Supplement A: Medical Product Investigations

Introduction

Healthcare-associated infections (HAIs) and outbreaks can result from the use of contaminated medical products. Medical products include devices (also called instruments or equipment) and drugs (also called medications) as well as biological products, nutrition products, and patient care items.

The general principles outlined in the CORHA Principles and Practices (P&P) can be employed when responding to medical product contamination events. For example, these investigations often involve infection control assessments and require active coordination of investigation partners across multiple jurisdictions; readers are encouraged to develop familiarity with the full P&P text as those details are not repeated here.

However, there are some unique challenges associated with medical product contamination events which this supplement attempts to address. These include difficulty identifying connections between one or more patient infections and specific medical products. Often, documentation of medical product use is lacking in patient records. Likewise, the ability to identify or obtain potentially contaminated products may be limited, as when these have been used and replaced by new lots or product types.

Moreover, the source of contamination – whether user error or a manufacturing deficit – can be difficult to distinguish even when a clear association with medical product use is evident, particularly at early stages of an outbreak response. As a result, this type of investigation is often marked by tensions and a sense of urgency, as investigators seek to determine whether the outbreak is localized and contained or represents a product safety issue with broad potential for harm.

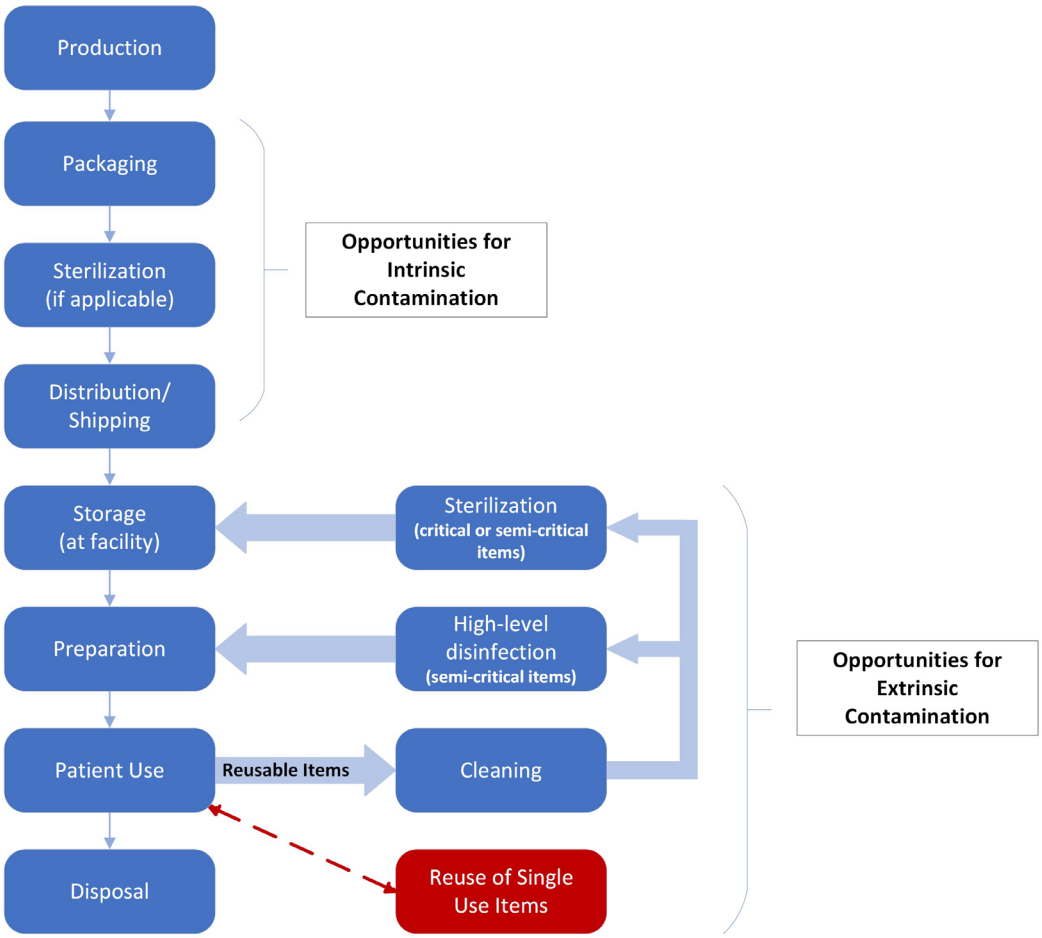
Background: Intrinsic & Extrinsic Contamination

Medical product contamination can result from errors that occur during their production, manufacturing, or packaging as well as during their transportation or storage. Contamination can also occur during the preparation and use of medical products at the point of patient care and may even result from intentional misuse or tampering.

Investigators find it helpful to distinguish two broad categories of medical product contamination. **Intrinsic contamination** occurs before the product arrives at the point of use in a healthcare facility. In addition to traditionally manufactured products, compounded pharmaceuticals are also included in this category when they are produced upstream of the receiving healthcare facility. **Extrinsic contamination**, on the other hand, results from errors during storage, preparation, and use in a healthcare facility. This can include inappropriate reuse of single use items and deficiencies in reprocessing of reusable items. As summarized in Figure 1, there are many points at which a medical

product could become contaminated; assessments related to root cause analysis should consider the possibilities of both intrinsic and extrinsic contamination events.

Figure 1. Opportunities for Intrinsic Contamination or Extrinsic Contamination, from Production through Patient Use and Reprocessing



Intrinsic contamination events can result in widespread outbreaks. These may affect patients in multiple states or regions of the United States or even be global in their scope. Notable incidents of intrinsic medical product contamination have included *Exserohilum rostratum* in methylprednisolone acetate from a compounding pharmacy, *Burkholderia cepacia* complex in oral docusate, *Serratia marcescens* in prefilled saline flushes, and *Mycobacterium chimaera* in heater-cooler devices. Depending on the gap in the manufacturing process, contaminated products may include parts of lots or entire lots and could involve all known lots of that product or only lots produced in a certain facility during a certain time period, or with certain raw materials.

Many examples of extrinsic contamination events are presented in chapter 2, table 2.2. Notable incidents have stemmed from unsafe injection practices and inadequate reprocessing of endoscopes. Unsafe injection practices, including reuse of syringes or single dose vials and preparation of parenteral

medications in contaminated environments (e.g., near sinks) have caused numerous outbreaks of hepatitis B virus and hepatitis C virus as well as outbreaks of bacterial and fungal pathogens. While extrinsic contamination often results from errors committed by healthcare personnel, it can also reflect problems with a product's design or instructions for use that predispose the product to becoming contaminated at the point of use. For example, Carbapenem-resistant Enterobacterales (CRE) transmission has been associated with duodenoscopes that were reprocessed in accordance with approved instructions and protocols investigation revealed that this endoscope product's intricate design made them very difficult to clean and disinfect.

Detection & Reporting

Many different pathogens or medical products can be involved in medical product contamination events. Table A.1 illustrates examples of organ systems, products and pathogens that can be encountered together in association with transmission events or outbreaks stemming from medical product contamination. The examples shown may span both intrinsic and extrinsic contamination events. In addition, pathogens that are introduced through a contaminated medical product to one organ system may be detected in another due to subsequent spread. Nonetheless, this table may be a helpful aid in recognizing and evaluating possible causes of product-related transmission relative to clinical illness and other factors. Practitioners should maintain a high index of suspicion for medical product involvement and recognize that individuals who are immunocompromised or receive frequent medical procedures may be at greater risk of infection.

Healthcare facilities and providers should report infections and potential outbreaks that are suspected to be linked to medical products. Product concerns should be conveyed early. For example, a single patient infection may warrant a notification to public health authorities if there is a severe outcome (e.g., hospitalization or death) and the infection type suggests a route of infection possibly related to a medical product (see Table A.1). Identifying and reporting associations between HAIs and medical products requires active efforts to identify relevant patient exposures. Reports can be directed to public health jurisdictions and regulatory agencies, including via FDA MedWatch, as well as to manufacturers.

Public health authorities should consider the possible role of medical products when investigating HAIs, even if this concern has not been raised by the facility. Due to the potential for widespread harm, they should engage state, local, and federal partners early in investigations of outbreaks that could be related to intrinsically contaminated medical products.

Investigation

Investigations of healthcare-associated outbreaks due to medical product contamination can be approached using many of the principles described elsewhere in the CORHA Principles and Practices. The remainder of Supplement A focuses primarily on investigation procedures for outbreaks that potentially involve drugs and devices, with an emphasis on intrinsic product contamination. For resources specific to blood, organ, and tissue contamination, see Box A.1.

Multiple avenues of investigation may need to be pursued simultaneously. Early in an investigation, working hypotheses related to both extrinsic and intrinsic contamination may be in play. Initial investigation activities may have to cover both of these bases. This could include targeted assessment of relevant healthcare delivery practices and rapidly correcting any identified gaps in infection control procedures. At the same time, it might also be helpful to sequester implicated products and collect information such as photos, product or medical lot numbers or identifiers, manufacturer instructions for use (IFUs), facility protocols, purchase orders, and other records related to the implicated product(s). See Box A.2 for a list of assessment questions and considerations for information collection when organizing a medical product-related investigation.

As outlined in Table A.1, previously observed patterns and associations, involving specific medical products, organ systems, pathogens and infection types, are useful to consider when initiating an investigation. To help distinguish intrinsic from extrinsic contamination, consider two hallmarks of intrinsic contamination. First, intrinsic contamination events are not readily explained by infection control practice deficiencies. Second, intrinsic contamination events are marked by the appearance of additional outbreak signals. Reporting product contamination concerns to FDA and CDC can help 'connect the dots.' In some cases, this can be supplemented by organizing active outreach (e.g., via CDC/Epi-X or clinician listservs) to determine whether similar concerns have been identified elsewhere.

Entities with detailed knowledge of the modes of contamination of medical products at the production, distribution, storage, and use stages should be engaged early and can include:

- Manufacturers
- Distributers
- Licensure Boards of Pharmacy, Medicine, Nursing, etc.
- State and Federal Public Health Agencies (e.g., CDC, FDA)
- Laboratory Partners
- Infection Prevention Personnel
- Healthcare Organizations

Collaboration and communication, particularly among public health authorities, healthcare facilities, and regulatory partners, serves to increase awareness, evaluate patterns and processes at a broader scale and confirm widespread intrinsic contamination events as early as possible. Additional communication activities, including engaging impacted patients, can be performed using the guidance outlined in Chapter 8: Communications, Media, Public Reporting, Notification, and Disclosure.

There are also unique product testing considerations for medical product investigations. For example, suspected products or devices should be sequestered (i.e., cease use but do not discard). As outlined in Chapter 6, laboratories have differing capabilities; public health and regulatory partners can often facilitate product or environmental testing support in a manner that is consistent with requirements pertaining to documentation and chain-of-command for sample transport.

Concluding a Medical Product Investigation

Chapter 5 describes important steps for concluding an investigation that also apply to medical product contamination including:

- Implementing control measures (e.g., infection control practices, product recall and/or removal)
- Ongoing surveillance and detection protocols depending on the product/device distribution
- Monitoring until no additional cases are detected

In addition to the above steps, medical product contamination investigations may also involve some unique opportunities for implementing lessons learned. This can include process improvement and quality assurance efforts at the manufacturing, distribution, or facility level to detect and prevent future events. These collaborative processes can be important not just for the stakeholders involved in a specific event but also for professional organizations and regulatory authorities at a national level that ultimately lead to improved patient safety and outcomes.

Summary

Medical products play crucial roles in medical diagnosis and treatment in U.S. health care settings. They can also present infection risks. Early detection of medical product safety signals, combined with robust investigations, are needed to:

- Evaluate and confirm the presence of a medical product infection risk, and
- Inform decision-making, e.g., whether to initiate product removal or regulatory action.

Additional 'Keys to Success' related to medical product investigations have been summarized in Box A.3. Working together, public health, healthcare, regulatory authorities, and other medical product investigation partners can support swift actions to identify causes, contain threats, and prevent harms.

Box A.3. CORHA Keys to Success: Medical Product Investigations

1. Maintain a high index of suspicion for medical product contamination and report concerns to appropriate public health and regulatory agencies (including FDA MedWatch),as well as to manufacturers.
2. Consider both intrinsic and extrinsic contamination opportunities when formulating initial investigation steps and control actions.
3. Include individuals with specific product or device manufacturing expertise and engage state and federal support resources early in an investigation.
4. Communicate investigation findings to investigation partners and affected patients and healthcare providers to support improved outcomes.
5. Leverage lessons learned to help detect and prevent future events (e.g. inform process improvement and quality assurance efforts at the manufacturing, distribution, or facility level).

Table A.1. Groupings of Organ Systems and Infection Types with Contaminated Medical Products and Pathogens		
Organ System	**Contaminated Medical Product**	**Example Pathogens, by Source**
Bloodstream Infections	• Intravenous lines, ports, or tubing • Wound care products/dressings • Medications or products administered intravenously	Environmental • Nontuberculous mycobacteria • *Serratia marcescens* • *Stenotrophomonas maltophilia* • *Burkholderia cenocepacia* Skin flora • *Staphylococcus* species
Skin & Wound Infections	• Intravenous lines, ports, flushes, or tubing • Skin care cleaning products or dressings (e.g., alcohol prep pads, bandages, etc.) • Wound care products/dressings	Skin flora • *Staphylococcus* species Environmental: • *Bacillus cereus* • *Aspergillus*
Gastrointestinal Infections	• Duodenoscopes, endoscopes, etc. • Ingested products (e.g., medications, infant formula and other nutritional products) • Products administered through feeding tubes (e.g., nasogastric tubes or PEG tubes)	Environmental (e.g., soil, water, gastrointestinal flora) • *Escherichia coli* (*E. coli*) • Carbapenem- or vancomycin-resistant Enterobacterales (CRE, VRE) • *Listeria monocytogenes* • *Burkholderia cepacia*
Neurologic Infections	• Medications or products used during lumbar punctures • Medications or products administered through patches, ports, implants or catheters with delivery into the central or peripheral nervous system • Medications or products administered ocularly (e.g., drops, implants, ophthalmic procedures, drains, etc.)	Environmental • Fungal species • Nontuberculous mycobacteria

Respiratory Infections	• Ventilators, intubation sequence products • Aerosolization and nebulizer products	Environmental (e.g., soil and water) • *Pseudomonas aeruginosa* • *Stenotrophomonas maltophilia*
Genitourinary Infections	• Urinary catheters • Ureteroscopes or devices used for treatment or diagnosis of genitourinary conditions	Environmental (e.g., soil, water, gastrointestinal flora) • *Pseudomonas aeruginosa* • *E. coli* • CRE/VRE

Box A.1 Resources for Investigations of Blood, Biologic, Tissue, and Organ Contamination

Centers for Disease Control and Prevention – Blood Safety
https://www.cdc.gov/bloodsafety/monitoring/blood_safety.html

National Healthcare Safety Network - Biovigilance Component
https://www.cdc.gov/nhsn/biovigilance/index.html

U.S. Food and Drug Administration – Biologics
https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics

U.S. Food and Drug Administration – Tissue
https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/tissue-safety-availability

Centers for Disease Control and Prevention Transplant-Transmitted Infection Process
https://www.cdc.gov/transplantsafety/hc-providers/tti_toolkit.html

HRSA Organ Procurement & Transplantation Network (OPTN)
https://optn.transplant.hrsa.gov/professionals/by-topic/patient-safety/

Box A.2.
CORHA Potential Medical Product-Related Outbreak: Assessment Questions

This tool is also available on the CORHA website (link)

High-level questions about the situation

- What types of adverse events have been identified? How was the situation detected and brought to light? To whom were the concerns reported and when?
- What patient harm has occurred, such as infections, serious complications/injuries, deaths?
- What are the specific product concerns? What is the potential for further patient harm at this facility or elsewhere?
- Which parties are currently involved in this investigation? How can we best organize ourselves to assess the situation and make sure that any necessary controls or actions get implemented?
- Who are the stakeholders in the investigation, including medical product, epidemiologic/public health perspective, laboratory, and healthcare facility/providers perspectives? What are their roles and responsibilities and immediate next steps and timelines? Are there any stakeholders missing, and if so what are the plans to engage them?
- Have the key stakeholders agreed upon the primary objectives and roles/responsibilities for collecting and sharing information? What are the immediate next steps and deliverables?
- What information is needed to support timely decision-making (e.g., whether to institute a product recall)?
- What are the most effective ways of gathering and sharing this information?
- What are the investigation objectives/goals? Are the goals clear?
- Have short-term and long-term goals been identified and placed in a timetable?
- What steps are needed to assure a timely and coordinated response moving forward? Is there a need for an Incident Command System (ICS) structure at the local, state, or federal level?

Key Questions – Descriptive Epidemiology

- What is/are the primary clinical outcome(s) or presentation(s) of concern?
- Have specific pathogens been identified; if so, from what specimen source(s)?
- What is the magnitude of impact as currently understood in terms of the numbers of patients currently affected and the number/location of facilities that are reporting adverse events?
- Describe the setting, the primary affected patient population; does this include children, pregnant women, the elderly or immunocompromised?
- Is there a working hypothesis for root cause(s)?
- What other possible source(s) of contamination and possible route(s) of transmission require evaluation?
- Has a case definition been established? Are there criteria available to classify cases as suspect, possible, or confirmed?
- Is there a need for additional case finding (consider person-place-time) and others with potential exposure?
- How should this be organized and who will implement and lead this?
- What information needs to be collected as part of case finding activities (e.g., patient characteristics, healthcare exposures, laboratory findings)? Has there been a call for cases at the local, state (e.g., Health Alert Network, known as HAN), or national (e.g., Epidemic

Information Exchange, called Epi-X) level? If so, what was the message and how was it delivered?
- Based on currently available information, is there a need to implement enhanced infection control practices within affected facilities?
- Have public health partners taken steps to ensure that patient isolates will be saved? Has any testing been performed on patient or product samples? If so, what were the dates of the testing and what are the preliminary findings? What types of testing are still needed to inform decision-making?
- Are unopened product samples available to be collected?

Product-related questions
- Does patient-level documentation (e.g., medical record) indicate the exact product name, the product manufacturer, product code, lot number, and expiration date? If not, are there receipts or invoices from the time of the treatment or procedure to assist in identifying these data?
- What is the exact product name? Is there a product code?
- Who is the manufacturer?
- What is the lot number and expiration date?
- Can you provide pictures of the product, including how it is packaged and stored?
- Can you provide pictures or Internet links for product brochures, instructions for use (IFU), and other documentation?
- Can you describe how this product is used?
- Can you describe how this product is reprocessed?
- Can you describe how reprocessing information (such as biological indicators, chemical indicators, and physical parameters) is collected and monitored?
- If the product is reusable, has it been quarantined?
- Has a third-party service or repair organization been involved in the maintenance of the device?
- Has a MedWatch report been filed by the healthcare facility?

For devices,
- What is the intended function of the device? (What is it FDA-cleared for?) What was it being used for?
- Is the device still working properly? Has any malfunction or damage been identified?
- Can a Unique Device Identifier be located?
- Is the device part of a kit? Does the device have accessories? If so, what are the accessories? Are any of these components sterile, reprocessed or part of a kit?
- Is this a water-containing device or is water or ice used with the device? If so, is the water (or ice) sterile, filtered, or tap?
- Is the device intended to be sterile or non-sterile?
- Is this a single-use device?
- Does the device require reprocessing? If so, explain how, where, and by whom.
- Is there a facility document that describes how reprocessing should occur?
- Does the device require maintenance? If so, what is the schedule? When was maintenance last performed? By whom? Was any damage identified?

- When was the device acquired and first put into use? What is the vendor's role?
- What is the current status (e.g., still in use, removed from service) of the device?
- What steps have been taken to evaluate use of the device with regards to: Routine handling (including adherence with IFUs and any applicable infection control practices)? Reprocessing and/or maintenance?

For drugs,

- What is/are the clinical indications/applications? How is/are the drugs in question being administered and for what purpose?
- What is the drug FDA-approved for? What was it being used for?
- Are the drugs labeled as sterile or non-sterile?
- Were they supplied as part of a kit?
- In what form were the drugs supplied (e.g., vial, bag, syringe)?
- For manufactured drugs, provide the National Drug Code (NDC) and lot number, or, if applicable, the Investigational New Drug (IND) Application identifier.
- For drugs supplied by a compounder, provide pharmacy information.
- How were the drugs acquired (e.g., from a distributor, OTC, online)?
- How are the drugs stored prior to being administered? Under what conditions?
- How were the drugs manipulated between receipt at your facility and administration? Under what conditions? By whom?
- Did multiple patients receive drug from a single-use medication container or from a multi-dose medication container? Explain.
- If any of the drugs are controlled substances, how is security maintained? Is the drug delivered in a multi-dose vial or container? If so, are the opened date and expiration date clearly labeled?
- What is the current status (e.g., still in use, removed from service) of the drug(s)?
- Is there any remaining drug available to be saved or tested?
- Is this an unopened product (e.g., unaccessed vial) or has it been opened?
- Does the saved drug product have the same lot number and expiration date as what the patient received?
- What steps have been taken to evaluate use of the drug with regards to: Storage, handling, preparation and administration (including adherence with IFUs and applicable infection control practices or pharmacy standards)?
- Evaluation of potential for abuse, mishandling or tampering?

For the most up-to-date version please visit: https://www.corha.org/resources/corha-interim-potential-medical-product-related-infection-outbreak-assessment-questions/

Key Resources & Additional Reading

Medical Product Investigations – Key Resources

1. Dolan SA, Arias KM, Felizardo G et.al. APIC position paper: Safe injection, infusion, and medication vial practices in health care. Am J Infect Control. 2016 Jul 1;44(7):750-7.
2. FDA. MedWatch. Accessed at: https://www.accessdata.fda.gov/scripts/medwatch/index.cfm.
3. FDA. Sharing Non-Public Information. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM446165.pdf.

Contaminated Medical Products – Selected Examples

Endoscopes

1. Botana-Rial M, Leiro-Fernández V, Núñez-Delgado M, Álvarez-Fernández M, Otero-Fernández S, et. al. A Pseudo-Outbreak of Pseudomonas putida and Stenotrophomonas maltophilia in a Bronchoscopy Unit. 2016;92(4):274-278.
2. FDA. Infections Associated with Reprocessed Duodenoscopes. Available at: https://www.fda.gov/medical-devices/reprocessing-reusable-medical-devices/infections-associated-reprocessed-duodenoscopes
3. Guy M, Vanhems P, Dananché C, Perraud M, Regard A, et. al. Outbreak of pulmonary Pseudomonas aeruginosa and Stenotrophomonas maltophilia infections related to contaminated bronchoscope suction valves, Lyon, France, 2014. Euro Surveill. 2016 Jul 14;21(28).
4. Humphries RM, Yang S, Kim S, Muthusamy VR, Russell D, et. al. Duodenoscope-Related Outbreak of a Carbapenem-Resistant Klebsiella pneumoniae Identified Using Advanced Molecular Diagnostics. Clin Infect Dis. 2017 Oct 1;65(7):1159-1166.
5. Kumarage J, Khonyongwa K, Khan A, Desai N, Hoffman P, Taori SK. Transmission of multi-drug resistant Pseudomonas aeruginosa between two flexible ureteroscopes and an outbreak of urinary tract infection: the fragility of endoscope decontamination. J Hosp Infect. 2019 May;102(1):89-94.
6. Rahman MR, Perisetti A, Coman R, Bansal P, Chhabra R, Goyal H. Duodenoscope-Associated Infections: Update on an Emerging Problem. Dig Dis Sci. 2019 Jun;64(6):1409-1418.

Heater-Cooler Devices

1. CDC. Contaminated Heater-Cooler Devices: Health Alert. Available at: https://www.cdc.gov/hai/outbreaks/heater-cooler.html
2. Lyman MM, Grigg C, Kinsey CB, et. al. Invasive Nontuberculous Mycobacterial Infections among Cardiothoracic Surgical Patients Exposed to Heater–Cooler Devices. Emerg Infect Dis. 2017 May; 23(5): 796–805.
3. Perkins KM, Lawsin A, Hasan NA, et al. Notes from the Field. Mycobacterium chimaera Contamination of Heater-Cooler Devices Used in Cardiac Surgery — United States. MMWR Morb Mortal Wkly Rep 2016;65:1117–1118.

4. van Ingen J, Kohl TA, Kranzer K, Hasse B, Keller PM, et. al. Global outbreak of severe Mycobacterium chimaera disease after cardiac surgery: a molecular epidemiological study. Lancet Infect Dis. 2017 Oct;17(10):1033-1041.

Medication/Product

1. Dolan SA, Littlehorn C, Glodé MP, Dowell E, Xavier K, et. al. Association of Bacillus cereus infection with contaminated alcohol prep pads. Infect Control Hosp Epidemiol. 2012 Jul;33(7):666-71.
2. Kainer MA, Reagan DR, Nguyen DB, et. al. Fungal Infections Associated with Contaminated Methylprednisolone in Tennessee. N Engl J Med. 2012 Dec 6; 367(23): 2194–2203.
3. West K, Janelle S, Schutz K, Hamilton S, Mayo K, et. al. Outbreak of Serratia marcescens bacteremia in pediatric patients epidemiologically linked to pre-filled heparin flushes. Infect Control Hosp Epidemiol. 2019 Jul 25:1-2.
4. Hudson MJ, Park SC, Mathers A, Parikh H, Glowicz J, Dar D, Nabili M, LiPuma JJ, Bumford A, Pettengill MA, Sterner Jr MR. Outbreak of Burkholderia stabilis infections associated with contaminated nonsterile, multiuse ultrasound gel—10 states, May–September 2021. Morbidity and Mortality Weekly Report. 2022 Dec 12;71(48):1517.
5. CDC. Outbreak of Extensively Drug-resistant *Psuedomonas aeruginosa* Associated with Artificial Tears. Available at: https://www.cdc.gov/hai/outbreaks/crpa-artificial-tears.html
6. Schwartz NG, Hernandez-Romieu AC, Annambhotla P, Filardo TD, Althomsons SP, Free RJ, Li R, Wilson WW, Deutsch-Feldman M, Drees M, Hanlin E. Nationwide tuberculosis outbreak in the USA linked to a bone graft product: an outbreak report. The Lancet Infectious Diseases. 2022 Nov 1;22(11):1617-25.
7. Hartnett KP, Powell KM, Rankin D, Gable P, Kim JJ, Spoto S, Breaker E, Hunter R, Dotson N, McAllister G, Stevens V. Investigation of Bacterial Infections Among Patients Treated With Umbilical Cord Blood–Derived Products Marketed as Stem Cell Therapies. JAMA Network Open. 2021 Oct 1;4(10):e2128615.

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