73-84; ** Doebbeling, Epidemics: Identification and management. In: Wenzel ed. Prevention and Control of Nosocomial Infections. Baltimore MD: Williams & Wilkins; 1992: 177:206

"By definition, all outbreaks are preventable."

Richard P. Wenzel

Nosocomial Infections

- **Endemic infections**
  - sporadic
  - 1/3 preventable?
  - majority of infections
- **Outbreaks/Epidemics**
  - significant increase from endemic rate
  - minority of infections
  - 100% preventable



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Implicit Assumptions

- Case definition has not changed.
- Methods for diagnosing the disease or identifying the organism have not changed.
- Case finding methods have not changed.

Pseudoepidemic

- Real clusters of false infections
- False clusters of real infections

Pseudoepidemics

- 20 (11%) of 181 nosocomial epidemics investigated by the CDC between 1956 and 1975 were pseudoepidemics.
- 55% resulted from errors of collecting, handling, or processing specimens.
- 30% resulted from surveillance artifacts.
- 15% resulted from errors of clinical diagnosis.

Weinstein and Stamm Lancet 10/22/77

Goals of an Outbreak Investigation

- Identify the etiologic agents
- Identify the reservoir(s)
- Identify the mode of transmission
- Eliminate the reservoir(s) and transmission
- Prevent future outbreaks

Two Approaches to Outbreak Investigation

- Quick and dirty
- Detailed epidemiologic and laboratory investigation

The Quick and Dirty Outbreak Investigation

- Quickest
- Least expensive
- Approach
  - Case definition
  - case-ascertainment
  - line list
  - Identify common exposures
  - Introduce control measures.

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The Detailed Outbreak Investigation

- Personnel and resource intensive
- Combines epidemiology and laboratory investigations.
- Least expensive
- Approach
  - Case definition
  - Case-ascertainment
  - Line-list
  - Epidemic curve
  - Comparative study (case-control, cohort, personnel, etc.)
  - Laboratory studies (e.g., inanimate/animate cultures, isolate comparison)
  - Observational studies
  - Introduction of control measures
  - Post-outbreak surveillance to document termination of the outbreak

Microbiology Laboratory

- Important source for case finding if you know the etiologic agent
- Identify the organisms as completely as possible
  - Genus and species
  - Epidemiologic typing
- **Save all isolates!!!**

Case Definition

- A description of the cases that changes as new data are accumulated, include time, place and person.
- Example (who, what, when and where):
- SSI outbreak. Pus at the operative site in a patient in the SICU at Hospital A from May 1-10, 2005 with wound or blood cultures positive for MRSA that has a particular PFGE pattern.

Literature Review

- What is the usual reservoir?
- What is the usual mode of transmission?
- Has it been reported to cause outbreaks?
- What factors were important in those outbreaks? (IV lines, contaminated products or food items, respiratory therapy, breaks in sterile technique, etc.)?

Define the Extent of the Problem

- Surveillance system
- Microbiology laboratory
- Employee health
- Other healthcare facilities
- City, county, state, federal health agencies
- Reference laboratories

Attack Rate

- Number of patients affected divided by number of patients at risk
- Number of infections divided by number of patients at risk
- Number of adverse outcomes divided by number of patients at risk

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Epidemic Period

- The time from the onset of the first case to the cases currently under investigation

Pre-Epidemic Period

- Arbitrarily defined period of time that is long enough to provide sufficient cases of a low frequency event
- Usually at least 6 months of surveillance data should be examined
- 12 months will avoid seasonal bias

Epidemic Curve

- Graphic display of outbreak with time (minutes, hours, days, weeks, months, years) on the X-axis and the number of persons meeting the case definition on the Y-axis.
- Both pre-epidemic and epidemic periods should be plotted.

Search for Risk Factors: The Line Listing

- Admission date
- Infection data
- Demographic data
- Underlying diseases
- Pre-infection exposures to
  - service
  - Ward, unit, bed or room e.g., operating)
  - Diagnostic tests
  - Therapeutic interventions
  - Personnel

Form a Hypothesis

- Using data from the epidemic curve, line-listing, literature, etc. form a hypothesis regarding:
  - the reservoir
  - the mode of spread

Test the Hypothesis Using a Comparative Study

- Case-control study
- Cohort study
- What factors determine the choice?
  - Number of cases
  - Duration of the outbreak
  - Rarity of the adverse event
  - How much time you have

Test the Hypothesis Using a Case-Control Study

- Cases are compared to controls.
- The proportion in each group exposed to various risk factors are compared.
- Were case-patients exposed to a risk factor that controls were not exposed to?
- Is the association statistically strong (Chi-square or Fisher's exact test $p < 0.05$)?

Selecting Controls

- Choose patients from appropriate subpopulation
- 2 to 4 controls per case, if fewer than 10 cases
- Initially don't match
  - Stringent matching obscures risk factor
  - Can't analyze matched variables

Clues Important in Investigating an Outbreak

- Multiple organisms causing infection at a single site or associated with invasive procedures may suggest problems with aseptic technique
- A single organisms, particularly clonal, suggests a common source.
- The epidemic curve may suggest the mode of transmission
- An unusual organism may be a clue to a problem (*Enterobacter cloacae*, *Enterobacter agglomerans*, *Salmonella muenchen*)

Epidemiologic Typing

- Epidemiologically related isolates:
  - Are derived from a single clone
  - Share characteristics that differ from those of epidemiologically unrelated isolates
- Are isolates from $\geq$ 2 patients or from patients & environment the same or different?
- Doesn't replace epidemiological analyses!!!

Evaluating Typing Systems

- **Typeability**:
  Ability to obtain an unambiguous positive result for each isolate analyzed
- **Reproducibility**:
  Ability to give the same result each time a strain is tested
- **Discriminatory power**:
  Ability to differentiate among unrelated strains

Hierarchical Approach to Typing

- Start with simple, inexpensive, readily available tests
- Do more expensive, more difficult, less readily available tests only if the clinical, epidemiologic, and microbiologic data indicate that they are necessary

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Phenotypic Techniques

- Colony morphology
- Biotyping
- Serotyping
- Phage typing
- Immunoblotting
- Antimicrobial susceptibility
- Multilocus enzyme electrophoresis

Characteristics of Phenotypic Typing Systems

Typing System	Proportion of Strains Typeable	Reproducibility	Discriminatory Power
Biotyping	All	Poor	Poor
Antibiogram	All	Good	Poor
Serotyping	Most	Good	Variable
Phage typing	Most	Fair	Variable
Immunoblotting	All	Good	Good
MLEE	All	Excellent	Good

Maslow & Mulligan ICHE 17:595-604;1996

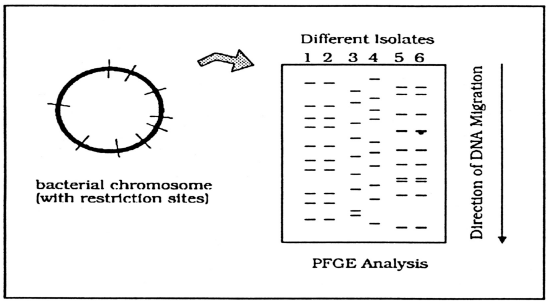
Molecular Techniques

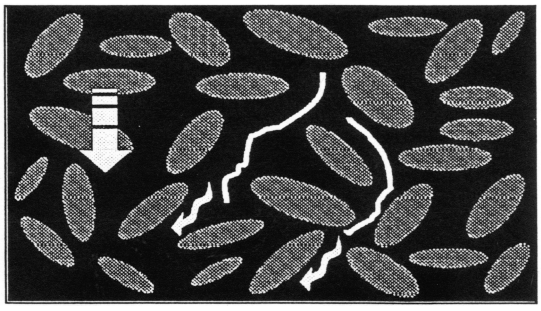
- Cellular fatty acids
- Pyrolysis mass spectrometry
- Whole cell polypeptide analysis
- Plasmid pattern analysis (PPA)
- Ribotyping
- Pulsed Field Gel Electrophoresis (PFGE)
- Polymerase chain reaction (PCR)

Characteristics of Genotypic Typing Systems

Typing System	Proportion of Strains Typeable	Reproducibility	Discriminatory Power
PPA	Most	Fair	Variable
REA	All	Variable	Variable
Ribotyping	All	Excellent	Good
PFGE	All	Excellent	Excellent
PCR	All	Excellent	Unknown

Maslow & Mulligan ICHE 17:595-604;1996





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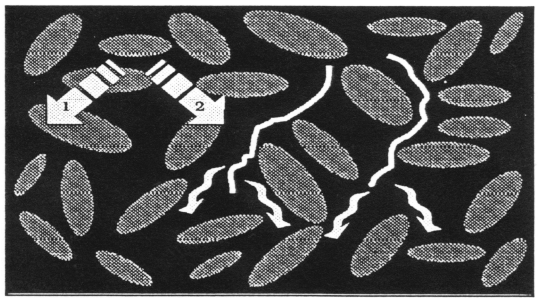
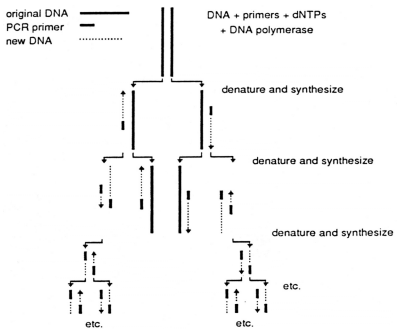


PFGE: Advantages

- Less hands-on-time
- All organisms should be typeable
- Less nonspecific shearing of DNA
- Fewer bands per pattern/easier to read
- Does not require probes; can be extended to include probes
- May be more discriminatory than ribotyping

PFGE: Disadvantages

- High start-up costs
- Method/interpretation not standardized
- May need two gels to visualize upper and lower MW ranges
- Takes longer than PCR



Polymerase Chain Reaction

- Arbitrarily primed PCR (AP-PCR)
- Randomly amplified polymorphic DNA (RAPD)
- Specific sequence polymorphisms
- Polymerase chain reaction ribotyping

PCR: Advantages

- Rapid
- Relatively inexpensive
- Universally applicable
- Types organisms that:
  - grow slowly or not at all in vitro
  - are nonviable
  - are in tissues
  - are hazardous to grow

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PCR: Advantages

- Can use sheared/single-stranded DNA
- Can use nanogram amounts of DNA
- Good discrimination for some organisms
- Can use endonucleases to increase discrimination
- Equipment/method can be used for diagnostic tests

PCR: Disadvantages

- Amplifies any contaminating DNA
- Sensitive to conditions--Mg, temp
- Method/interpretation not standardized
- May be difficult to identify good primers
- Each primer requires a separate gel
- Limited data

Comparison of Typing Methods

	PPA	PFGE	PCR
Supplies $/run	8	17	8
Hands on time (min)	120	125	90
Overall time (days)	1.5	5	1
Equip. costs ($)	2,000-4,000	15,000-20,000	10,000

One Hospitals Approach

- The microbiology lab:
  - saves all isolates from normally sterile body sites and all nosocomial infections
  - processes surveillance cultures and cultures of the environment as necessary
  - does ribotyping (via RiboPrinter) and/or PFGE to determine whether isolates are the same

***Serratia marcescens* Bloodstream Infections in a Surgical Intensive Care Unit**

Background

Events at Hospital A:

- **July to September 1998**
  - **9 episodes of *Serratia marcescens* bloodstream infection in the Surgical Intensive Care Unit (SICU).**
- **September 1998 to February 1999**
  - **Extensive culturing did not reveal a source.**
- **By March 1999**
  - **More than 10 additional *S. marcescens* bloodstream infections detected; CDC assistance requested.**

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Background

- **Hospital A**
  - **455 bed tertiary care facility**
  - **Level 1 trauma center**
  - **Several Intensive Care Units (ICU)- geographically separated**
  - **Surgical Intensive Care Unit (SICU)**
    - **Three stations**
    - **150-200 admits per month**
    - **Most common admission-post cardiac bypass**
    - **12% admits trauma**

Background

***S. marcescens*, gram-negative bacilli**

- **Found in water and the environment.**
- **It is not a part of the normal human flora.**
- **Rare, but serious cause of infection***
  - **Urinary tract**
  - **Wound**
  - **Bloodstream**
- **Hospital outbreaks from diverse sources.**

* Yu VL, *Serratia marcescens*-Historical perspective and clinical review. New Eng J Med 1979;300:887-893

S. marcescens Outbreaks

Source	Reference
Pressure transducers	Donowitz, JAMA, 1979 Villarino, JCM, 1989
Flexible bronchoscopy	Web, Chest, 1975
Heparized saline solution	Cleary, Am J Pract Infect Control, 1981
Cleaning solutions, soaps	Ehrehkranz, Lancet, 1980 Archibald, ICHE, 1997
Employees hands/nails	Passaro, JID, 1997
Reduced nurse:patient ratio	Archibald, Ped Infect Dis, 1997

Comparisons

Review of clinical microbiology data for Serratia spp. blood culture isolates at Hospital A:

Location:

SICU	Hospital-Non SICU	p-value
(Isolates/1000 patient days)*		
6.17	0.056	<0.001

In SICU over time:

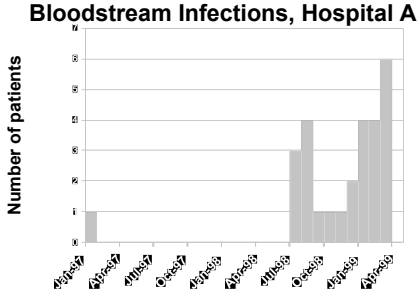
7/98-3/99	7/97-6/98	p-value
(Isolates/1000 central line days)*		
8.07	0.13	<0.001

* Emori G, et. al., National Nosocomial Infections Surveillance (NNIS) System: Description of surveillance methods, American Journal of Infection Control, 1991,19: 19-35.

Case Definition

- **Case-patients: SICU patients at Hospital A with a *S. marcescens* bloodstream infection**
- **Epidemic Period: June 30, 1998-March 18, 1999**

Distribution of *S. marcescens* Bloodstream Infections, Hospital A



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Case-Patient Characteristics (n=26)

Male, n (%)	**17 (65)**
Age, years mean (range)	**48 (17-87)**
SICU stay, days median (range)	**14 (3-40)**
Mortality, n (%)	**3 (12)**

Case-Infection Characteristics n=26 (%)

Polymicrobial	**8 (31)**
– with *Enterobacter sp.*	**7 (27)**
Persistent bacteremia	**13 (50)**
On antibiotics at time of culture	**18 (69)**

Control/Containment

- Assessment for patient colonization
  - Evaluation of all SICU patients on the one day 3/17/99
    - Tracheal or urine sample within 7 days*
    - Of 24 patients samples, only 1 patient with tracheal Serratia colonization
- Review of microbiological data for clinical isolates of Serratia spp. at other anatomical sites-rare

* Yu VL. *Serratia marcescens*-Historical perspective and clinical review. New Eng J Med 1979;300:887-893

Control/Containment

- Assessment for environmental contamination
  - Cases in all 3 nursing stations, in >10 patient rooms
  - Multiple cultures (>50 done by infection control staff 9/98 to 3/99)- no Serratia spp.

Case Control Study Definitions

- **Epidemic period: June 30, 1998-March 18, 1999**
- **Case-patients: SICU patients with an *S. marcescens* bloodstream infection**
- **Control-patients: Randomly selected SICU patients with a ≥48 hour stay during epidemic period and with no gram-negative organism bloodstream infection**

Summary of Factors Evaluated*

Non-significant

- Gender
- Age
- Surgical procedure
- Intubation/mechanical ventilation
- Respiratory care
- APACHE II on admit
- Mortality**

*9 Page questionnaire

**Increased for cases if definite and possible cases included

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Risk Factors for *S. marcescens* Bloodstream Infection

Characteristic	Cases n=26 (%)	Controls n=65 (%)	Odds Ratio	p-value
Trauma	16 (62)	14 (22)	6	< 0.001
Transfusion	26 (100)	52 (80)	Undefined	0.02
Bronchoscopy	11 (42)	4 (6)	11	< 0.001

Evaluation of Fentanyl Exposures

Fentanyl Exposure	Cases n=26 (%)	Controls n=65 (%)	Odds Ratio	p-values
Fentanyl in SICU	25 (96)	29 (45)	31	<0.0001
Continuous infusion in SICU	25 (96)	24 (37)	42	<0.0001
Days of fentanyl, median (range)	5 (1-27)	2 (1-7)	------	<0.0001
Total amount (cc)	28,000	6,100	------	<0.0001

NB: 17 cases had Fentanyl infusions at time symptoms

Medications

- Fentanyl*†
  - Analgesia and sedation
  - Opiate narcotic, 80 times more potent than morphine
  - Used widely at Hospital A- OR, SICU, MICU
  - Can be given multiple routes
    - Continuous infusion ✓
    - Intravenous bolus ✓
    - Epidural infusion ✓
    - Oral x

*1999 PDR; †Berens A, Voets A, Demedts P. Illicit fentanyl in Europe. Lancet. 1996;347:1334-1335

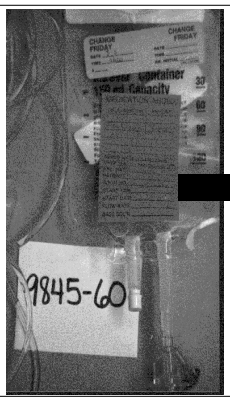
Tracking of Medications - an Observational Study

Did the Fentanyl get contaminated?

How?

Contamination:

- Intrinsic - in manufacture
  - No reports to FDA- by Adverse Event Reporting System (AERS)
- Extrinsic - after manufacture



Infusions bags are taken from 2 cases (#21 & #24) at the time of their symptoms

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Laboratory Cultures

Fentanyl related:

Ampules outside SICU	negative
Ampules inside SICU	negative
Equipment, infusion bags	negative
Infusions	positive*

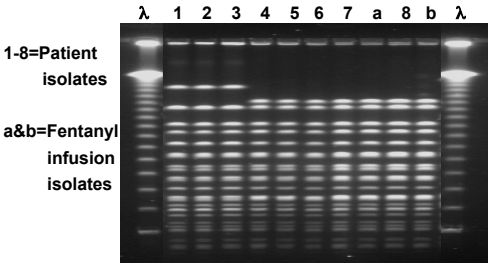
* Cultures positive for ***S. marcescens, E. cloacae*** from infusions from 2 cases

Laboratory Results

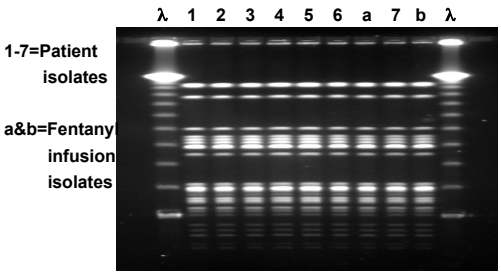
- *S. marcescens* isolates from 24/25 case-patients related by pulsed-field gel electrophoresis (PFGE)*
- All 7 Enterobacter isolates were indistinguishable by PFGE
- Confirmed fentanyl infusion growth

*Exception: 1 cases where *S. marcescens* was not related, did not get fentanyl infusion

PFGE *S. marcescens* Patient and Fentanyl Isolates



PFGE *E. cloacae* Patient and Fentanyl Isolates



Personnel Study

- **Patient care provided by many healthcare workers**
- **Reviewed medical records for exposure to healthcare workers**
  - **~ 100 SICU nurses**
  - **~ 80 physicians**
  - **~ 50 respiratory therapists (RTs)**

Respiratory Therapist (RT) Exposures

Therapist	Cases n=26 (%)	Controls n=65 (%)	Odds Ratio	p-value
RT3	18 (69)	20 (31)	5.1	0.001
RT11	19 (73)	25 (39)	4.3	0.004
RT13	19 (73)	21 (32)	2.8	0.04
RT16	19 (73)	32 (49)	5.7	<0.001
RT18	**23 (88)**	**24 (37)**	**13.1**	**<0.0001**

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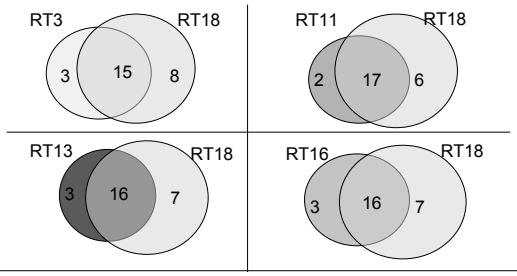
Respiratory Therapist Exposures for 26 Case-Patients



Implicated Healthcare Worker

RT18

- **SICU supervisor**
- **Associated with most case-patients (23/26)**

- **Witnessed tampering with fentanyl infusions of a case-patient (#21)**

Hospital Administration Actions

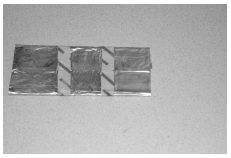
- Removed RT18
- Asked consent to :
  - Search
  - Culture hands and antecubital fossa
  - Test for drugs (hair testing)

Multivariate Model for *S. marcescens* Bloodstream Infections

Exposure	Cases n=26 (%)	Controls n=65 (%)	Odds Ratio	p-value
Continuous fentanyl infusion	25 (96)	24 (37)	44	0.001
RT3	18 (69)	20 (31)	9.5	0.02
RT18	23 (88)	24 (37)	6.7	0.002

Laboratory Analyses- Implicated Healthcare Worker (RT18)

Hand cultures done by handiwipe methods*
Hands & antecubital fossa cultures negative



* Petersen N, Collins D, Marshall J. A microbiological assay technique for hands. Health Lab Sci 1973;10:18-22

Laboratory Analyses- Implicated Healthcare Worker (RT18)

Hair testing for fentanyl **positive**
--Evidence of habitual use

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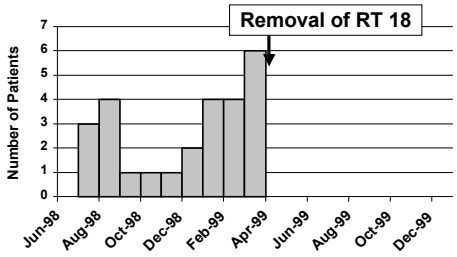
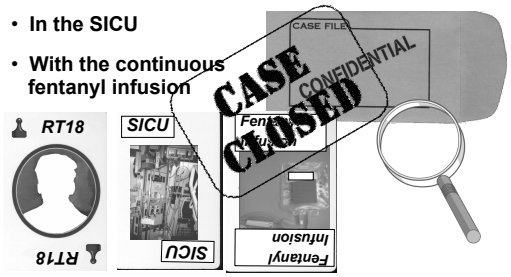
Distribution of *S. marcescens* Bloodstream Infections After Intervention



Mystery Solved by Epidemiology & Laboratory

- RT18
- In the SICU
- With the continuous fentanyl infusion



How Fentanyl Became Contaminated?

- During manipulation by implicated employees hands

- Reuse of Devices-needles

- Common source of liquid for replacement of fentanyl

Laboratory Cultures

Environment / water sources*:

Sinks and showers (>15)	negative
Bottles of fluid	negative

*American Public Health Association, American Water Works Association and Water Environment Federation. Standard methods for the examination of water and wastewater.1998;20:9-19

Public Health Scope

- National estimates*: 4.2 % of hospital workers admit to present illicit drug use (8.9% to past use)
- 1983 survey**: 214 (74%) of 289 U.S. anesthesia residency training programs reported at least one drug abuse/dependence
  – Meperidine and Fentanyl most common

* Substance Abuse and Mental Health Services Administration (SAMHSA). Drug use among U.S. workers: Prevalence and trends by occupation and industry categories.1996:15-71.
**Ward C, Ward G, Saidman L. Drug abuse in anesthesia training programs. JAMA.1983:250;922-925.

Summary

- Outbreak of *S. marscecens* bloodstream infections in the SICU of Hospital A associated with contamination of fentanyl
- Epidemiology, a witnessed event, and drug testing suggest extrinsic contamination by a single healthcare worker
- Use of epidemiology and laboratory methods aided in termination of outbreak
- The outbreak had complicating factors

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Epilogue

- Official CDC reports were disseminated to Hospital A administration
- RT18 was permanently relieved of his duties
- A Hospital A official presented the findings to the District Attorneys Office- case not pursued due insufficient evidence
- State Health Department Officials informed

Summary

- **An outbreak occurring at your facility may be an indicator of a nationwide outbreak.**
- **Combined laboratory and epidemiologic investigation can identify the source of the outbreak.**
- **Investigation-based prevention interventions can terminate the outbreak.**

Thank You!