Identifying and Responding to Medical-Product Associated Illness Outbreaks
Focus on Pharmacy Compounding

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FDA Intergovernmental Meeting on Pharmacy Compounding
Overview

- Pharmacy-compounded sterile preparations are an important component of our healthcare system.
- Identification and investigation of contaminated medications is a core public health activity.
- CDC, along with FDA and state/local public health partners, has been increasingly responding to outbreaks linked to pharmacy compounding.
- Monitoring the safety of non-manufactured (e.g. compounded) injectable medications poses challenges.
CDC/DHQI Major Goals

Safe Healthcare is Our Priority

Prevent Healthcare Associated Infections
  - Device or Procedure Related
  - Setting or Practice Related

Prevent Adverse Drug Events
  - Monitor Vaccine Safety

Identify Emerging Threats in Healthcare Settings
  - Prevent Occupational Infections among Healthcare Workers
  - Improve Healthcare System Preparedness to Respond to Threats

Prevent Infections by Multidrug Resistant Organisms
  - Minimize Antimicrobial Resistance
  - Promote Appropriate Use of Antimicrobial Drugs
CDC Healthcare Outbreak Response Activities
Division of Healthcare Quality Promotion (DHQP)

- Responsibility for investigating infections and other adverse events related to healthcare delivery
- Consults (mostly with state health departments) are a major part of our daily activity
  - Cases, clusters, infection control breaches
- Over the past five years, we have averaged about one field investigation (“Epi-Aid”) per month
- Medical product-associated outbreaks
  - Many outbreaks and clusters potentially involve contamination of parenteral medications
Injectable Medications
Intrinsic vs. Extrinsic Contamination

- Safe healthcare delivery relies on supply of safe sterile injectable medications (free of intrinsic contamination)
  - Oversight required to assure injectable medications are supplied in a sterile form
    - Majority are manufactured → FDA
  - Maintain sterility from point of manufacture or production to point of administration
  - Extrinsic contamination can result from mishandling of medications during preparation and administration

CDC addresses and promotes “Injection Safety” through guidelines and educational efforts

ONE NEEDLE, ONE SYRINGE, ONLY ONE TIME.
Safe Injection Practices Coalition
www.ONEandONLYcampaign.org
Investigations Involving Injectable Medications: Intrinsic vs. Extrinsic Contamination

- Infections may signal a wider problem
  - Require investigation by public health partners
  - Association with injections vs. other procedures
  - Multiple drug products are often involved

- Example: case of endophthalmitis in a patient who received injections at an eye clinic
  - Could represent EXTRINSIC contamination from clinic error
  - Could represent INTRINSIC product contamination, especially if compounded product was source of injectable medication
Fungal Endophthalmitis Associated with Compounded Products

Christina A. Mikosz, Rachel M. Smith, Moon Kim, Clara Tyson, Ellen H. Lee, Eleanor Adams, Susanne Straif-Bourgeois, Rick Sowadsky, Shannon Arroyo, Yoran Grant-Greene, Julie Duran, Yvonne Vasquez, Byron F. Robinson, Julie R. Harris, Shawn R. Lockhart, Thomas J. Török, Laurene Mascola, and Benjamin J. Park; for the Fungal Endophthalmitis Outbreak Response Team

- March 2012 – CA health department notified of a cluster of 9 cases of fungal endophthalmitis
- All case-patients had vitrectomy procedures at a Los Angeles ambulatory surgery center during October-December 2011
- Local health department determined all cases associated w/ single lot of Brilliant Blue G dye from a FL compounding pharmacy
- Multistate investigation involving CDC, FDA, pharmacy boards and health departments
Epidemic curve of confirmed and probable cases of postprocedural fungal endophthalmitis, by week of procedure.
Figure 1. Confirmed and probable cases of postprocedural fungal endophthalmitis, by state, United States, 2011–2012. Infections occurred after exposure to a product from Franck’s Compounding Lab (Ocala, FL, USA), through March 2012, when the implicated product was recalled. *In California, cases were associated with exposure to each product.
Main Street Family Pharmacy – Newbern, Tennessee

Source: Tom Wilemon, The Tennessean
Multistate Investigation of Suspected Infections Following Steroid Injections, 2013

- During April-May, several patients presented with cyst or abscess, months after receipt of injections at a primary care clinic
  - Illinois Health Department notified
  - Patients received steroid injections (methylprednisolone acetate, MPA) from compounded 10 ml preservative-free “multi-dose” vials

- Two North Carolina patients with skin abscesses following receipt of steroid injections reported to MedWatch
  - Same medication and same compounding pharmacy as Illinois cases
  - Triggers a rapid and coordinated response involving various components of FDA and its field offices, CDC, state health departments and pharmacy boards

- Main Street Family Pharmacy recalled injectable steroids on May 24; extended to all sterile products on May 28

http://www.cdc.gov/hai/outbreaks/TN-pharmacy/
A total of 26 patients in 4 states developed a suspected infection associated with injection of a product, labeled as sterile, that was distributed by the Main Street Family Pharmacy (Newbern, TN) since December 1, 2012.

Health departments determined 96 facilities in 17 states received recalled MPA. 81 facilities in 15 states administered MPA; these were provided instructions on product recall/testing, patient notification, case finding and reporting.

http://www.cdc.gov/hai/outbreaks/TN-pharmacy/
Additional Findings and Messages

• CDC and FDA identified bacteria and fungi cultured from unopened vials of preservative-free MPA

<table>
<thead>
<tr>
<th>Medication</th>
<th>Lot Number</th>
<th>Preliminary Microbial Identification</th>
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</thead>
<tbody>
<tr>
<td>PF MPA 80 mg/mL - 10 mL per vial</td>
<td>011413dan</td>
<td>Bacillus pumilus, Bacillus cereus/thuringiensis/mycoides*, Roseomonas gilardii, Acinetobacter ursingii, Alternaria sp., Cladosporium sp.</td>
</tr>
<tr>
<td>PF MPA 80 mg/mL - 10 mL per vial</td>
<td>010913dan</td>
<td>Bacillus licheniformis, Penicillium sp.</td>
</tr>
</tbody>
</table>

• Healthcare providers were reminded of their responsibilities
  – Ensure that all recalled products from MSFP are no longer in use
  – Complaints from patients exposed to products from MSFP should be promptly reported to FDA MedWatch and health department
  – Use individual containers of compounded or preservative-free medicine for a single-patient only
  – Promptly report to MedWatch any infection that might be related to a medication or medical device, even absent a recognized outbreak
Detecting and Responding to Pharmacy Compounding Outbreaks

Shared responsibility which requires coordination and timely flow of information
Summary & Closing Thoughts

- Shared goal: robust system for identifying—and investigating—adverse events that are potentially associated with medications produced and distributed under 503A/B
- State and local health departments have a firm legal foundation to respond to, request information from, and investigate potential disease outbreaks and cases of reportable diseases
- This hinges on signal detection and reporting
  - Will require investment in educating and equipping healthcare providers and patients (the end users)
“Response Takes Many Forms”
Examples from the CDC Side

- First 24 hours: Devised response strategies, arranged and managed partner communications, and assisted with series of press releases from FDA and 3 state health departments
- Days 2-4: Developed case report forms, a risk-based patient-centered notification framework, and scripts for facilities to use when contacting patients
- Over the following weeks, actively coordinated and led the multi-state health department response, which involved: conference calls with affected states, FDA, and the TN Board of Pharmacy; laboratory testing of clinical specimens as well as speciation of bacterial and fungal contaminants detected by FDA in product samples; media interviews; development and frequent updates of a dedicated CDC web site ([http://www.cdc.gov/hai/outbreaks/TN-pharmacy/index.html](http://www.cdc.gov/hai/outbreaks/TN-pharmacy/index.html)); and monitoring overall progress at the state and facility levels.