Coccidioides and the Holes in Swiss Cheese

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Disclosures

- None
- Not an expert in crisis management

Objectives

- Review the events surrounding April 2
- Decontamination process
- Results of staff exposure
- Perspectives from Incident Management process
- Review the lessons learned esp. for laboratory safety

Coccidioides immitis/posadasii

- 1st described in 1892 in an Argentine soldier
- In 1936 “Desert Fever” linked to *Coccidioides immitis*
- Extensive characterization given population expansion westwards and advent of WWII
- Dr. Charles Smith laid the foundation of modern knowledge
  - Influx of military personnel & POWs to region
  - Mechanisms of infection and clinical findings
  - Skin test positivity defining asymptomatic cases and geographic risk
  - Risks for severe disease

Hirschmann. Clin Infect Dis. 2007; 44:1202-7

Coccidioides and Lab Safety

- 1st accidental lab exposure occurred in 1929
- Harold Chope
- Arthroconidia inhalation from old culture
- Developed acute pulmonary infection 9 days later
- Recovered after protracted illness
- Individual cases in laboratory workers since
- Published larger scale laboratory event?

Hirschmann. Clin Infect Dis. 2007; 44:1202-7

Brief Primer

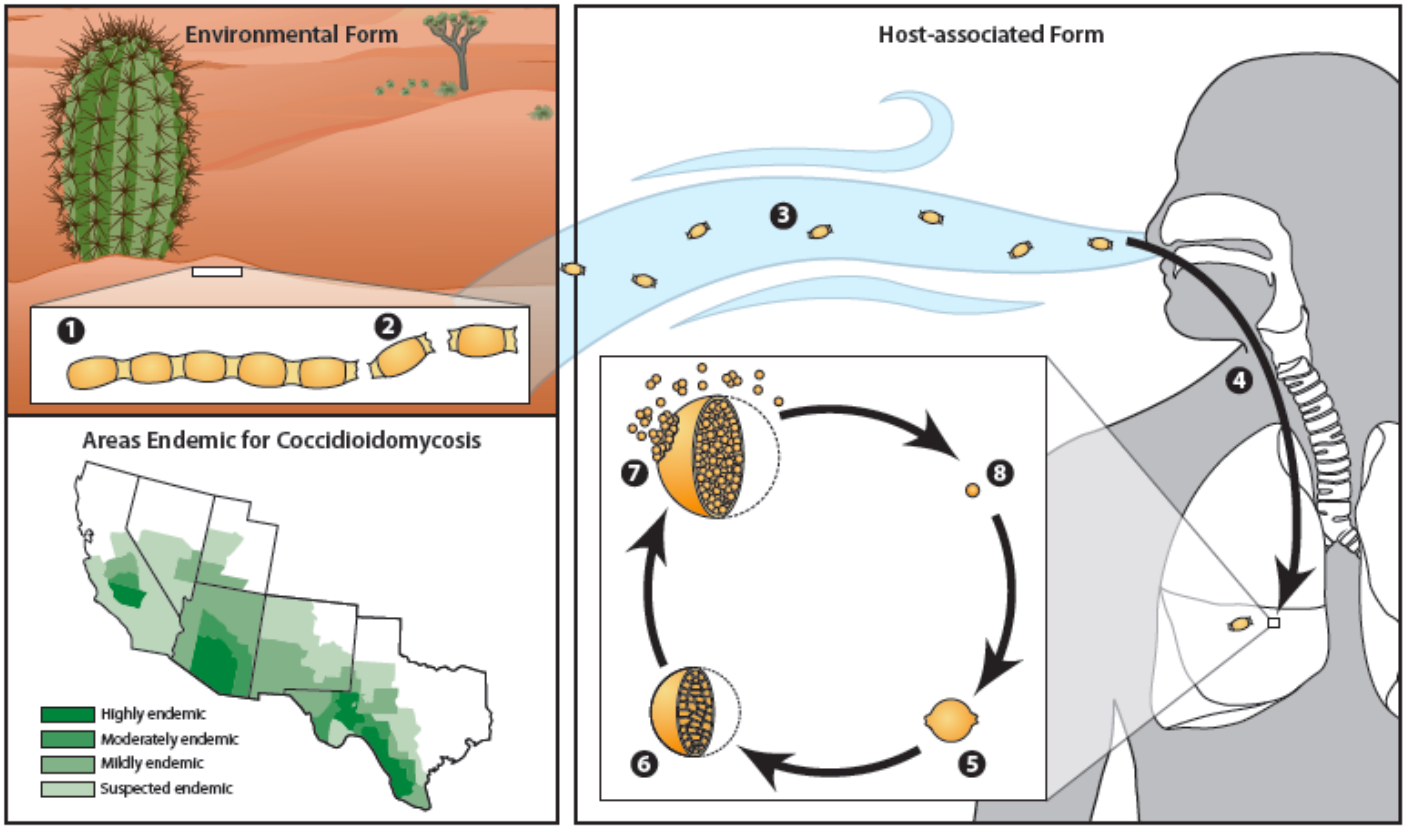
- 50% of cases symptomatic
  - Pulmonary (self limited to life threatening)
  - Extra pulmonary (0.5%): MSK, dermatological, CNS
  - Filipino/African descent, 3rd trimester, immunocompromised
- Incubation period 1-4 weeks
- Infectious dose as low as 1-10 arthroconidia
  - Severity of illness dose dependent
- Serology very sensitive/specific
  - IgM within 7-21 days
  - IgG within 2-3 mos

Thompson *et al.* Clin Infect Dis 2011; 53(6):e20-24

Brief Primer

- Mold phase
  - Environmental/soil
  - Diagnostic stage seen within the lab
  - Alternating arthroconidia with fragile attachment
  - Very easily detached for inhalation
  - Poses laboratory hazard

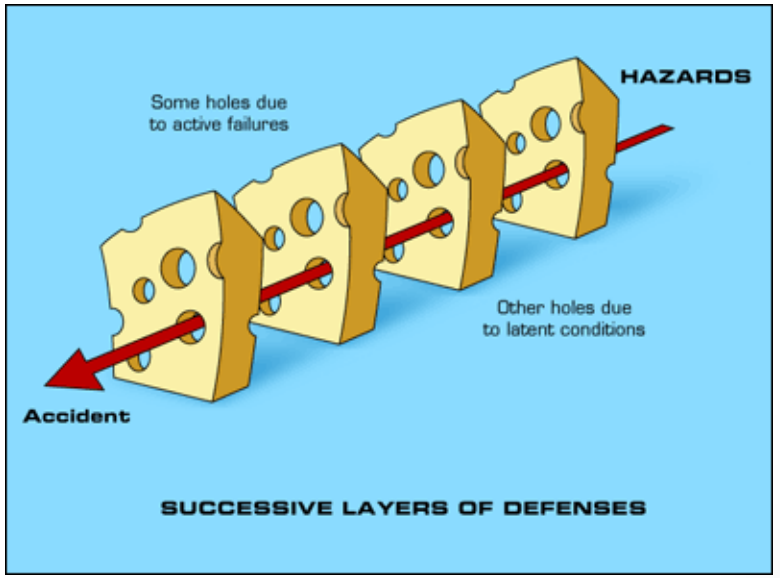
Life Cycle



In the environment, *Coccioides ssp.* exists as a mold (1) with septate hyphae. The hyphae fragment into arthroconidia (2), which measure only 2-4 µm in diameter and are easily aerosolized when disturbed (3). Arthroconidia are inhaled by a susceptible host (4) and settle into the lungs. The new environment signals a morphologic change, and the arthroconidia become spherules (5). Spherules divide internally until they are filled with endospores (6). When a spherule ruptures (7) the endospores are released and disseminate within surrounding tissue. Endospores are then able to develop into new spherules (6) and repeat the cycle.

Swiss Cheese Model

- Understand system failures
- Every process step is a “slice”
  - Slices provide defense
  - Steps can fail in various ways (# of holes)
  - Probability of failure proportional to hole size



Background

- Waterloo Wellington Regional Micro lab (WWRML)
  - Housed in an old part of Grand River Hospital (1950s)
  - Pre-dates “modern equipment”
  - Predominantly bacteriology lab
  - Serves many key patient populations at 2 major hospitals
    - Respirology
    - 3 ICUs (2 med/surg & 1 CVSx)
    - Hematology-oncology
  - No direct mycology work on any sample
    - All respiratory isolates sent to Public Health Ontario labs (PHOL)
    - Fungal growth on bacteriology media
      - Preliminary testing for *Aspergillus sp.* by microscopy in BSC
      - All sent to PHOL

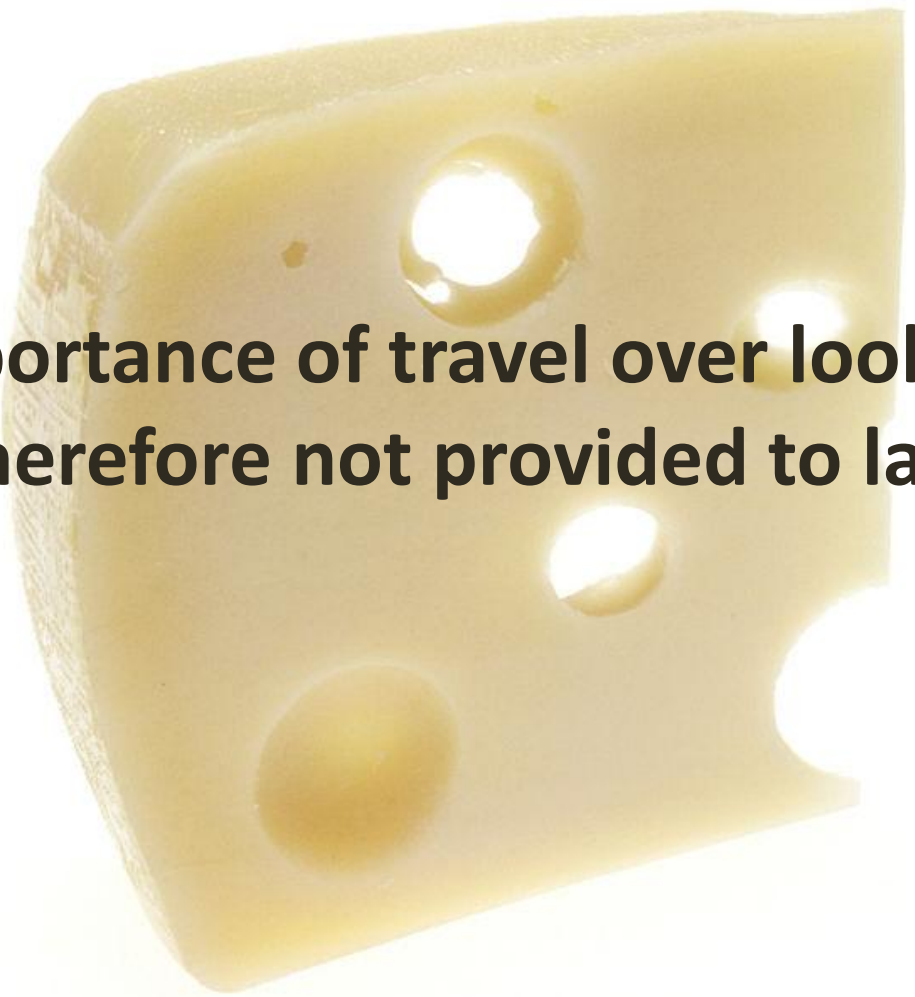
Hole #1

We not looking for or thinking about weird fungus and molds (hence very limited knowledge & experience in our MLTs)

Prologue – March 16 to April 1

- 55 yr. male was admitted with CAP
- Standard antibiotics given
- CXR – infiltrate plus ipsilateral effusion
- Sputum not taken
- Diagnostics/therapeutic thoracentesis
- Patient recently in Arizona approx. 2 weeks prior
  - Not relayed to WWRML nor factored into the DDx
- Pleural fluid microbiology (SBA/CHOC) at 48 hrs.
  - G+ bacilli consistent with *Corynebacterium sp.*
  - Yeast like colony

Hole #2

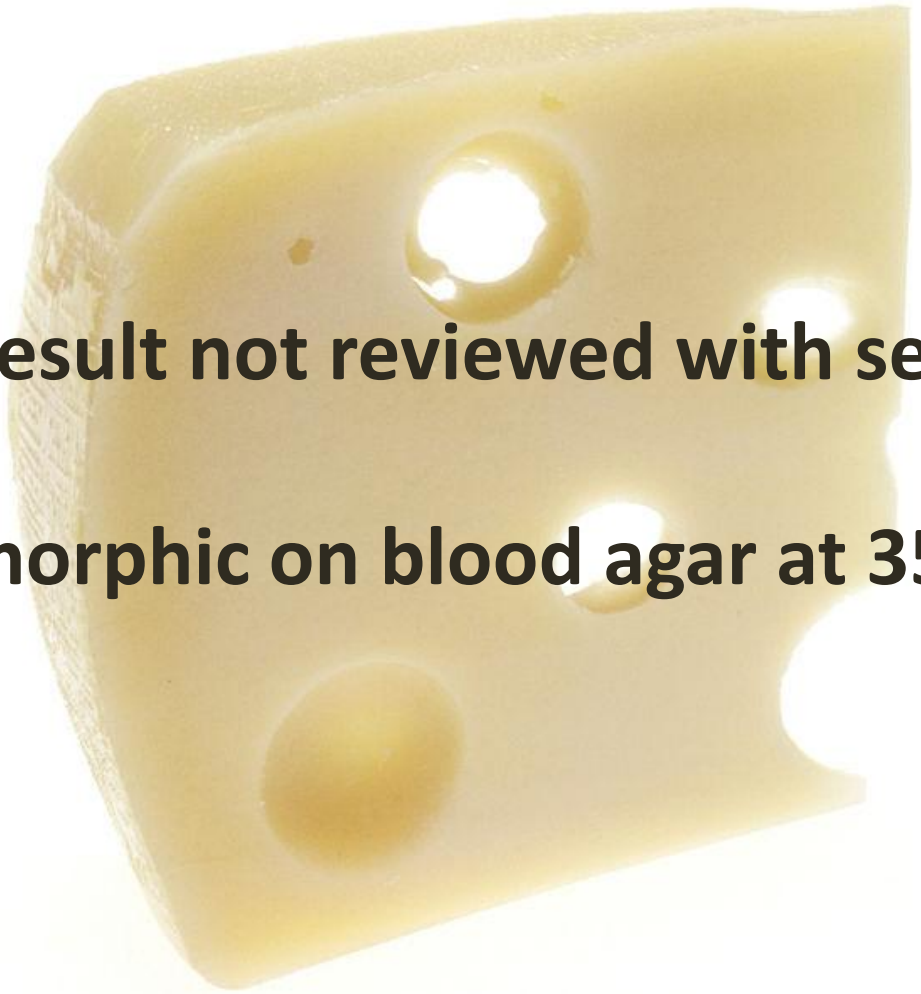


Importance of travel over looked
Therefore not provided to lab

Prologue – March 16 to April 1

- Yeast wet mount looks filamentous
  - Outside of BSC – typical practice
- MLT contacts MRP due to unusual yeast
  - Travel history still not clicking
- MRP suggests it's a contaminant
  - Specimen re-tested
  - Sub cultured "yeast" sent to reference lab
- SBA/CHOC plates kept at room temperature
  - "Keeps Bin"
  - "Buddy" sealed in Para-film

Holes #3 &4



Unusual result not reviewed with senior staff

Dimorphic on blood agar at 35°C

Prologue – March 16 to April 1

- March 19 plates
  - ‘Yeast’ grows again
  - Filamentous on wet mount
  - No senior MLTs or Med Micro alerted
  - Presumed that these plates were discarded that day
  - No documentation exists to confirm
- 2 separate MLTs have done wet mount preps outside BSC
- 2 Para-filmed plates stored at room temperature
- 2 weeks pass……

Prologue – March 16 to April 1

- March 30 at 4:48 pm (Friday)
  - PHOL confirms yeast as *Coccidioides immitis/posadasii*
  - Alerted by phone/fax
- Unable to reach MRP/inpatient respirology service
- Discussion about staff exposure to yeast
  - Thought to be low risk
  - Meeting to review with occupational health on Monday AM

Hole #5

Unaware of Retained Plates in “Keeps Bin” (overlooked given exposure discussion)

April 2…

- Occupational Health Meeting (10:30 am)
  - Reviewed events
  - Identified potentially exposed MLTs
  - Commented on low risk of exposures given immature mycelium
- “Where are the plates?”
- Dead silent…..
- Realization of retained plates & disposal date
- 7 day cycles for “Keeps Bin”
- Lots of phone calls

April 2…

- Events in the lab (learned retrospectively)
  - At approx. 7:45 am the 2 week “Keep Bins” were dumped into the biohazard bin
  - Unsure of the following:
    - Did the plates open on initial dumping?
    - Was the lid used on the bin consistently?
    - How much more was dumped on top?
    - How many times was the bin “bellowed” open and closed?
- Approx. 11:30 am the microbiology lab was evacuated
- Exposure time of approximately 4 hours

April 2…

- Entire Dept. of Laboratory Medicine evacuated 1 hr. later
  - Knowledge that micro lab was under positive pressure
  - Doors in microbiology kept open (climate reasons)
  - Recirculation of air in other parts of department
- Area sealed off
- All HVAC shut off
- Met and reviewed the situation with senior staff
  - Where the plates discarded?
  - Was the seal compromised?
- Made contact with OAHPP Emergency Management team

April 2…

- Member of our “HazMat” team suited up and entered
  - Plates present in bin
  - Seals compromised
  - Plate surfaces covered with white fluffy mold
- Incident Management System commenced
- Laboratory services officially shut down
- Occupational Health began decontamination of staff

Hole #6

“Buddy” Para-filmed plates not as reliable (vs. individual sealed plates esp. 2 weeks old)

Challenges that Day

- Not knowing the exact nature of HVAC for department
  - Full knowledge at 10 pm that night
- No facilities to decontaminate 90 staff
  - Staff coming/going
  - 1 very cold shower on site
  - Professional decontamination team – all male
- Assembling a staff exposure list for follow up
- Immediate communication to medical staff
  - Seriousness of event and impact on patient services
- Finding the external expertise to help
- Arranging lab services for patients

Live at Work for a Week

- Lots of teleconferences & emails
- Issues to re address with changing information
  - Health & safety of staff
  - Extent & procedure for decontamination
    - Lab space, equipment, personal belongings
    - Risk to patient care areas
  - Communications
    - Exposed staff
    - Hospital and local media
  - Short and long term plans for business continuity
    - In house and partner hospital
    - ICUs, Oncology, OBGYN/Peds/NICU, elective surgery
  - How to account for & report on the lost samples

Handicapped

- Very little firm knowledge
- No previous published precedent
- Outside of the endemic area
  - Ontario is not Arizona
- No rapid answers to key questions

VIEWPOINTS

Expert Opinion: What To Do When There Is *Coccidioides* Exposure in a Laboratory

David A. Stevens,[1,2,3,4,5] Karl V. Clemons,[1,4,5] Hillel B. Levine,[4] Demosthenes Pappagianis,[7] Ellen Jo Baron,[5,6] John R. Hamilton,[3] Stanley C. Deresinski,[1,5] and Nancy Johnson[2]

Departments of [1]Medicine and [2]Infection Control and [3]Clinical Microbiology Laboratory, Santa Clara Valley Medical Center, and [4]California Institute for Medical Research, San Jose, [5]Division of Infectious Diseases and Geographic Medicine and [6]Clinical Microbiology Laboratory, Stanford University Medical School, Stanford, and [7]Department of Medical Microbiology, University of California, Davis, California

Inadvertent exposure to *Coccidioides* species by laboratory staff and others as a result of a mishap is not an uncommon cause of infection in clinical microbiology laboratories. These types of infection may occur in laboratories outside the endemic areas, because the etiologic agent is unexpected in the submitted specimens and because personnel may be unfamiliar with the hazards of dealing with *Coccidioides* species in the laboratory. Coccidioidal infections are often difficult to treat, and outcomes can be poor. Here, we emphasize prevention and an approach to a laboratory accident that minimizes the risk of exposure to laboratory staff and staff in adjacent areas. On the basis of an artificially large exposure to arthroconidia that may occur as a result of a laboratory accident, a conservative approach of close observation and early treatment of exposed staff is discussed.

Coccidioides is a fungus maintaining a saprophytic cycle in soil in geographic regions with hospitable climatic conditions. In soil, it grows as mycelia, eventually bearing arthroconidia, the infectious propagule. The conidia are inhaled, initiating a respiratory infection. In some people, particularly those of dark-skinned races, immunosuppressed patients, and pregnant women, the infection can disseminate and cause life-threatening conditions. Most persons with only a primary infection do not require treatment, but all with disseminated disease do [1, 2]. Of the deep mycoses, coccidioidomycosis is thought to be the least responsive to treatment [1, 2].

Accidental laboratory exposure to *Coccidioides* species is the major cause of clinical laboratory-acquired fungal infections [3]. With the increase in travel and tourism to endemic regions, exposure to patient specimens for culture becomes even more likely. We have received queries regarding clinical laboratory exposure to *Coccidioides* species. The consequences of past exposure have been described elsewhere [4], but to our knowledge, this subject has not been fully addressed for 26 years [4]. The Web site for the Centers for Disease Control and Prevention indicates that "there are currently no guidelines about *Coccidioides* exposure in the laboratory" [5]. Thus, we have formulated a recommended plan for dealing with such incidents. Useful background reading regarding the pathogenesis of coccidioidomycosis [1], laboratory safety in general [6], and laboratory safety with regard to fungal pathogens in particular [7, 8] is given in the references.

Prevention. The most important step is preventing such exposures. Most queries have come from laboratories outside the endemic area. A mold culture was opened, and later it was realized that the plate contained coccidioidal arthroconidia. The principle to be followed is as follows: no culture of an unknown mold should be opened outside a biological safety cabinet appropriate for containing *Coccidioides*. *Coccidioides* growth may be visible in 48 h as grey-white wisps on culture media, later as white and/or buff-colored colonies with aerial hyphae. The formation of alternating barrel-shaped arthroconidia begins as early as 4 days of culture [9]. Further information about the maturation of *Coccidioides* and the degree of risk is presented below. If physicians would regularly alert the laboratory that *Coccidioides* is suspected in a submitted specimen or that the patient has a history of travel to endemic areas, then this information would require laboratory staff to maintain appropriate precautions.

A technique used in some laboratories to avoid the problem of examining an unknown mold that might prove to be *Coccidioides* is to freeze a petri dish with an

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1058-4838/2009/4906-0014$15.00
DOI: 10.1086/605441

External Partners

- OAHPP team
- Decontamination company
- Environmental hygienist
- CDC & NML
- Provider of lab services
  - SMGH
  - HRLMP
  - GGH
- Sales reps and biotech companies
- (Tim Horton's)

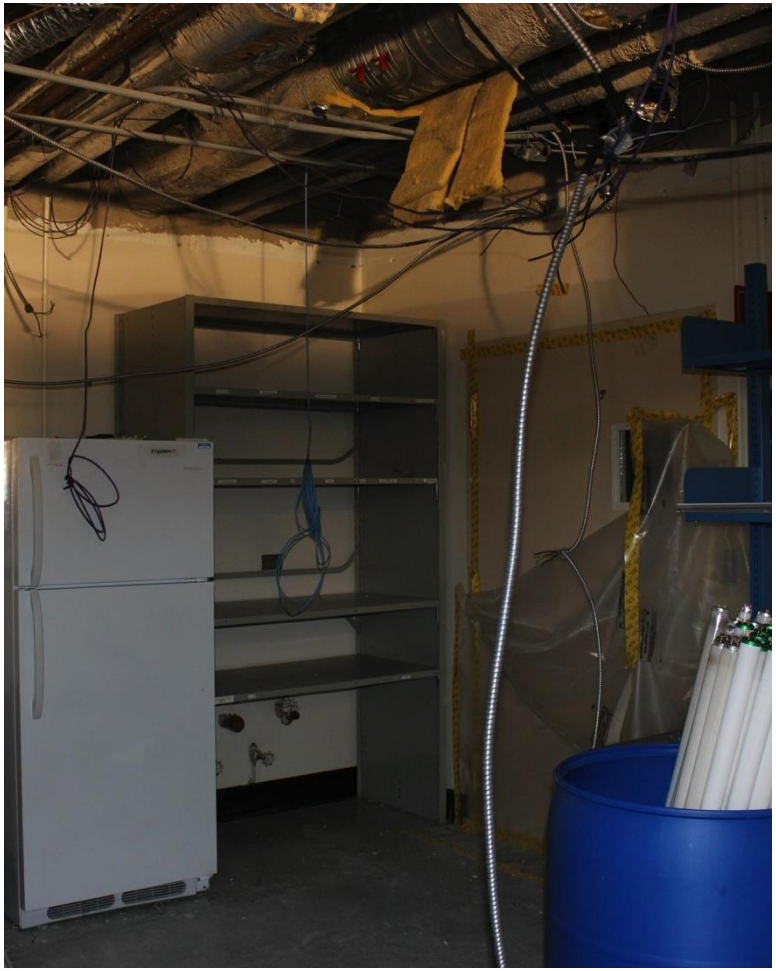
Decontamination

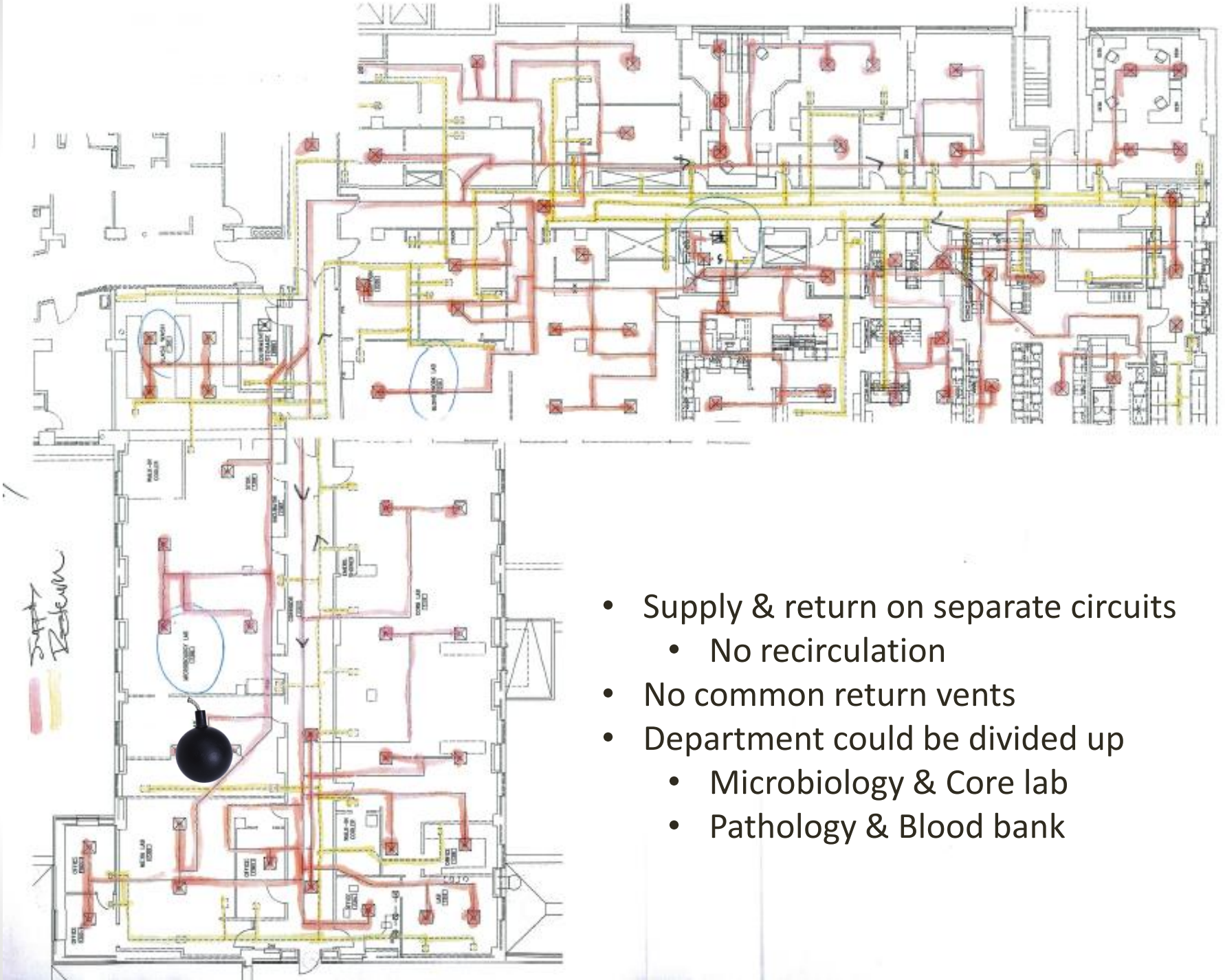
- Unknowns made for tough choices
  - Actual spore exposure beyond the bin?
  - Effects of positive pressure & possible air recirculation?
    - Within Microbiology? Rest of the lab?
  - How does one gauge effectiveness of decontamination?
  - Preventing damage to analytical machines?
    - With their tiny cooling fans
- Incubation period prevented clinical cases demonstrating extent of spread
  - Vice versa given low infectious dose
- Under the gun to get it done!

Decontamination

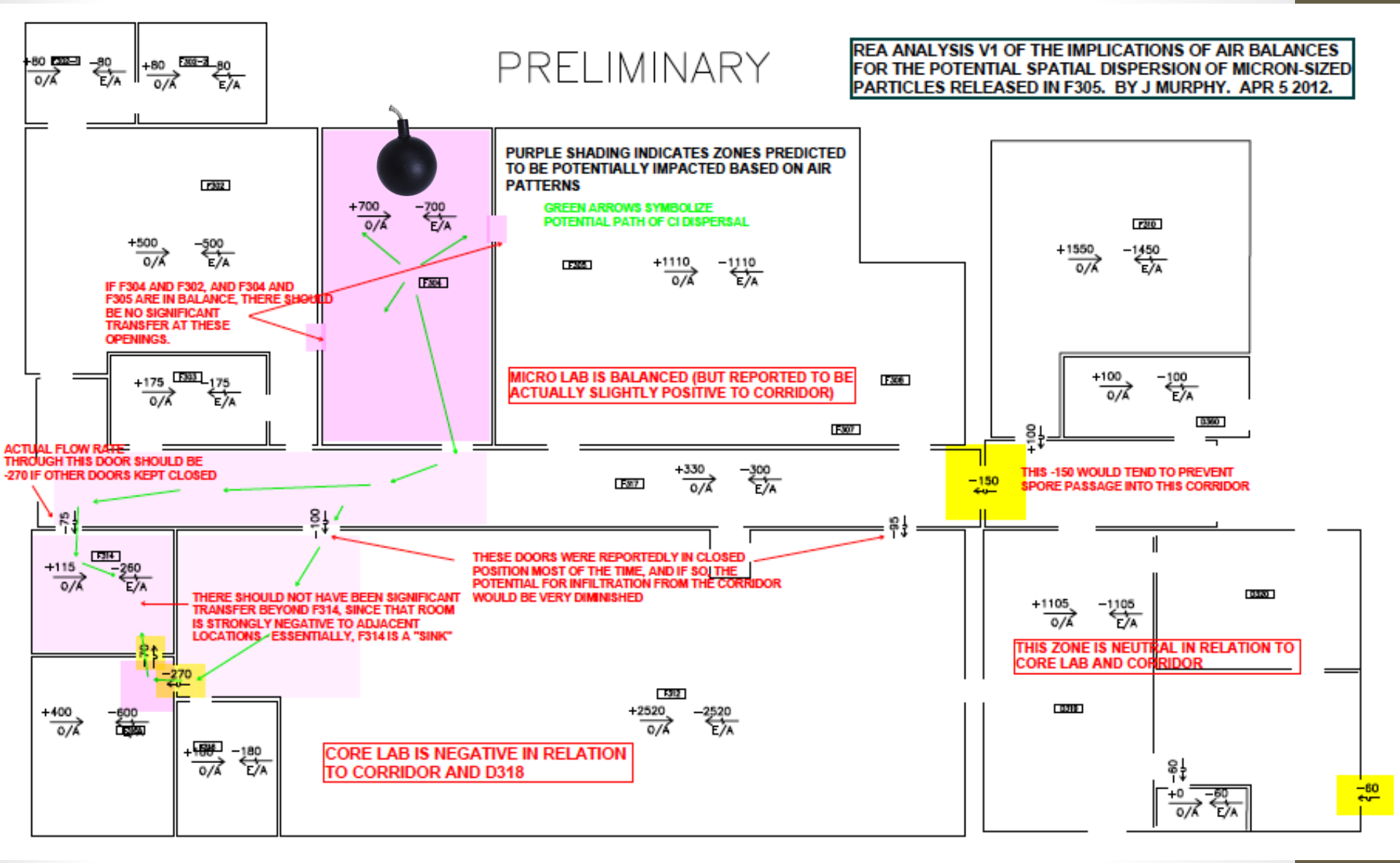
- Environmental hygienist
  - Spore release and air flow modeled
  - Tape lift surface sampling for microscopy
- Advice from CDC and NML
  - Accelerated 4.5% hydrogen peroxide
  - H_2O_2 fogging contemplated
    - Too much uncertainty about leakage to patient care areas

KA-BOOM





- Supply & return on separate circuits
  - No recirculation
- No common return vents
- Department could be divided up
  - Microbiology & Core lab
  - Pathology & Blood bank


PRELIMINARY
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PURPLE SHADING INDICATES ZONES PREDICTED TO BE POTENTIALLY IMPACTED BASED ON AIR PATTERNS
GREEN ARROWS SYMBOLIZE POTENTIAL PATH OF CI DISPERSAL
IF F304 AND F302, AND F304 AND F305 ARE IN BALANCE, THERE SHOULD BE NO SIGNIFICANT TRANSFER AT THESE OPENINGS.
MICRO LAB IS BALANCED (BUT REPORTED TO BE ACTUALLY SLIGHTLY POSITIVE TO CORRIDOR)
ACTUAL FLOW RATE THROUGH THIS DOOR SHOULD BE -270 IF OTHER DOORS KEPT CLOSED
THESE DOORS WERE REPORTEDLY IN CLOSED POSITION MOST OF THE TIME, AND IF SO, THE POTENTIAL FOR INFILTRATION FROM THE CORRIDOR WOULD BE VERY DIMINISHED
THIS -150 WOULD TEND TO PREVENT SPORE PASSAGE INTO THIS CORRIDOR
THERE SHOULD NOT HAVE BEEN SIGNIFICANT TRANSFER BEYOND F314, SINCE THAT ROOM IS STRONGLY NEGATIVE TO ADJACENT LOCATIONS. ESSENTIALLY, F314 IS A "SINK"
THIS ZONE IS NEUTRAL IN RELATION TO CORE LAB AND CORRIDOR
CORE LAB IS NEGATIVE IN RELATION TO CORRIDOR AND D318
+700 0/A −700 E/A
+500 0/A −500 E/A
+1110 0/A −1110 E/A
+1550 0/A −1450 E/A
+175 0/A −175 E/A
+100 0/A −100 E/A
+330 0/A −300 E/A
+115 0/A −260 E/A
+2520 0/A −2520 E/A
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+0 0/A −60 E/A
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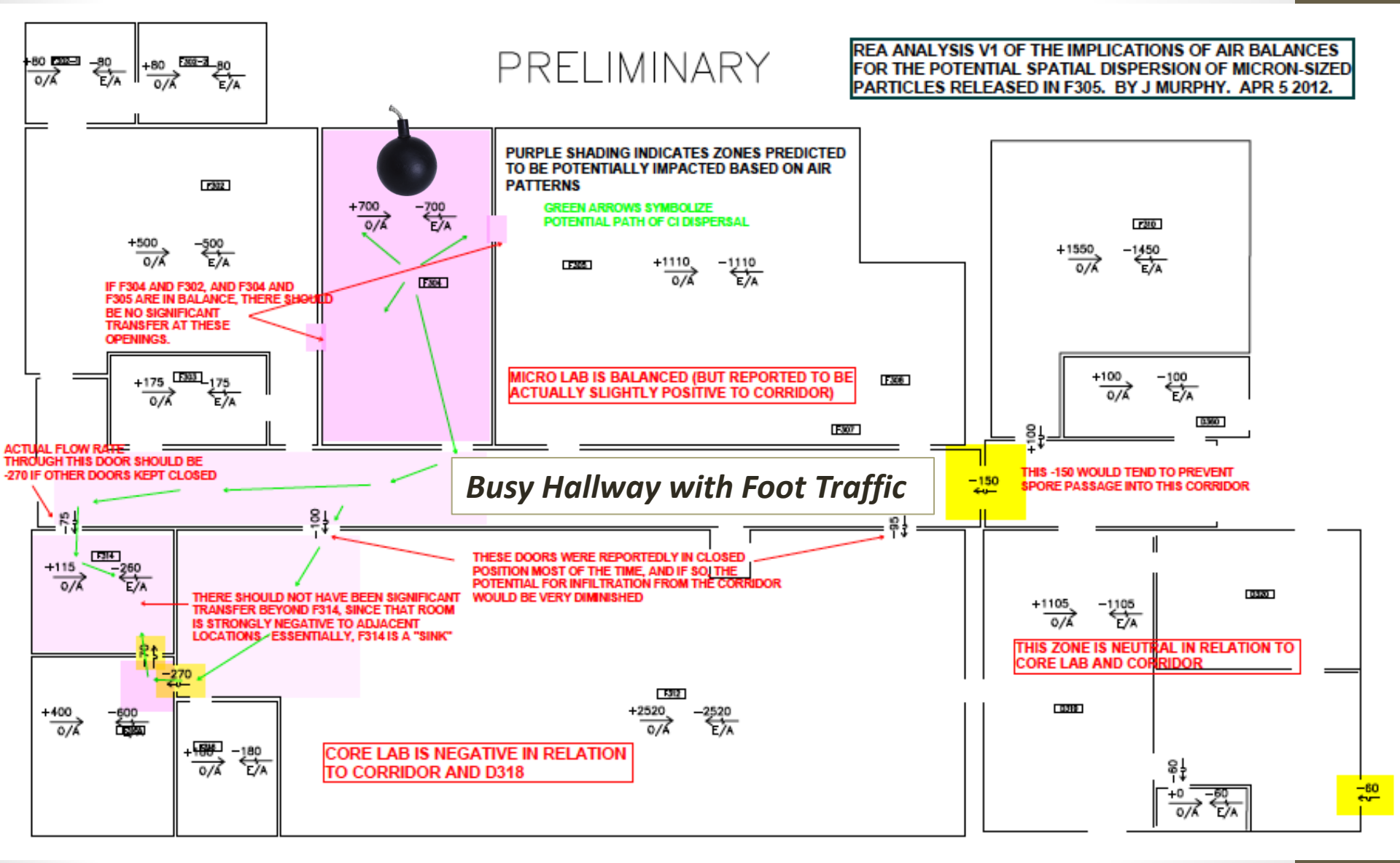
−270
−80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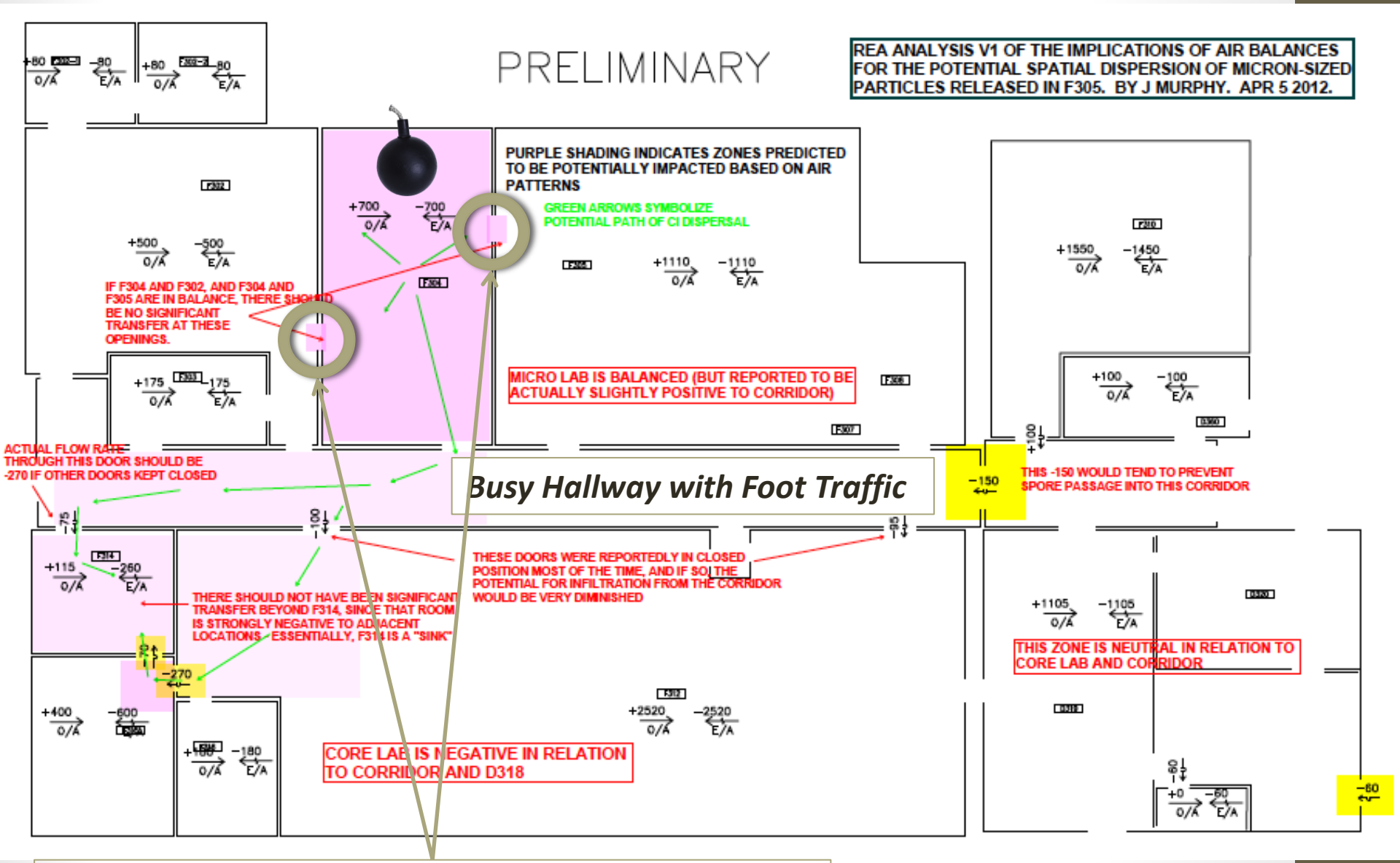
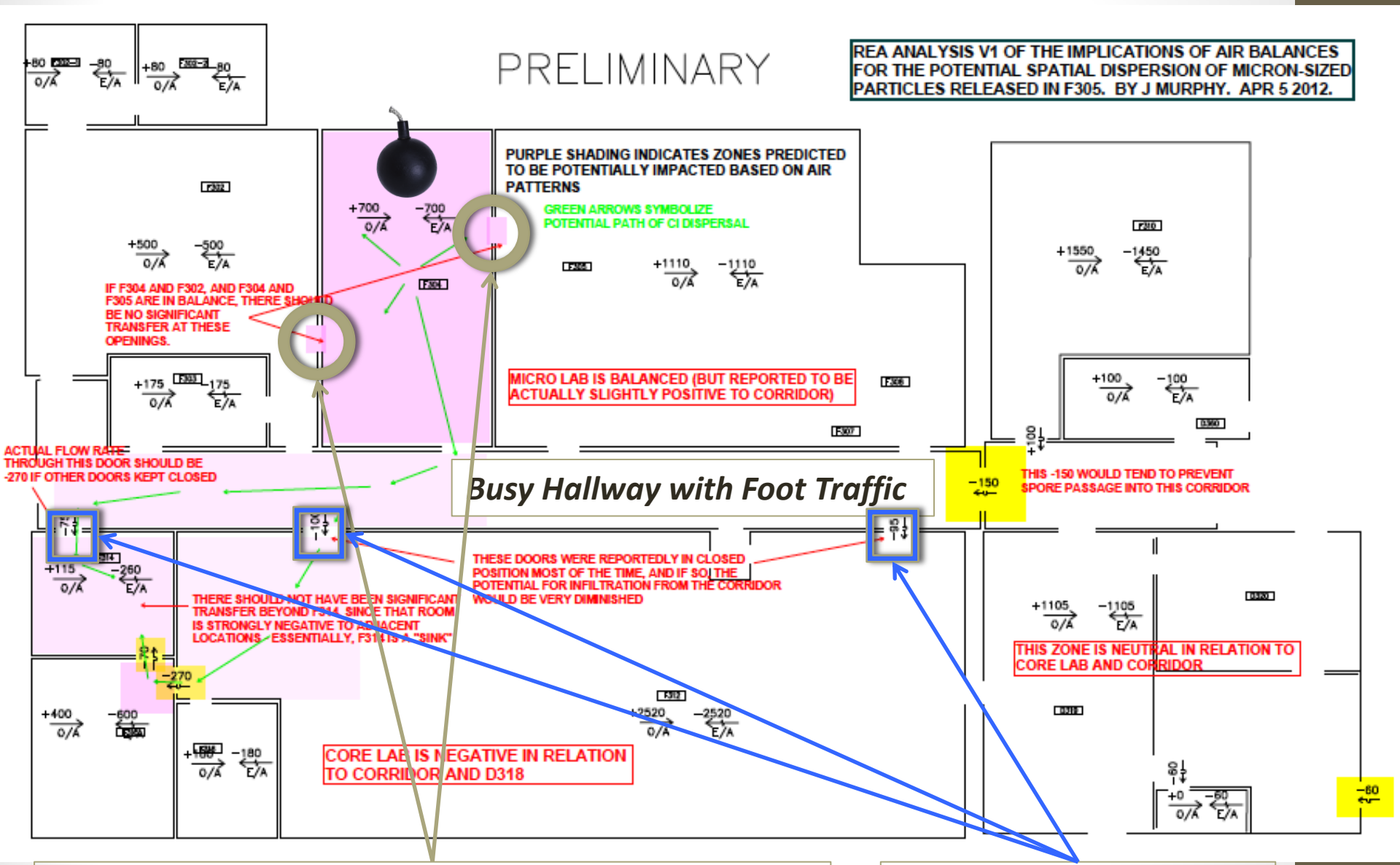
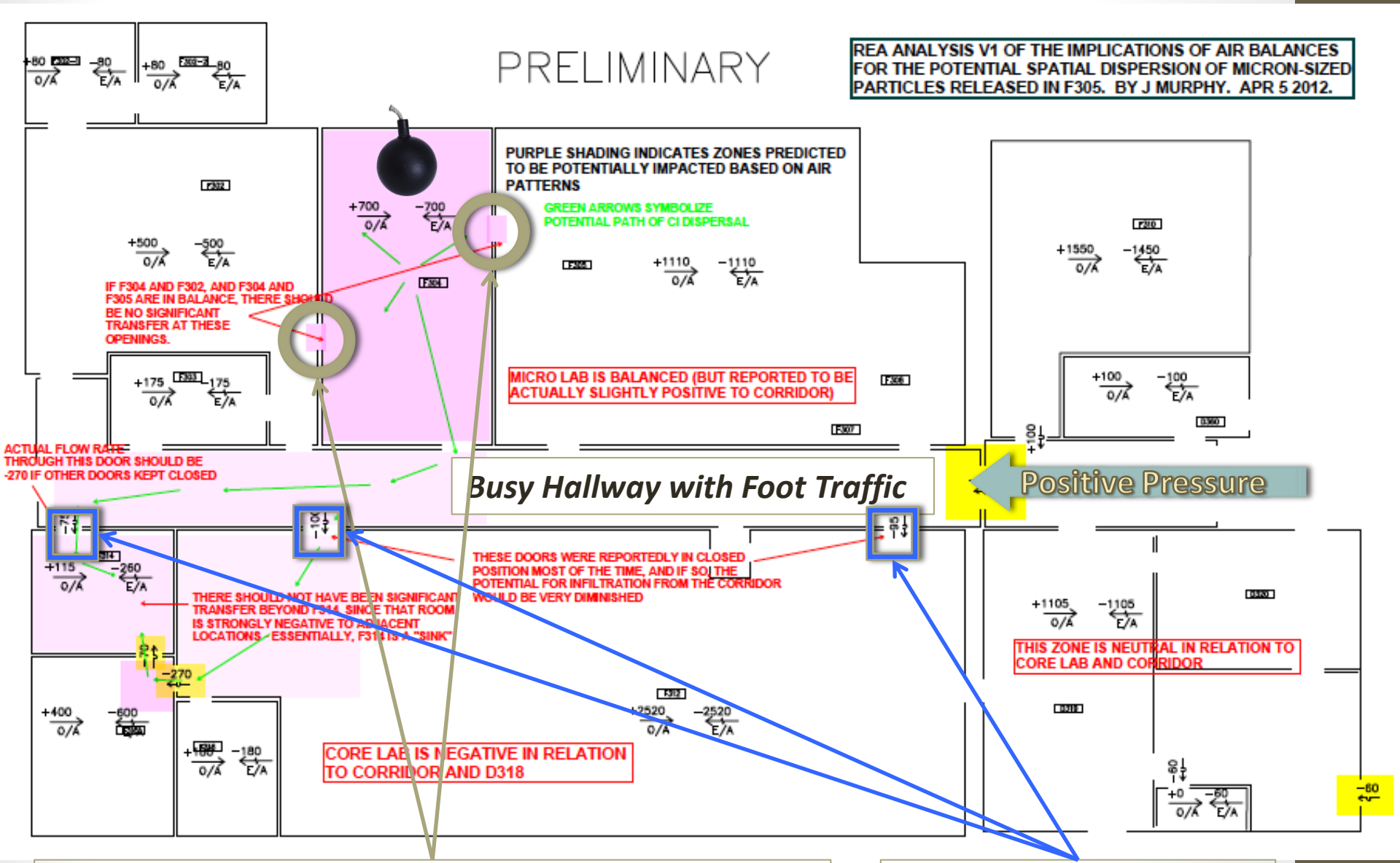


Frequent intracompartmental travel in Microbiology



Frequent intracompartmental travel in Microbiology

Doors open or used often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Frequent intracompartmental travel in Microbiology
Doors open or used often

Decontamination

- Spore dispersion model
  - Microbiology lab & adjacent hallway
    - Atmosphere concentration dropped rapidly over 4 hours
    - Limited area for surface contamination (if at all)
  - Protective effect of air exchanges of HVAC
    - Should of left exhaust fans on
- All tape lift samples negative for arthroconidia
  - Could not prove/refute dispersion model
  - Insufficient environmental spore counts on surfaces
  - Chemical based quality indicator

Decontamination

- Dispersion model guided final decision
- Pathology & Blood bank were deemed no risk
  - Saved a lot of irreplaceable pathology samples
- Microbiology & Core lab received full decontamination
  - Recognition that Core lab may not be affected
  - Little appetite to risk staff safety twice
  - The model had limitations & lacked clinical outcomes
- Time does equal money
  - Had to be $$$ and/or able to tolerate 4.5% H_2O_2
  - Had to be non air exposed (e.g. freezer stocks)
- All surfaces passed using quality indicator

Clinical Outcomes

- 90 staff underwent decontamination April 2
  - 13 staff from Microbiology
- Under Occupational Health's purview
  - Questionnaire
    - Personal itinerary that morning
    - Clock time and duration in high risk zones
  - Serology
    - Baseline, 2-3 & 6 weeks post exposure
    - Delayed IgG with fluconazole?
  - Informed consent for post exposure prophylaxis (fluconazole)
  - Education on symptoms to report
- REB required consent to report each data point
  - 70% overall; 100% of microbiology

Thompson *et al.* Clin Infect Dis 2011; 53(6):e20-24

Clinical Outcomes

- Risk strata guided by spore dispersion model
  - Tape lifts did not help rule in/out areas
  - Very aware of the low infectious dose
  - People were not “static” in their rooms
- Most difficult part to manage and message!
  - Individual risk tolerance
  - Fear
  - Rational use of fluconazole prophylaxis
    - esp. with no proven benefit in occupational exposures

Clinical Outcomes

High Risk

- Microbiology lab
- Propensity for disseminated infection
  - Pregnancy
  - Ethnicity
  - Immunocompromised
- In Microbiology close to time of spore release

Medium Risk

- Hallway
- Core lab
- Transient exposures in microbiology

Clinical Outcomes

- Prophylaxis
  - All microbiology staff (100% uptake)
  - Medium risk location but with risk of disseminated disease
  - Medication stopped
    - No symptoms
    - 3 week serology negative
  - Hard to retract the message on this as data evolved
- Ensured sufficient antifungal supply for possible cases

Clinical Outcomes

- Serology
  - IgM/IgG EIA, CFT and Immunodiffusion
  - 2 IgM + at baseline (EIA only) - asymptomatic
  - No seroconversions through 6 weeks
- Symptom reporting
  - Some anxiety and background noise
  - Brief fevers or influenza like illness (≤48 hrs.) most common
    - 5 NPS for respiratory viral PCR (15 targets)
      - 1 positive for coronavirus
      - Respiratory viral outbreak due to working in close quarters
  - No convincing cases
    - Thought 3 MLTs at ground zero would get ill

Disaster Averted

- In the end something stopped the spores
  - Dispersion model predicted rapid atmospheric removal
    - May not explain why all micro MLTs were saved
    - Model was correct with limited surface contamination
  - Unknowns
    - Lid on the bin
    - Seal broke later
    - Electrostatic effect of biohazard bag
  - Good old fashion luck despite confluent growth
- Pain of possibly over decontaminating core lab
  - Had a major impact on our hospital
    - Equipment loss & extra cost/time
    - Headache of temporary business continuity
    - Key patient services with increased TATs (e.g. CBC taking 10 hrs.)

Business Continuity

- Biggest focus once decontamination plan set
- Massive IT mobilization to start up a temporary site
- Short term challenges
  - Surge capacity at SMGH
  - Handling special populations/situations
  - Managing TATs
    - Surge in STAT requests
  - Getting IT to interface systems
    - Efficient ordering
    - Reduce paper results and result viewing
  - Finding temporary equipment & physical space for temp. lab

Business Continuity

- Longer term challenges
  - Managing the paper results/data entry
  - Staff fatigue & frustration
  - Further refining TATs
  - Determining order of re sequencing of testing
    - Equipment & supplies
    - Quality control
    - Staffing

Debriefing

- Number of stakeholders
  - Ministry of Labor
  - Insurance company
  - OLA
  - Risk Management
    - Lost patient data/samples
  - Quality Management
    - Root cause analysis
  - Board and SLT
- Lots of debriefing….

The Holes in Review

- Not looking for or thinking about weird fungus
- Very limited knowledge & experience in our MLTs
- Importance of travel over looked & not provided to lab
- Unusual result not reviewed with senior staff
- Dimorphic on blood agar at 35°C
- Unaware of Retained Plates in “Keeps Bin”
- “Buddy” Para-filmed plates not as reliable

Improbable vs. Impossible

- Rare organism under rare circumstances
- How does one ensure lab safety?
  - Universal vs. targeted approach
  - Proactive solutions vs. reactive solutions
  - Time/work efficient
  - Challenging number of possible combinations
  - Building experience when infrequent
  - Coal face commitment to policies/procedures
- Most solutions
  - Spotting the risky organism (front end)
  - Minimizing dangerous steps in growth phase (back end)
  - Avoiding past mistakes

Our Fixes

- Education & Cultural
  - CAP external proficiency for fungal microscopy
  - Enhanced biological safety module for yearly review
  - Improve MLT comfort to review odd cases/isolates
  - Re enforce notion of trusting experience/instincts
  - Added notations to various SOPs to highlight risky situations
    - e.g. small colonies at day 2-3 on CHOC from blood cultures

Our Fixes

- Analytical Steps
  - Lactophenol cotton blue as fungal stain
  - Hands off all white molds
  - All molds are individual Para-filmed/bagged
  - Minimal mold work up for *Aspergillus sp.* (microscopy)
  - Plates are preemptively sealed/bagged & initially opened in BSC
    - Kept for extended incubation
      - Esp. respiratory and/or at room temperature (e.g. *Norcardia*)
    - Clinical history suggests a Level 3 organism
    - Previous significant isolate
  - Engage additional precautions if suspicious isolate

Our Fixes

- Post analytical
  - LIS flags Level 3 organisms to cues MLT
  - All “Keeps Bin” samples
    - Kept Para-filmed/bagged separately at 4°C
    - Minimum plates kept pending reference lab report
    - Recorded what/where samples are kept on work sheet
  - Required documentation that samples autoclaved
  - Bench biohazard bins are smaller & bag lined
    - Tied off and discarded into larger bin with minimal disruption

Trial by Fire

- 2 Level organisms since April 2012
- *Brucella melitensis* bacteremia
  - Perfect!
  - Front end protection
  - Universal processing of blood cultures in BSC
  - Roaring loud and clearly heard

Trial by Fire

- *Burkholderia pseudomallei* CF patient
  - CF sputum ordered
  - Worked up as *B. cepacia* from selective media (not in BSC)
  - 2 MLTs exposed (low risk)
  - Vitek 2 flagged it with 99% identification
  - Prompted senior MLT review
  - Colony morphology “roared” but no one listened

What About the Other *Coccidioides*?

- WWRML processed BAL samples a chronic pneumonia patient
  - February 2012
  - No travel history provided (but was in Arizona)
  - No growth on SBA/CHOC locally
  - Heavy growth on mycology media at PHOL
- Blind spot created for April's event
  - Our "yeast" looked *Candida sp.* like
  - No roar to hear

Summary

- Unusual events do happen
- Concern from a very high risk *Coccidioides* exposure seemed not materialize
- Decontamination of laboratory space presents unique challenges
- Unexpected interruption of laboratory services has ripple effects
- Sometimes there are no right or easy answers
- Good partnerships and help from colleagues were critical for our recovery