Practical guide to outbreak investigations

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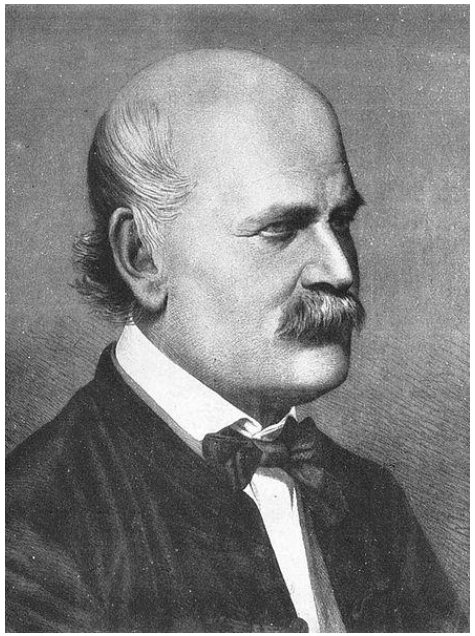
Los Angeles County Department of Public Health



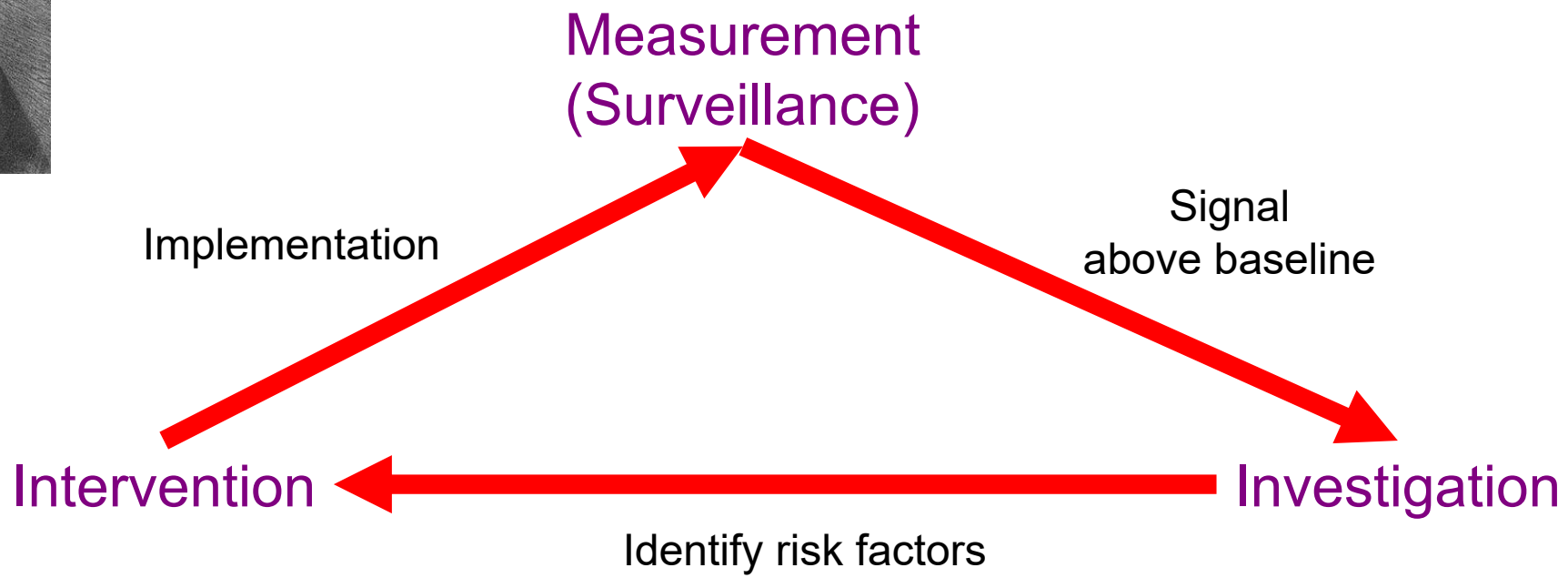
Objectives

- Outline the critical steps in outbreak investigations.
- Identify common pitfalls
- Learn a few practical pearls learned in the trenches



Clinical Epidemiology & Infection Prevention in the 21st Century

Essentially the same process & principles as Semmelweis developed in 19th century



Helpful hints before we get started

- Be organized!
  - Start outbreak report from the beginning and add to it as the investigation progresses.
  - Record all dates.
  - Collect all emails in a special file.
- Communicate early and often
  - Call a meeting with the local unit early and keep them informed.
  - Keep administration aware of the progress.
  - Develop a communication plan early (external and internal).
- Don’t reinvent the wheel—ask colleagues



Most importantly: Lock your door and don't answer the phone when you are trying to get work done.



General scheme of outbreak investigations

loosely based on Goodman, et al. Am J Epidem 1990;132:9-16.

County of Los Angeles Public Health

Identification of potential outbreak

Verify diagnosis

Confirmation of increased rate

Create a line lis

Create a case definition
Time, place, clinical factors

Call Health Dept

Test hypothesis
Case control study
Environmental cultures

Develop hypothesis
Review literature
Speak to experts

tive c inding
ening, lab

Set-up database
Definitions
terminology

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Surveillance

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This is a marathon, so pace yourself…..



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Let’s work through a real-life outbreak:



2014…







NEWS









By —
Associated Press

Leave your feedback

Share

What to know about Crimea, the peninsula Russia seized from Ukraine in 2014

1. https://www.theguardian.com/world/2014/oct/15/ebola-epidemic-2014-timeline
2. https://www.nationalgeographic.com/health/article/new-ice-bucket-challenge-als-mental-health
3. https://www.pbs.org/newshour/world/what-to-know-about-crimea-the-peninsula-russia-seized-from-ukraine-in-2014
4. https://www.cnet.com/reviews/apple-watch-series-1-review/
5. https://news.wttw.com/2016/08/02/black-lives-matter-coalition-releases-1st-official-platform

Sentinel case

- Mid-December CEIP was contacted by ID physician with case of CRE immediately after ERCP.
  - 40 F with lupus nephritis, h/o renal transplant, HCV
  - ERCP for dilated common bile duct and stones on CT
  - Blood cultures drawn on hospital day #2: *MDR K. pneumoniae*
- Immediate actions
  - Reviewed ERCP cleaning process
  - Initiated investigation--review of all CRE cases during 2014

Klebsiella pneumoniae susceptibility

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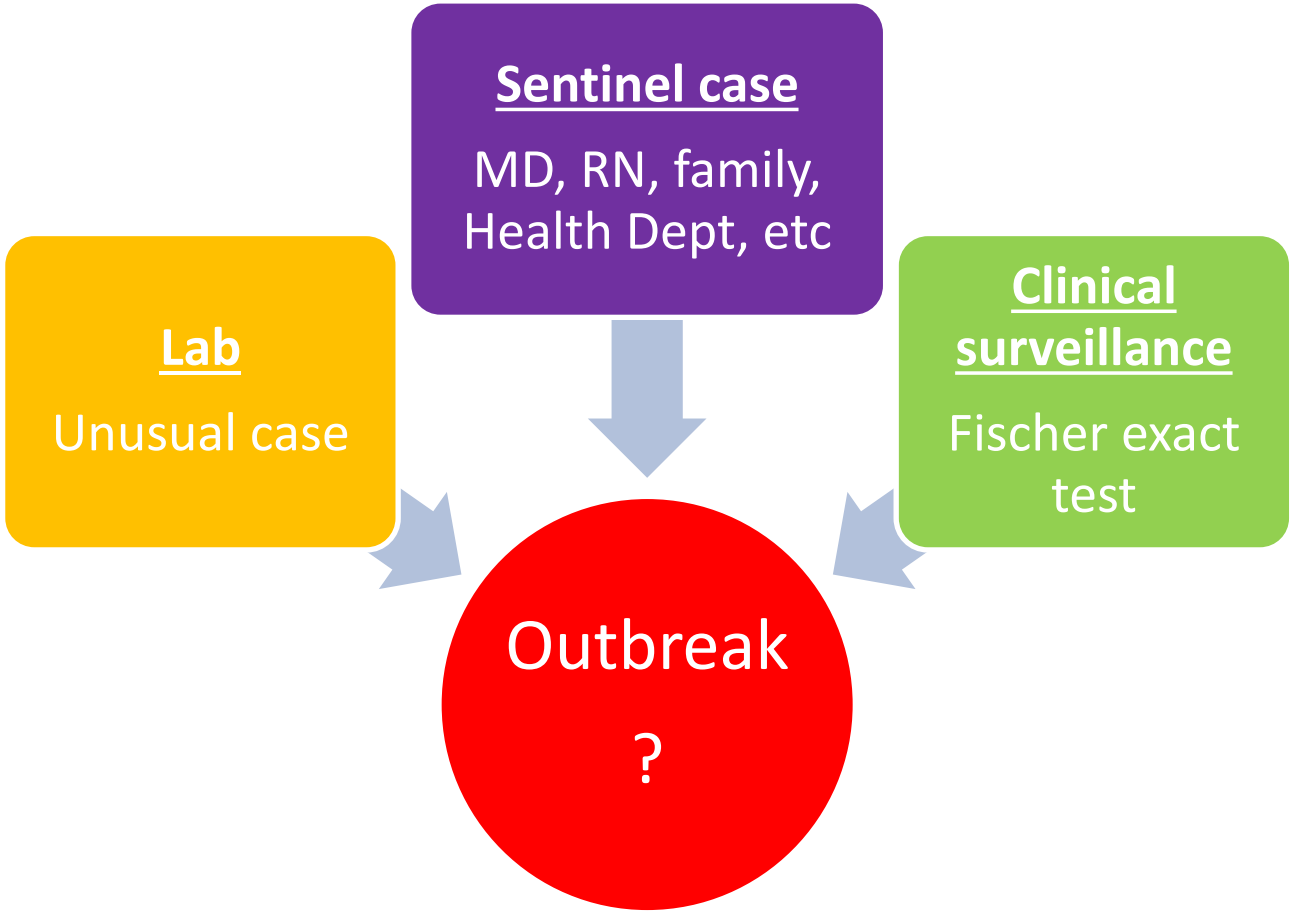
Antibiotic	MIC	Susceptibility interpretation
Amikacin	>32	Resistant
Ampicillin + sulbactam	>32	Resistant
Ceftriaxone	>32	Resistant
Ceftazidime + avibactam (not available at time)	4	Susceptible
Ciprofloxacin	>2	Resistant
Colistin	≤0.5	Susceptible
Doripenem	16	Resistant
Ertapenem	>2	Resistant
Gentamicin	>10	Resistant
Imipenem	4	Resistant
Meropenem	16	Resistant
Minocycline	2	Susceptible
Pipercillin + tazobactam	>256	Resistant
Tigecycline	4	Intermediate
Tobramycin	>10	Resistant
Trimethoprim/sulfamethoxazole	>4/80	Resistant

Identification of outbreak—keep an open mind



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Do we really have an outbreak?

- **Verify diagnosis and confirm clinical cases**
  - Review all potential cases to confirm diagnoses

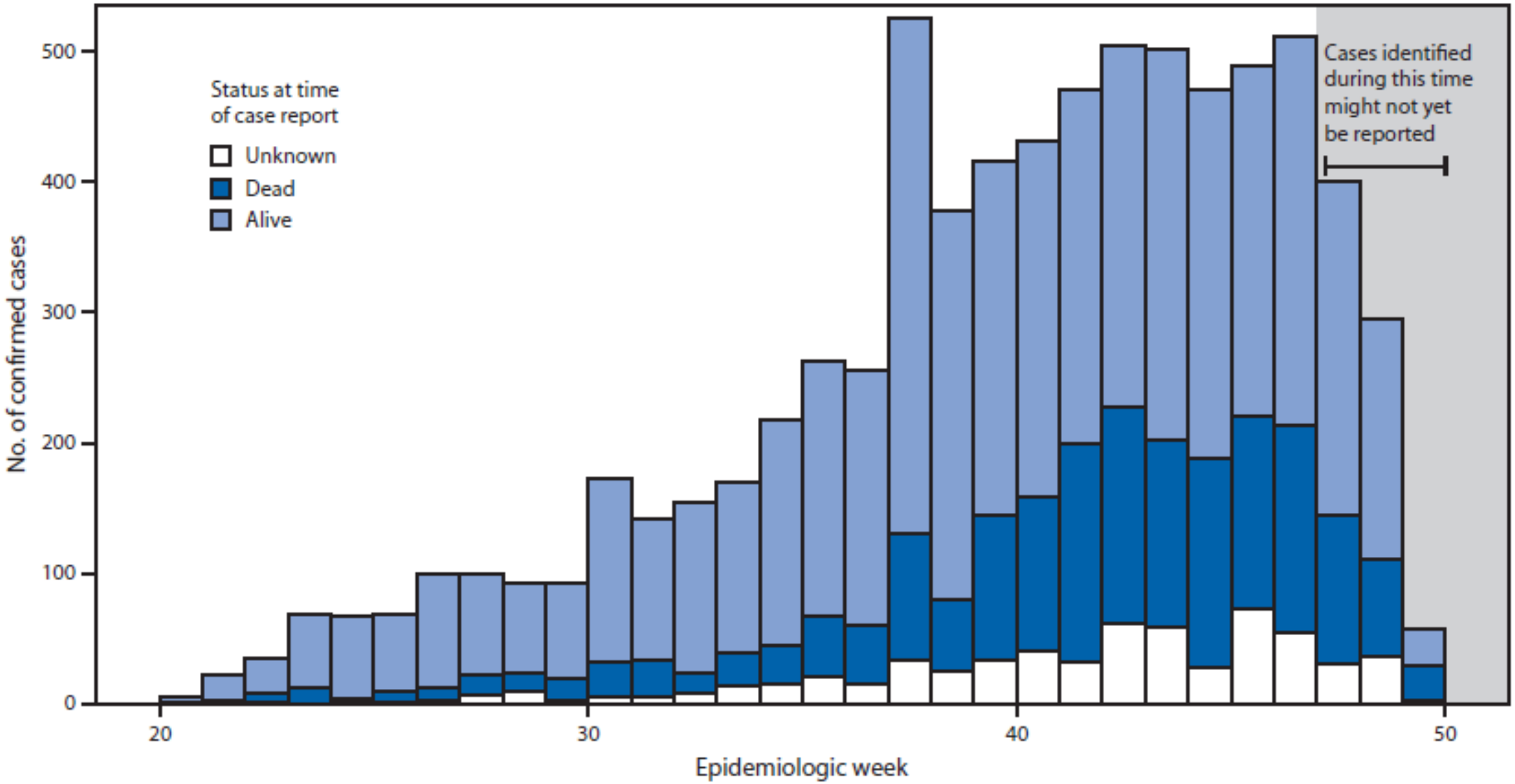
Helpful hint:
Write down all dates of admission, infection, procedures, locations and start a database.

- **Confirm increased infection rate vs. background**
  - Contact lab/epidemiology or other source for data on background rate
  - Build an epidemic curve
  - When do you know you have an outbreak?
    - Fischer's exact test—statistical test to determine if 2 groups are independent
    - Clinical decision—virulent, unusual organism

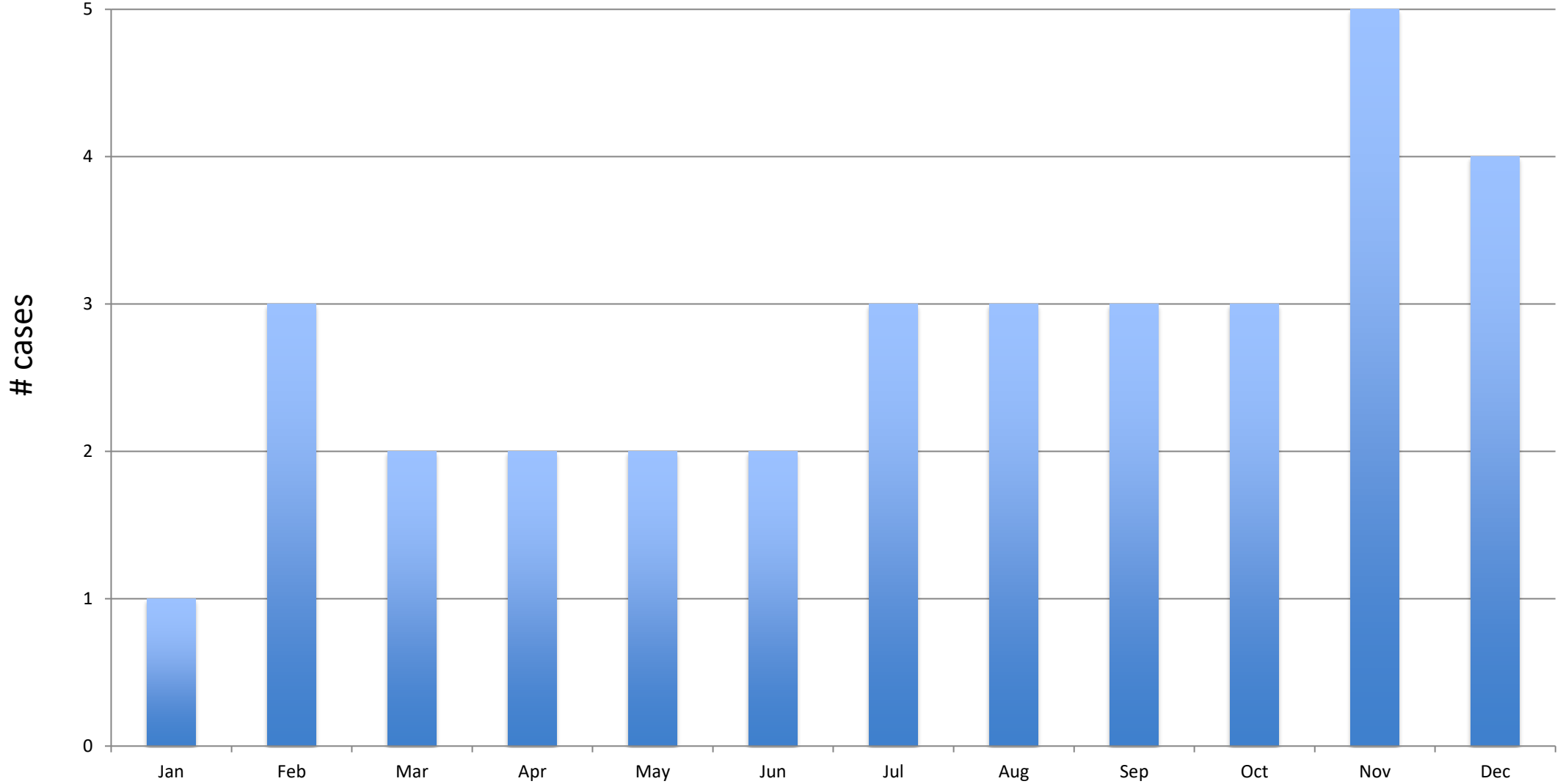
	CRE	Susceptible Kleb
Colonoscopy	12	7
ERCP	6	4
P >0.05		

	CRE	Susceptible Kleb
Colonoscopy	0	12
ERCP	16	1
P <0.0001		

Ebola example (CDC)



Baseline CRE cases at hospital, by month, 2014



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Creating a line list and case definition

Line list

- Compile list of all known affected patients
- Include important factors:
- Admission date, infection date, procedure dates, location

Review list

- Identify possible patterns
- Identify possible start date of all cases

Case Definition

- Must contain: time, place, person.
- Make it broad at first, you can narrow later
- Used to perform active case finding later…

Helpful hint:
Sit down with local constituents at this step. They may identify additional cases.

Helpful hint:
Don’t get too attached to your case definition...it should change as you discover more information.

Why is a written case definition important?

- Protects you from “mission creep” vs. having a less concrete definition.
- Forces you to review cases and develop theories that can help identify cause.
- Helps you do active case finding.
- Helps you construct an epidemic curve.
- Allows you to answer questions specifically from leadership, media.

Case definitions can be tricky

- Particulars:
  - 10 cases of MDR Klebsiella pneumonia, Urine, BSI, decub culture
  - First case: December 1, 2014, last case January 31, 2015
  - Location: PICU

Any case of Klebsiella diagnosed after Dec, 2014

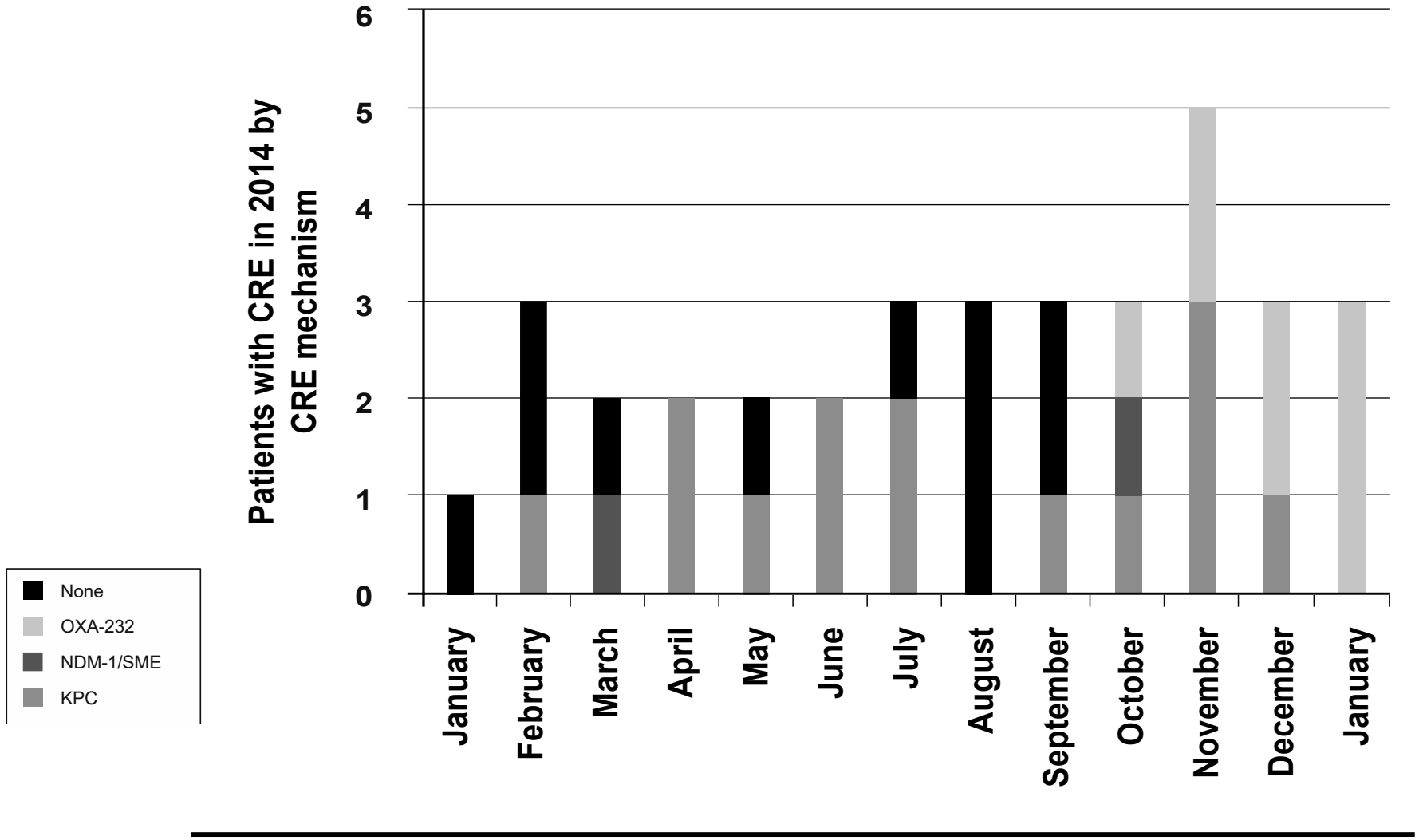
- Overly broad
- No location
- Will result in extra work, delay
- Not interested in community acquired, non-MDR cases

Any case of VAP, UTI due to MDR Klebsiella in the PICU after Dec 2014

- Too narrow
- Will result in missed cases
- Not specific enough with MDR definition

Any patient in the PICU between 12/1/14 and 1/31/15 who had a positive culture for Klebsiella resistant to meropenem at least 48 hours after admission.

Revised Epidemic curve



Case definitions change….with new information

- Case definition #1: Case of HA CR Klebsiella isolated from hospitalized a patient after hospital day #2 between January 1, 2014 and January 31, 2015.

↓ Refined time period & possible exposure

- Case definition #2: Case of HA CR Klebsiella isolated in patient at hospital after endoscopy between October 1, 2014 and January 31, 2015.

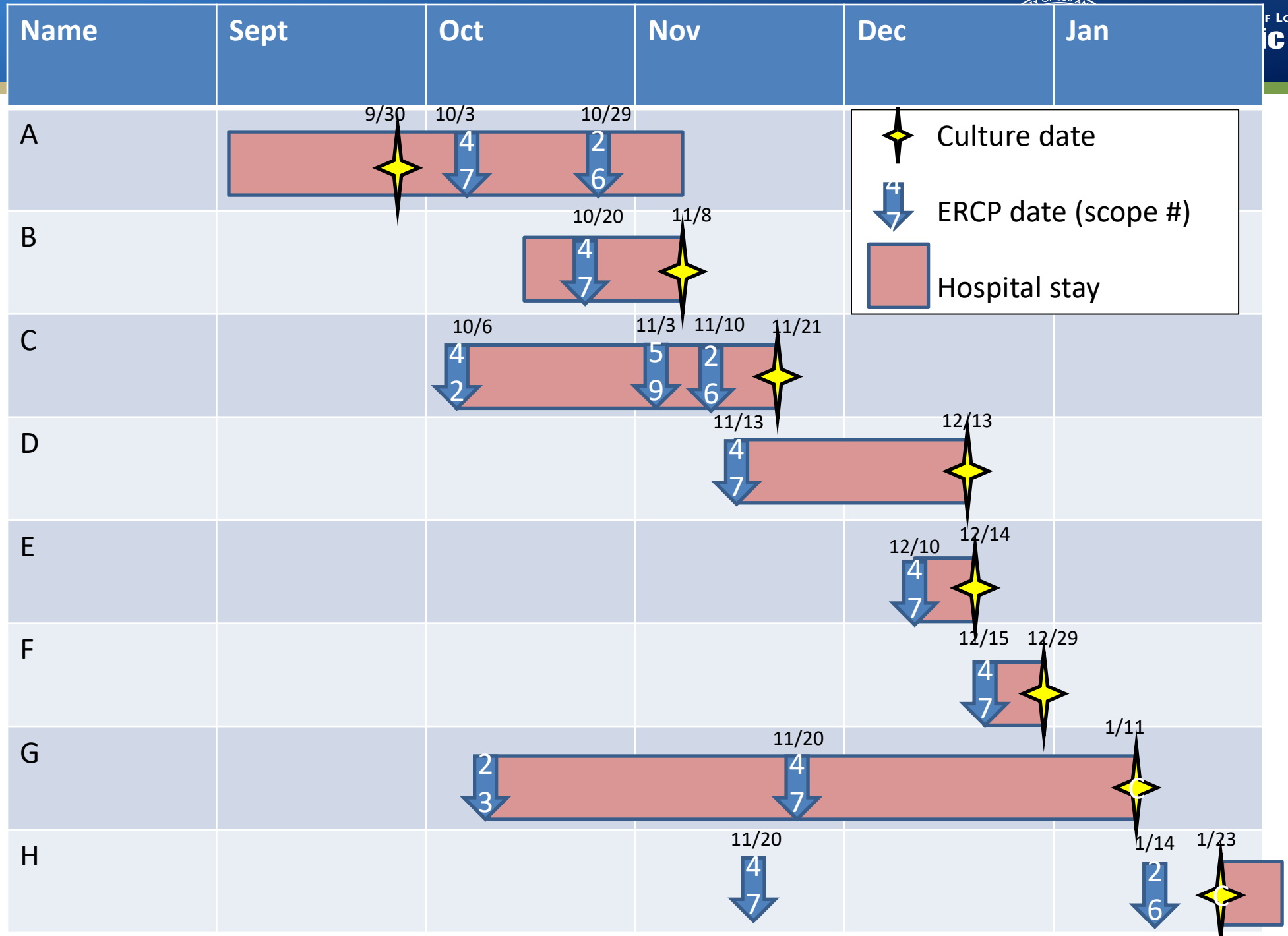
↓ Identified specific organism, expanded time & exposure

- Case definition #3: Case of Oxa-232 Klebsiella isolated in any patient at hospital between January 1, 2014 and January 31, 2015.

↓ Refined time period and exposure w WGS, epi investigation

- Case definition #4: Case of OXA-232 Klebsiella isolated in patient at hospital after duodenoscopy between October 1, 2014 and January 31, 2015.

Clinical infections



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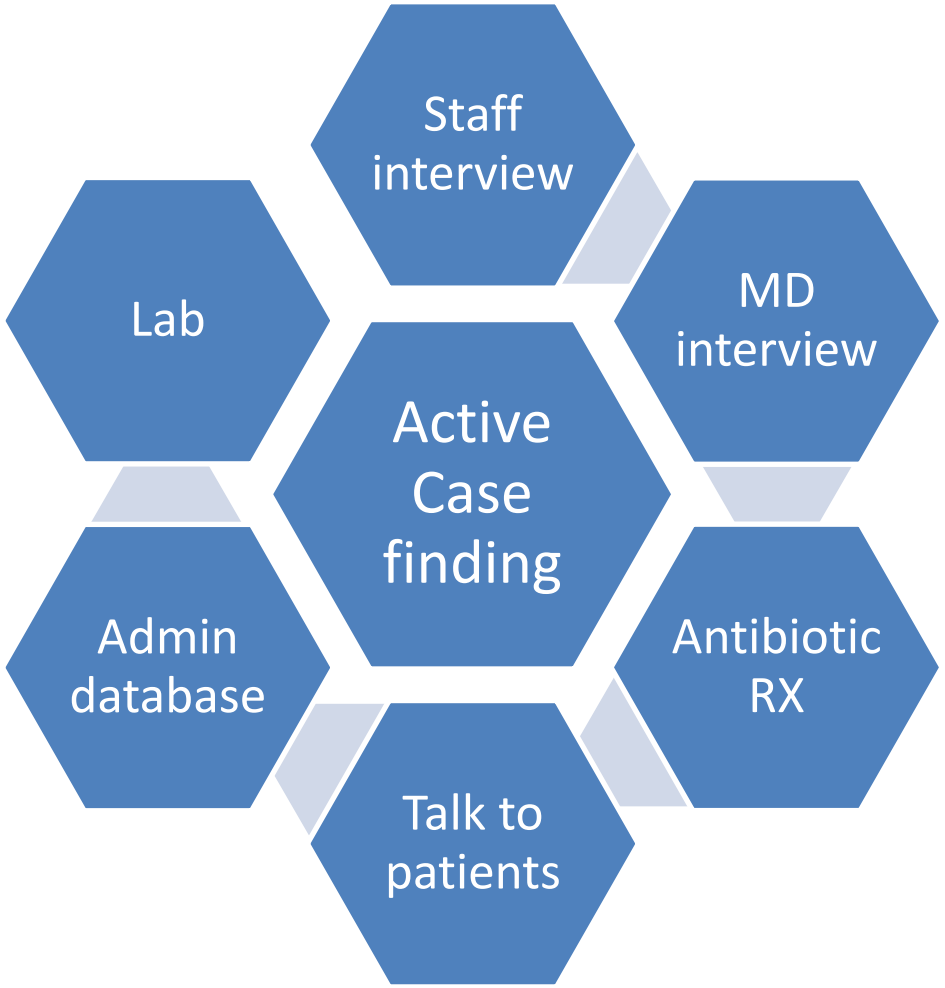
Active case finding is an art, not a science

- Don’t underestimate the database!



Helpful hint:
Take time to set-up your database correctly. You do not want to go back again…

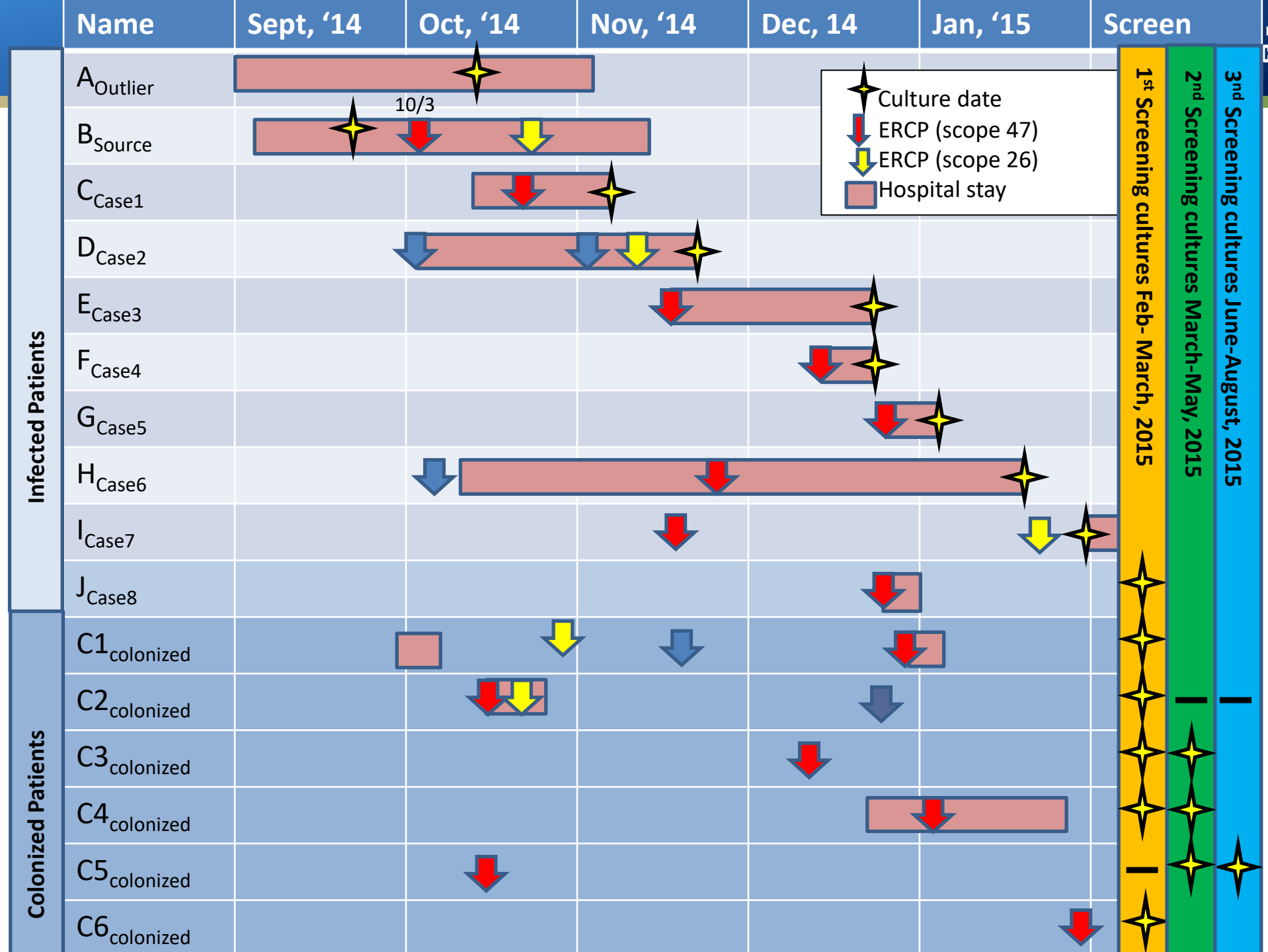
Helpful hint:
If you haven’t already contacted DPH, don’t wait any longer…

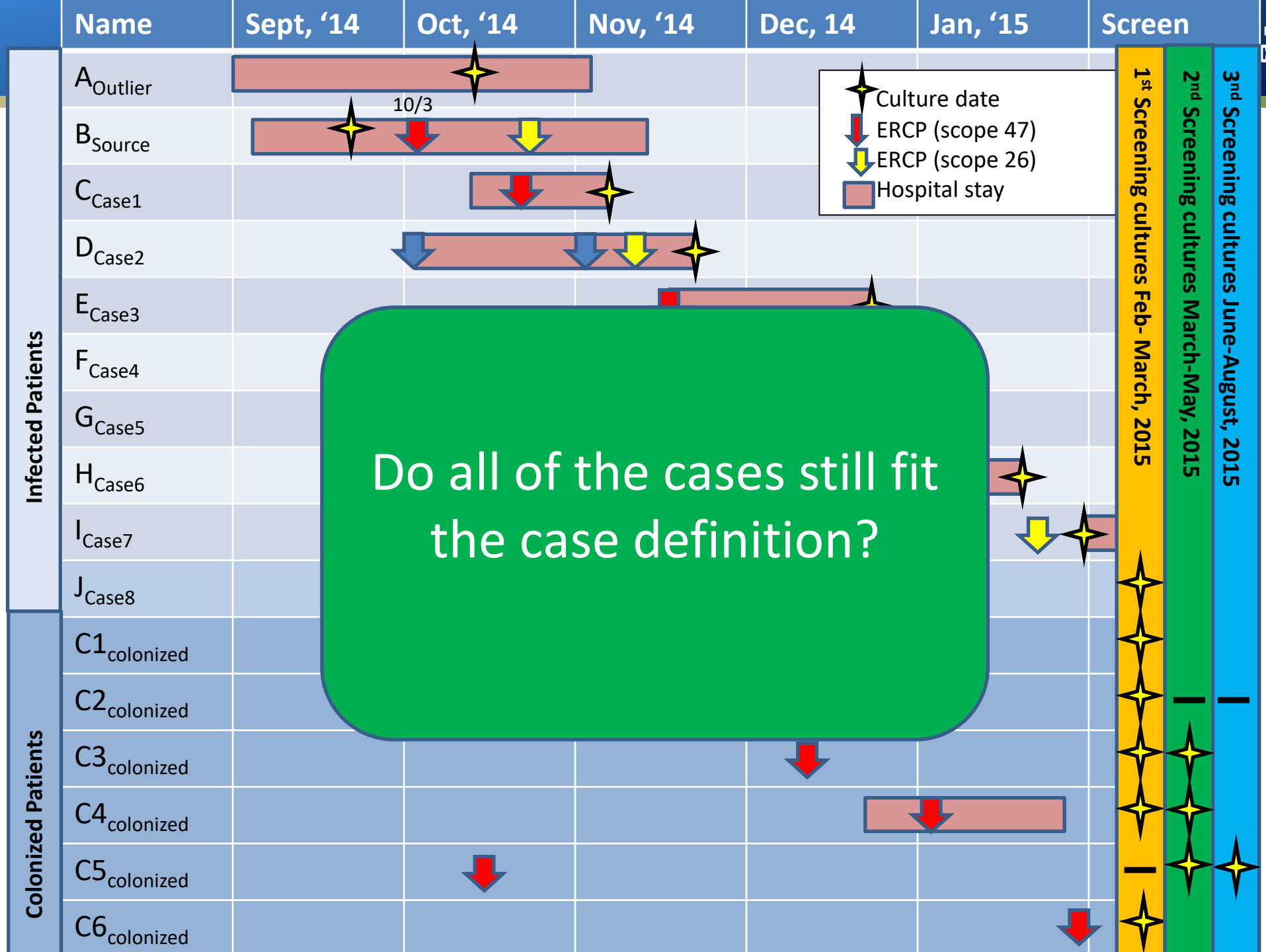
Helpful hint:
Consider notifying patients if not done already.

Active case finding

Case definition: Case of OXA-232 Klebsiella isolated in patient at hospital after duodenoscopy between October 1, 2014 and January 31, 2015.

- Developed a PCR for Oxa-232 & tested all CRE from 2011
- Contacted all patients with ERCP in exposure window and did screening for symptoms by phone.
- Developed CRE rectal swab test kit and sent it out to patients with FedEx return.
- Referred possible symptomatic cases to hospital ID clinic.


Name
Sept, '14
Oct, '14
Nov, '14
Dec, 14
Jan, '15
Screen
Infected Patients
Colonized Patients
A Outlier
B Source
C Case1
D Case2
E Case3
F Case4
G Case5
H Case6
I Case7
J Case8
C1 colonized
C2 colonized
C3 colonized
C4 colonized
C5 colonized
C6 colonized
10/3
Culture date
ERCP (scope 47)
ERCP (scope 26)
Hospital stay
1st Screening cultures Feb- March, 2015
2nd Screening cultures March-May, 2015
3nd Screening cultures June-August, 2015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C3 colonized
C4 colonized
C5 colonized
C6 colonized
10/3
Culture date
ERCP (scope 47)
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Hospital stay
Do all of the cases still fit the case definition?
1st Screening cultures Feb- March, 2015
2nd Screening cultures March-May, 2015
3nd Screening cultures June-August, 2015

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Develop a hypothesis and test the hypothesis

- You should already have some idea about what is going on…
  - Spend time to review literature
  - Speak to experts (don't reinvent the wheel)

- Testing the hypothesis

Field investigation
Interview staff
Watch process
Develop a process map

Case control study
Determine risk factors
Cohort studies
Determines risk for exposure

Molecular testing

Environmental testing



Case control studies can be tricky…

- Case control studies..
  - Aim: Identify important risk factors
  - Require adequate size
  - Time consuming
  - Control group can be hard to identify and matters greatly
    - May need to look at different comparator groups
    - Collect enough risk factors on all patients
    - If result are not significant, reassess (don't assume correlations don't exist)
- Cohort studies
  - Aim: Compare some outcome for exposed vs non-exposed
  - Good if you know the likely exposure

CRE
vs
age-matched
controls

Risk Factor	CRE N=50 (%)	Control N=70 (%)	Odds Ratio (95% CI)	p-value
Age at admission	55.4 (18.3, 92.0)	59.4 (18.1, 89.1)	0.99 (0.98, 1.01)	0.368
Female	40.0	40.0	1.26 (0.62, 2.55)	1
Length of stay	30.0 (1.0, 386.0)	4.0 (1.0, 369.0)	1.01 (1.00, 1.02)	<0.001
Specialty areas visited				
MPU	48.0	10.0	10.73 (4.20, 27.44)	<0.001
OR	40.0	38.6	0.86 (0.42, 1.78)	1
IR	28.0	11.4	2.52 (0.97, 6.54)	0.038
Dialysis unit	6.0	0.0	9.05 (0.29, 281.95)	0.070
APACHE II at admission	13.0 (3.0, 28.0)	8.0 (0.0, 23.0)	1.15 (1.07, 1.22)	<0.001
Any antibiotic exposure	96.0	65.7	6.91 (2.23, 21.38)	<0.001
≥ 1 colonoscopy	14.0	1.4	9.86 (1.18, 82.70)	0.009
≥ 1 upper endoscopy	20.0	5.7	4.40 (1.33, 14.51)	0.016
≥ 1 ERCP	22.0	0.0	66.04 (*)	<0.001
≥ 1 respiratory procedure	59.7	32.9	3.02 (1.46, 6.25)	0.003
≥ 1 operation	53.1	48.6	0.95 (0.47, 1.93)	0.630
≥ 1 IR procedure	35.1	15.7	2.90 (1.25, 6.73)	0.012
Transplant	20.0	18.6	1.05 (0.43, 2.56)	1
Active diagnosis of cancer?	22.0	21.4	1.08 (0.47, 2.51)	1
Cancer type				
Cholangiocarcinoma	4.0	0.0	9.05 (0.29, 281.95)	0.172
Colon	0.0	1.4	<0.01 (*)	1
Hepatocellular	0.0	1.4	<0.01 (*)	1
Lung	0.0	4.3	0.17 (0.01, 5.23)	0.265
Pancreatic	10.0	1.4	6.63 (0.75, 58.50)	0.081
Other	8.0	12.9	0.65 (0.21, 2.07)	0.585
Cirrhosis/ESLD	22.4	7.1	3.93 (1.31, 11.82)	0.033
End stage renal disease	16.0	4.3	3.59 (0.91, 14.24)	0.051
Central venous catheter	78.0	22.9	8.65 (3.87, 19.31)	<0.001
Foley catheter	66.0	31.9	3.23 (1.55, 6.70)	<0.001
Long term care facility in last 3 months	18.4	1.4	13.21 (1.62, 107.79)	0.001
Travel outside the US in last 6 months (if known)	15.0	2.7	6.17 (0.71, 53.87)	0.110

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Oxa-232 CRE
vs
Non-Oxa-232
CRE

Risk Factor	Oxa-232, N=11 (%)	Non Oxa-232, N=39 (%)	OR (95% CI)	p-value
Age at admission	58.6 (18.3, 77.9)	55.3 (18.3, 92.0)	1.01 (0.98, 1.04)	0.689
Female	18.2	46.2	0.93 (0.30, 2.87)	0.163
Length of stay	55.0 (1.0, 195.0)	28.0 (1.0, 386.0)	0.99 (0.99, 1.00)	0.736
Specialty areas visited				
MPU	90.9	35.9	30.36 (3.64, 252.97)	0.004
OR	54.5	35.9	0.89 (0.28, 2.90)	0.311
IR	36.4	25.6	0.83 (0.22, 3.11)	0.476
Dialysis unit	9.1	5.1	1.09 (0.09, 12.84)	0.534
APACHE II at admission	12.0 (4.0, 22.0)	14.0 (3.0, 28.0)	0.91 (0.82, 1.01)	0.115
Any antibiotic exposure	90.9	97.4	0.13 (0.01, 1.37)	0.395
≥1 colonoscopy	18.2	12.8	0.91 (0.16, 5.21)	0.641
≥1 upper endoscopy	45.5	12.8	4.33 (1.14, 16.43)	0.030
≥1 ERCP	72.7	7.7	60.00 (10.85, 331.70)	<0.001
≥1 respiratory procedure	38.9	69.2	0.28 (0.09, 0.91)	0.030
≥1 operation	54.5	52.6	0.49 (0.15, 1.60)	1
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Other	0.0	10.3	0.52 (0.05, 4.97)	0.563
Cirrhosis/ESLD	9.1	26.3	0.56 (0.13, 2.35)	0.415
ESRD	18.2	15.4	0.69 (0.13, 3.79)	1
Central venous catheter	63.6	82.1	0.22 (0.06, 0.75)	0.229
Foley catheter	36.4	74.4	0.13 (0.04, 0.47)	0.030
Long term care facility in last 3 months	9.1	21.1	0.22 (0.03, 1.92)	0.662
Travel outside the US in last 6 months	10.0	16.7	0.50 (0.05, 4.83)	1

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APACHE II at admission	12.0 (4.0, 22.0)	14.0 (3.0, 28.0)	0.91 (0.82, 1.01)	0.115
Any antibiotic exposure	90.9	97.4	0.13 (0.01, 1.37)	0.395
≥1 colonoscopy	18.2	12.8	0.91 (0.16, 5.21)	0.641
≥1 upper endoscopy	45.5	12.8	4.33 (1.14, 16.43)	0.030
≥1 ERCP	72.7	7.7	60.00 (10.85, 331.70)	<0.001
≥1 respiratory procedure	38.9	69.2	0.28 (0.09, 0.91)	0.030
≥1 operation	54.5	52.6	0.49 (0.15, 1.60)	1
≥1 IR procedure	22.2	41.0	0.41 (0.11, 1.48)	0.167
Transplant	18.2	20.5	0.78 (0.18, 3.35)	1
Active diagnosis of cancer?	27.3	20.5	1.49 (0.41, 5.42)	0.688
Cancer type				
Cholangiocarcinoma	18.2	0.0	17.83 (0.55, 574.38)	0.045
Pancreatic	9.1	10.3	0.52 (0.05, 4.97)	1
Other	0.0	10.3	0.52 (0.05, 4.97)	0.563
Cirrhosis/ESLD	9.1	26.3	0.56 (0.13, 2.35)	0.415
ESRD	18.2	15.4	0.69 (0.13, 3.79)	1
Central venous catheter	63.6	82.1	0.22 (0.06, 0.75)	0.229
Foley catheter	36.4	74.4	0.13 (0.04, 0.47)	0.030
Long term care facility in last 3 months	9.1	21.1	0.22 (0.03, 1.92)	0.662
Travel outside the US in last 6 months	10.0	16.7	0.50 (0.05, 4.83)	1

General scheme of outbreak investigations

loosely based on Goodman, et al. Am J Epidem 1990;132:9-16.

County of Los Angeles Public Health

Identification of potential outbreak

Verify diagnosis

Confirmation of increased rate

Create a line list

Create a case definition
Time, place, clinical factors

Call Health Dept

Set-up database
Definitions
terminology

Active case finding
Screening, lab

Develop hypothesis
Review literature
Speak to experts

Test hypothesis
Case control study
Environmental cultures

Institute control measures

Surveillance

Report

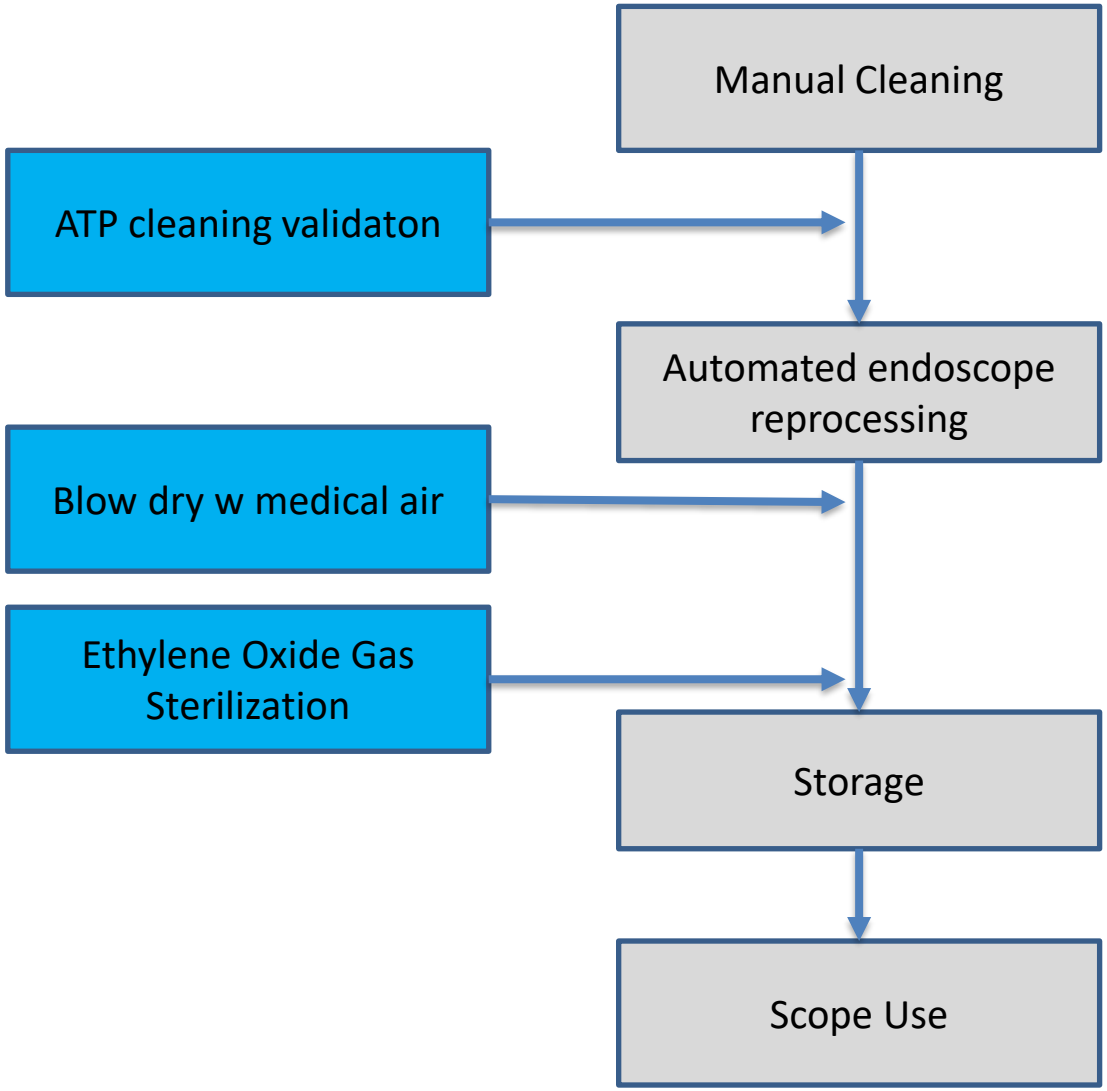


Instituting control measures

- Re-assess what you have already done
  - Does it still make sense?
- Review the literature & speak to facilities with similar issues
  - What did they do?
  - Is it applicable to your institution and patient population?
- Is the intervention sustainable?
- Did you get buy-in from colleagues and administration?

Helpful hint:
Take time to do it right!

Develop and articulate a simple, coherent plan…



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Report



The dreaded report….

- Produce interim reports

Carbapenem resistant Enterobacteriaciae (CRE) *Klebsiella pneumoniae* outbreak related to Duodenoscopy (ERCP), RRUMC, October, 2014 through January, 2015.

Investigators: Quen Cheng, MD, Alisa Trout, RN, Teresa Zaroda, RN, Dana Russell, MPH, CIC, Peera Hemarajata, PhD, Sangxin Yang, PhD, Romney Humphries, PhD, Daniel Uslan, MD, Zachary Rubin, MD.

Date of Report: January 29, 2015
Interim Report: February 6, 2015
Interim Report: February 18, 2015
Interim Report: April 24, 2015

- This could become a legal document, so be thorough and complete.
- Ensure that you have tied up loose ends.
- After-action meetings.
- Consider publication.

The outbreak never really ends…

- Expect CMS, CDPH, TJC, etc. to come and review the investigation and mitigation in place.
- Continue surveillance to ensure that the outbreak has subsided
  - Notify DPH of additional cases
  - Investigate each case to ensure that you didn't miss the source
- Ensure that others understand the investigation and can speak to regulators if you are gone…



Pearl 1: Patient notification

- Key step
- Do it wrong and increase the likelihood of lawsuits
- Suggestions:
  - Do it early
  - Do it in person > by phone > letter (I recommend sending letters regardless)
  - Take responsibility
  - Offer reassurance and follow-up
  - Stop the bills if possible
  - If patients hear about the outbreak from the news before you talk to them, they will be pissed!

Pearl 2: Communication plan is critical

- Internal communication→stop the rumors
  - Staff members (they will be impacted)
  - Patients in health system, but not involved
  - Send out communication early, but protect patient privacy

- External communication→
  - Involve hospital media relations early
  - Develop draft communication for immediate release if needed
  - If outbreak is large or very visible, consider setting-up phone hotline to answer questions.
  - Don’t read the public comments on the bottom of articles…

- Consider formal media training/consultant

of Los Angeles
ic Health

2 dead, nearly 180 possibly infected after 'superbug' outbreak at UCLA hospital

THE ASSOCIATED PRESS / Thursday, February 19, 2015, 7:37 AM

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UCLA superbug: Lawmaker asks Congress to investigate FDA response



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Mass shooting of six leaves one dead in


Officer shoots man, 26, dead on his


No more disappearing act!


MORE snow expected to fall

Superbug that's killed two in LA is linked to medical scope used on more than half a million people a year

LA Times

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UCLA superbug: Outbreak 'not a threat to public health,' officials say



Dr. Zachary Rubin speaks outside Ronald Reagan UCLA Medical Center on Feb. 19 about infections of patients with an antibiotic-resistant bacteria. (Anne Cusack / Los Angeles Times)

The Washington Post

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Morning Mix

FDA warns about medical scop
'superbug' bacteria hits UCLA

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By Lindsey Bever and Brady Dennis February 19

Follow @lindseybever Follow @brady_dennis

Los Angeles Health

Pearl 3: having a relationship with DPH really helps

- Involve them early
- Ask for resources if hospital is overwhelmed
- Expect recommendations for patient notification early
- Do some research yourself and have a draft response plan ready when DPH comes
  - You know the patients and facility better than DPH
  - You know what interventions are likely to be successful

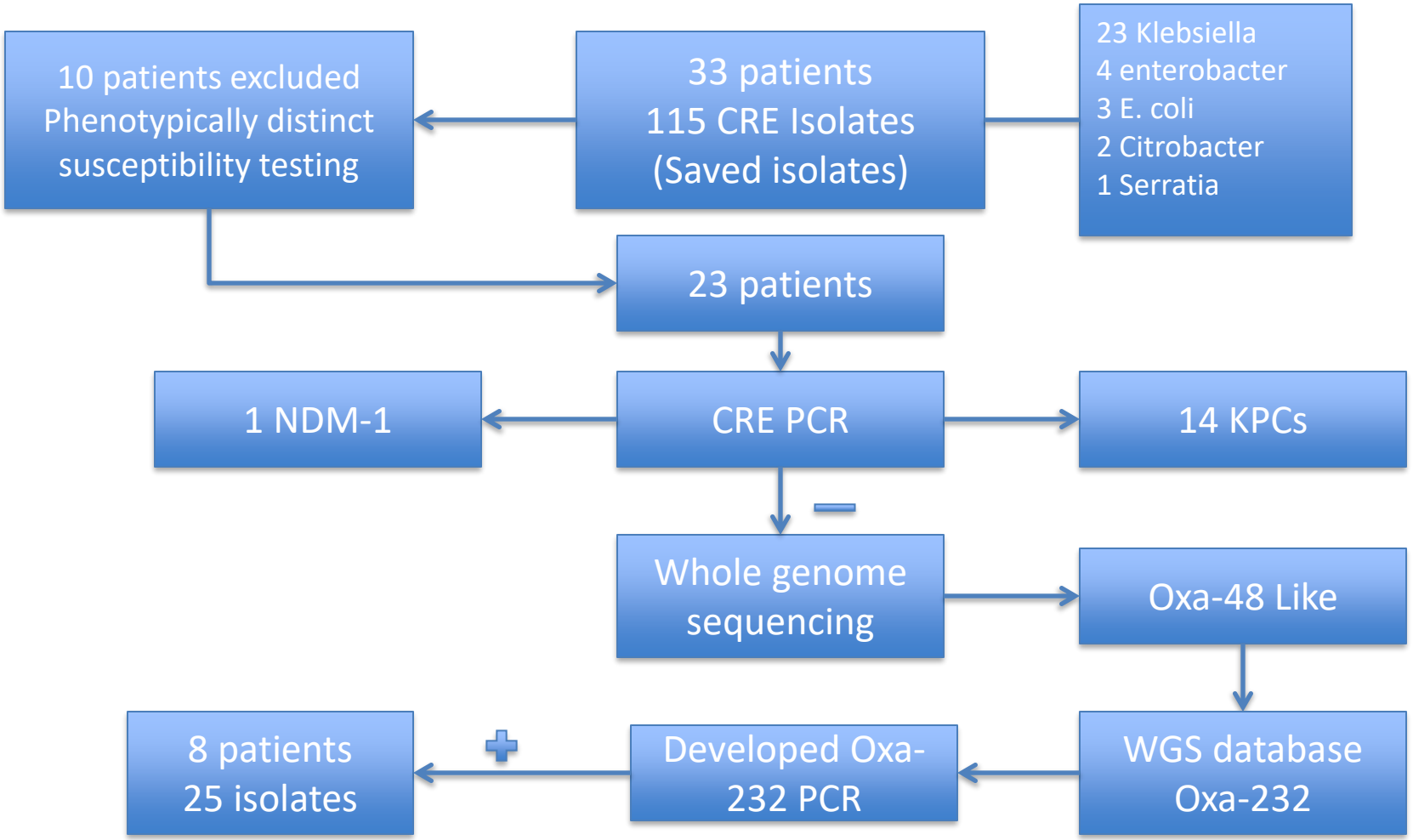
Pearl 4: When should we pull-out the shiny tools?

- Molecular testing
  - I recommend using them early if relationship between isolates is unclear
  - Be careful to understand the limitations of testing and whether technique adequately discriminates between strains (PFGE vs PCR vs WGS, etc.).

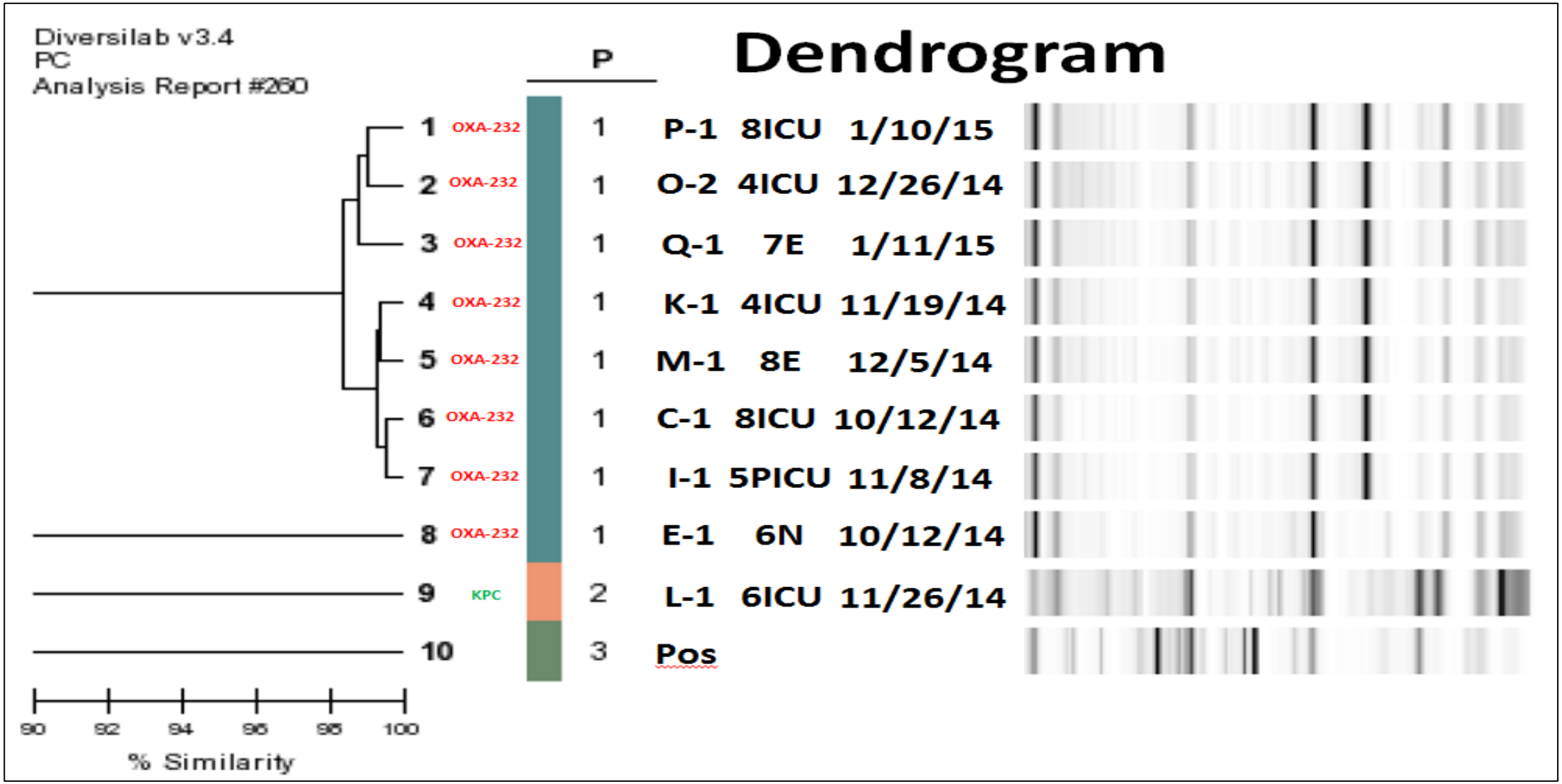
- Environmental sampling
  - Easy to do, difficult to interpret
  - Reserved for cases where there is evidence of environmental exposure

- Staff screening as source of infection
  - Almost never helpful
  - Think through implications prior to testing

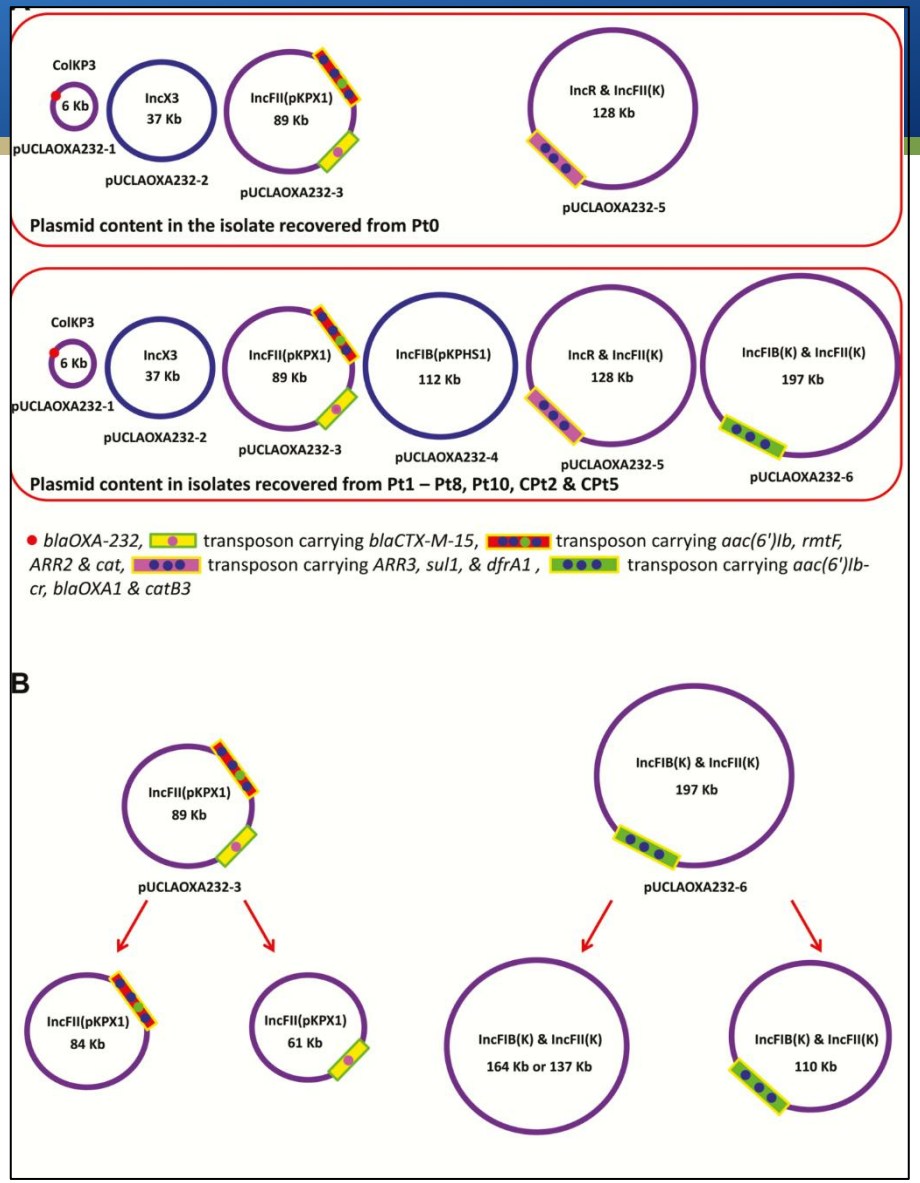
Molecular testing algorithm



Rep-PCR Results



Whole Genome Sequencing



Evolution and Transmission of Carbapenem-Resistant Klebsiella pneumoniae Expressing the $bla_{OXA-232}$ Gene During an Institutional Outbreak Associated With Endoscopic Retrograde Cholangiopancreatography

Clin Infect Dis. 2017;64(7):894-901. doi:10.1093/cid/ciw876

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Pearl 5: be organized

- Organization = greater efficiency
- Take time to reflect on what you are doing, don't be rash
- Ask for help early
  - Mobilize institutional resources
  - Contact health department
  - Contact other institutions with similar issues in past
- Involve unit leadership early, it helps with implementation later

Conclusions

- Outbreak investigations can be complex
- Ask for help early (Admin, health dept, colleagues at other institutions)
- Notify LACDPH (or local jurisdiction) early
- Notify patients early
- Develop a communications plan early
- Take time to make decisions, don’t make pressured, rash decisions
- Consider molecular testing early, but make sure you use the correct test
- Prepare for regulatory/licensing visits sooner than you think

Questions?

Thank you

