A Perfect Storm in the MDRO Era:
Discovery and Investigation of an Endoscopy-Associated CRE outbreak by WGS

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Living in a MDRO Era

MDRO in the Community

GI tract infections:

MDR Campylobacter

MDR Salmonella

MDR Shigella

Respiratory tract infections:

MDR Tuberculosis

MDR Strep Pneumoniae

MDRO in the Hospitals

Extended Spectrum Enterobacteriaceae (ESBL)

Vancomycin-Resistant Enterococcus (VRE)

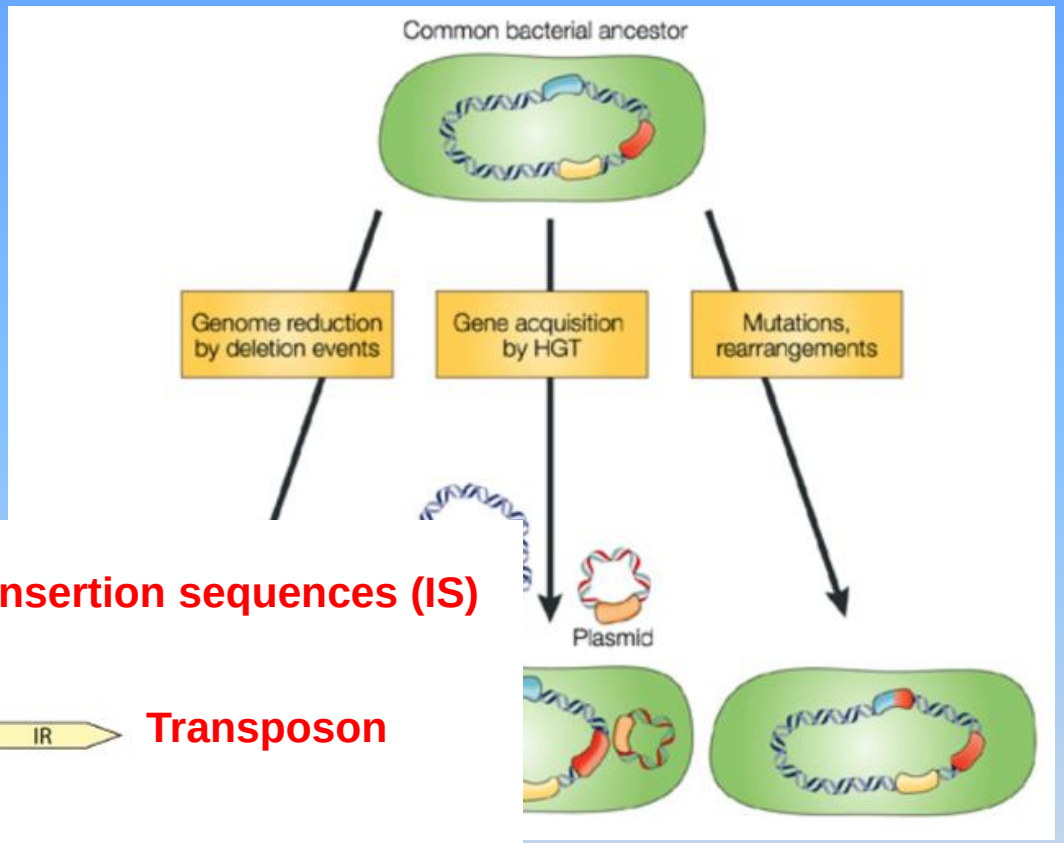
MDR Acinetobacter

MDR Pseudomonas Aeruginosa

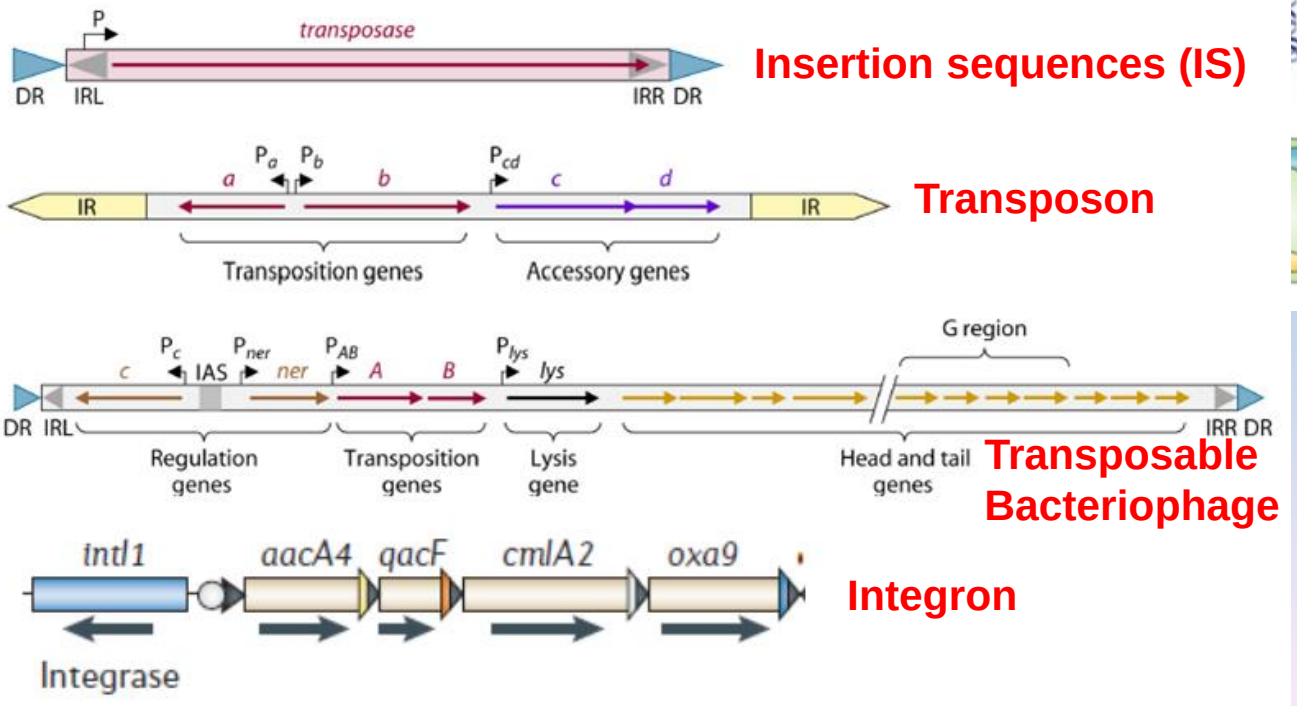
Fluconazole-Resistant Candida

Methicillin-Resistant Staphylococcus Aureus (MRSA)

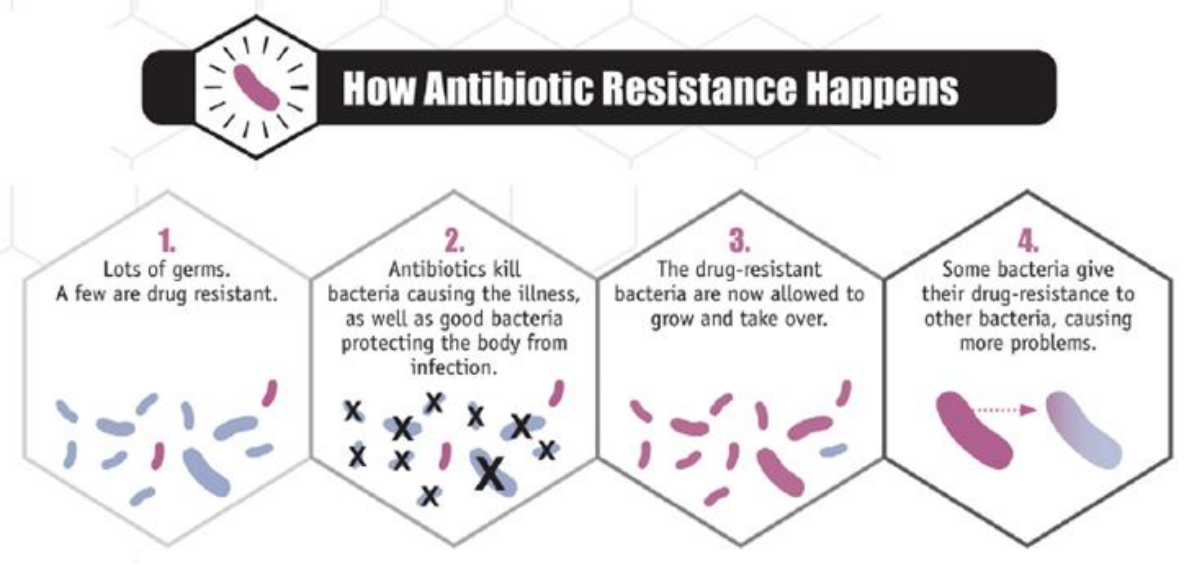
Bacterial Genomic Plasticity



Mobile Genetic Elements

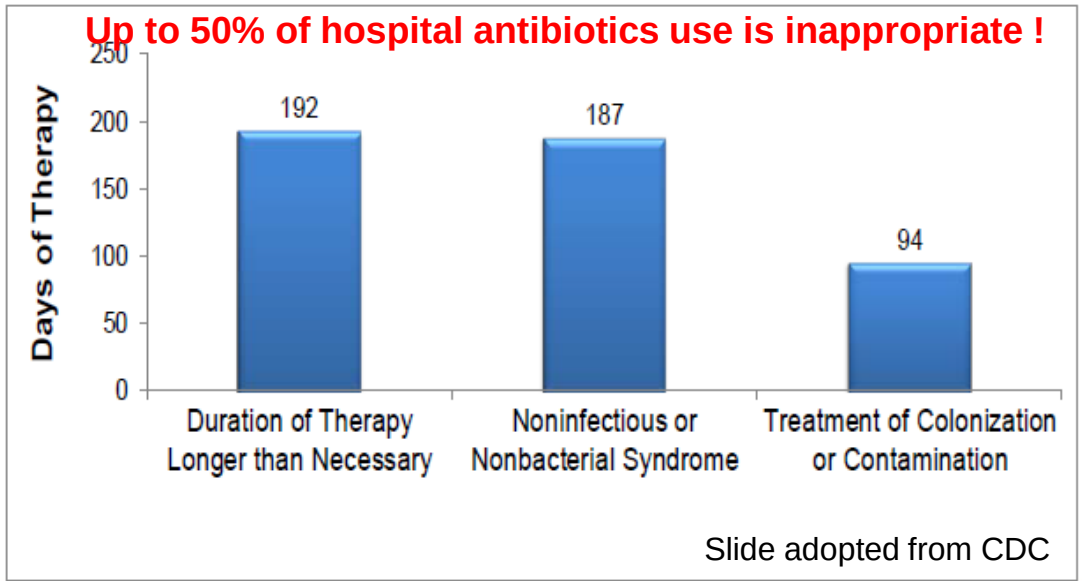


Antibiotic Abuse & Resistance



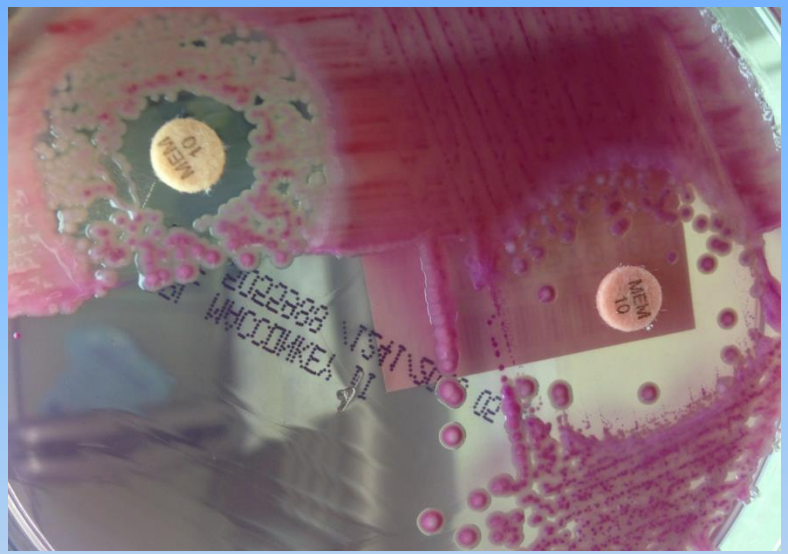
Resistance is inevitable !

Up to 50% of hospital antibiotics use is inappropriate !

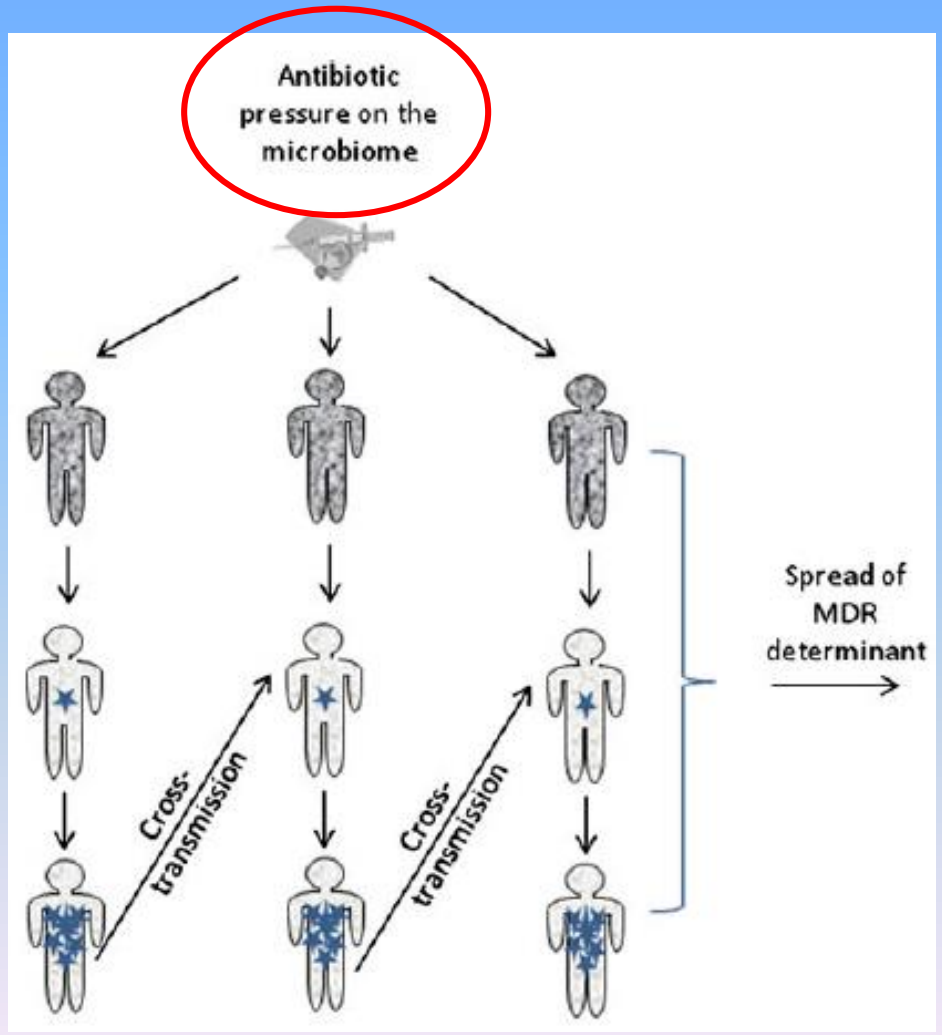


Slide adopted from CDC

Infection Control Challenges in Hospitals

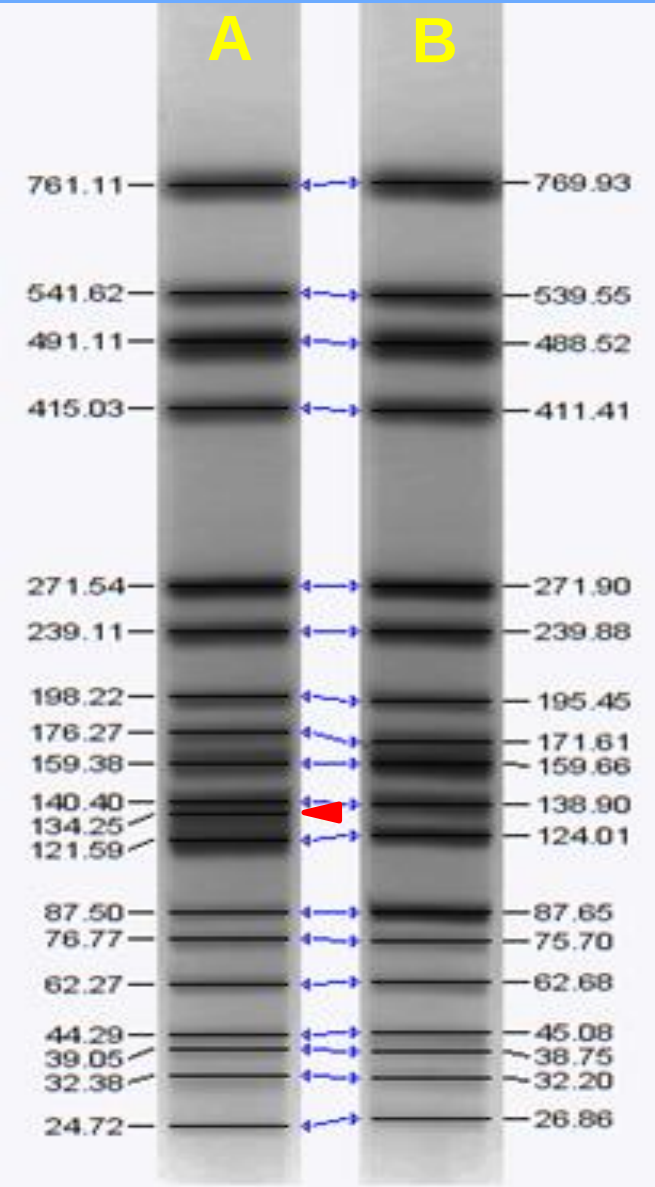


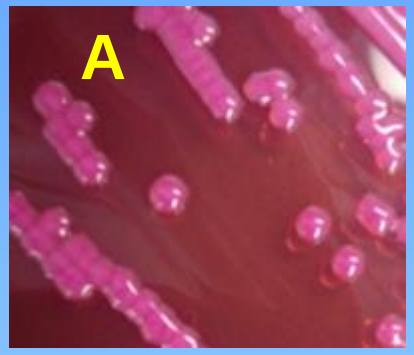
Carbapenem resistant Klesiella pneumoniae (CRKP) from rectal swab in an infected patient !!!

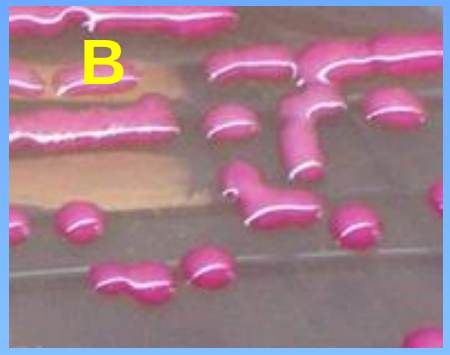


Tosh et al, Clinical Infectious Diseases 2012

How to Determine the Relatedness?



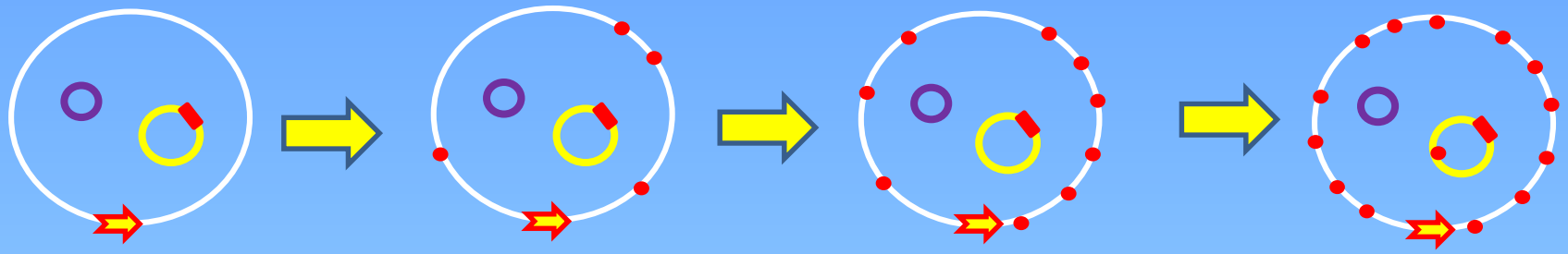




Conventional Methods for Molecular Epidemiology

- PFGE
- rePCR
- MLST
- Ribotyping
- IS6110
- Spoligotyping
- MIRU

Bacterial Genomic Variations

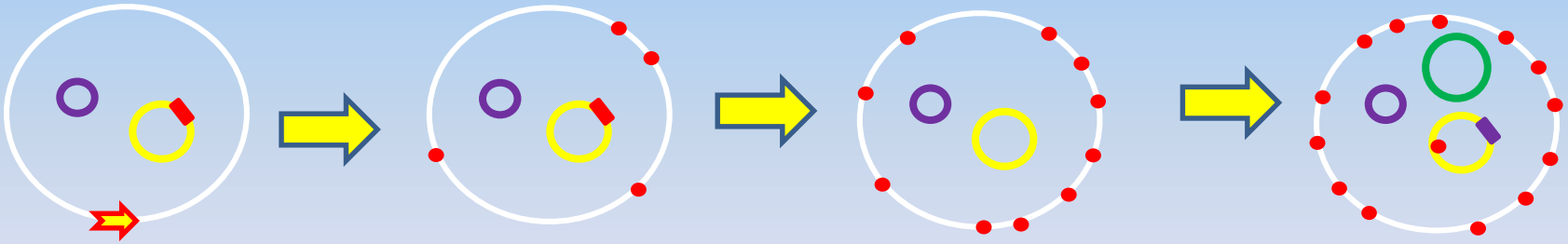


4 SNVs

9 SNVs

14 SNVs

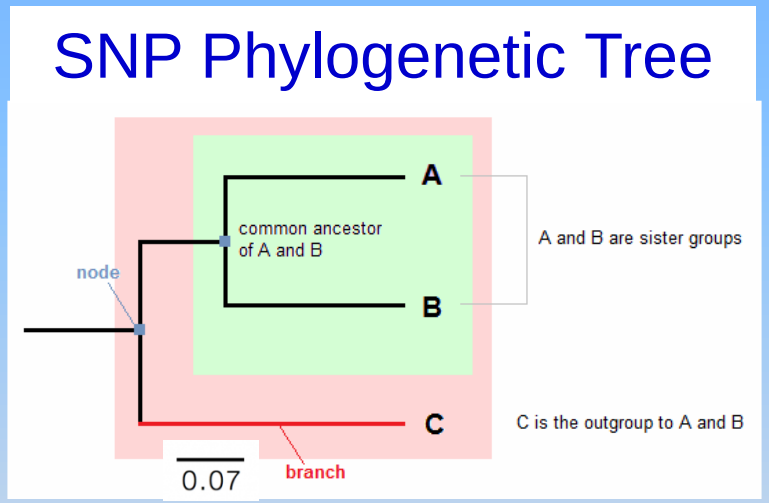
Molecular clock
→ SNV



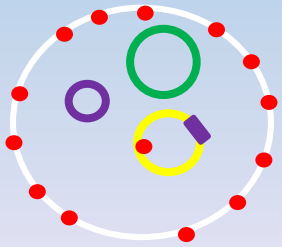
- *E. coli*: ~20 SNP/genome/year
- *K. pneumoniae*: ~10 SNP/genome/year

How to Compare the Bacterial Genomes?

??



Signature Plasmid



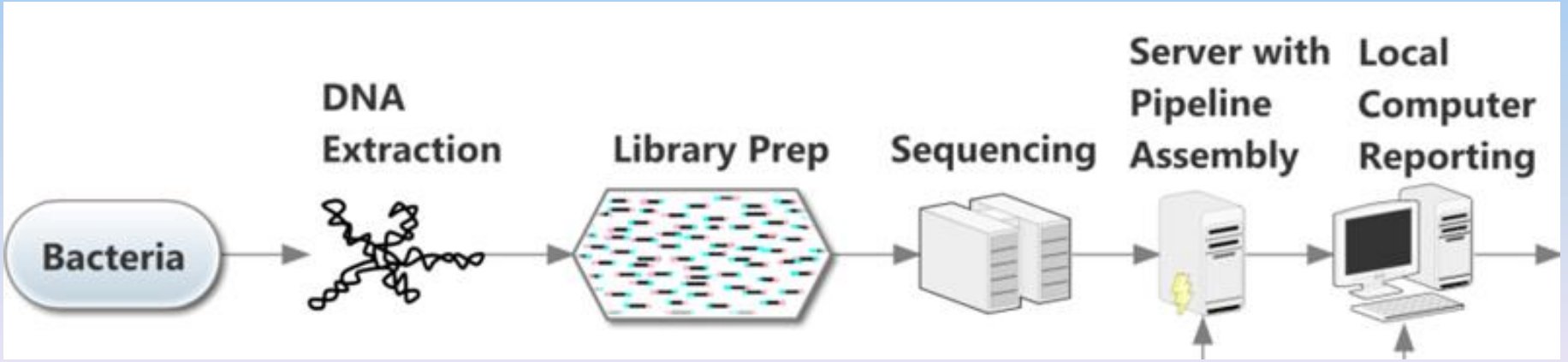
Branch Length: the number of changes divided by the length of the sequence (i.e., the number of changes per 100 nucleotide sites)

SNV = 13

Next-Gen Sequencing = High-Throughput Sequencing

- **Illumina MiSeq**
  - **Shorter Read Length (< 1kb)**

- **PacBio RS II**
  - **Longer Read Length (> 1kb)**



An UCLA Case

Amikacin Gentamicin Tobramycin	>32 >10 >10	R R R
Aztreonam, Cefepime, Cetazidime, Ceftriaxone	>32 >32 >32 >32	R R R R
Ertapenem Imipenem Meropenem	>8 2 >16	R I R
Ciprofloxacin Levofloxacin	>2 >8	R R
Piper-tazo	>128	R
Trim-sulfa	>4/80	R
Minocycline Tigecycline	>32 4	R I
Colistin	≤0.5	S

48 yo female with end stage liver disease, received liver transplant at UCLA in Sep 2014

Transplant was complicated by bile leak, stent placed by ERCP endoscope

Over next several weeks, she developed sepsis, and intra-abdominal infection and died 2 months post-op

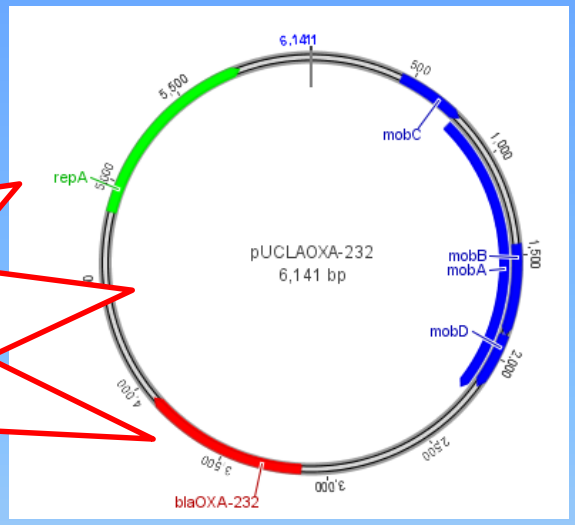
She had no travel history at all

⇦ **PCR negative for KPC, NDM-1, IMP, VIM, SME, OXA-48**

Highly Unusual CRE Discovered by WGS

WGS using Illumina MiSeq identified an unusual *K. pneumoniae* strain carrying *blaOXA-232* G

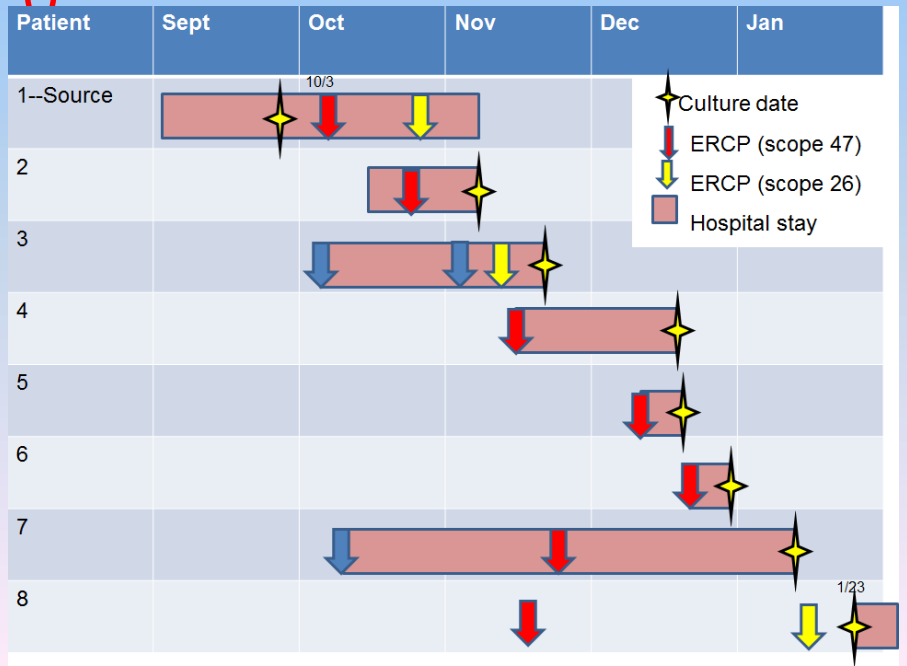
But the patient had no travel history!



- OXA-232: A novel OXA-48 like carbapenemase identified in 2011 in 3 patients transferred from India to France
- 1st OXA-232 CRE case in US: 2013 in Pittsburgh from a patient from India
- Most closely related to XH209, a novel strain reported from China in 2014

Discovery of an ERCP-Related OXA-232 CRE Outbreak

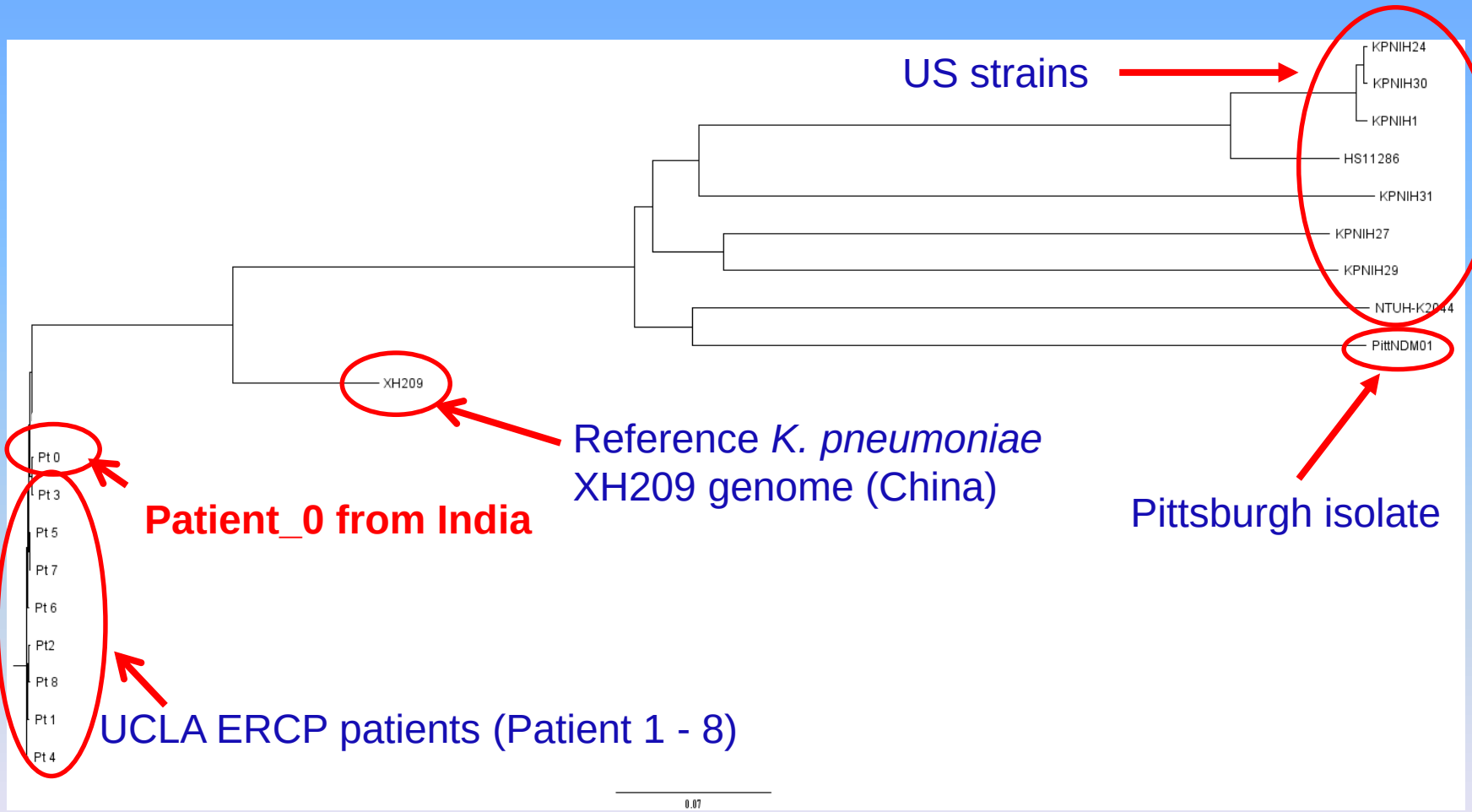
Patient #	Specimen Collection Date	Specimen Type	MHT	Carba NP	OXA-232 PCR	Imipenem	Meropenem	Ertapenem
0	10/12/2014	Respiratory	Positive	Negative	Positive	I (2)	R (>16)	R (>8)
1	10/12/2014	Abdominal Drainage	Positive	Negative	Positive	I (2)	R (>16)	R (>8)
2	11/9/2014	Blood	Positive	Negative	Positive	I (2)	R (>16)	R (>8)
3	11/21/2014	Blood	Positive	Negative	Positive	I (2)	R (>16)	R (>8)
4	12/5/2014	Skin Exudate	Positive	Negative	Positive	I (2)	R (>16)	R (>8)
5	12/26/2014	Respiratory	Positive	Negative	Positive	I (2)	R (>16)	R (>8)
6	1/10/2015	Blood	Positive	Negative	Positive	I (2)	R (>16)	R (>8)
7	1/11/2015	Abdominal Drainage	Positive	Negative	Positive	I (2)	R (>16)	R (>8)
8	2/7/2015	Back Fluid	Positive	Negative	Positive	I (2)	R (>16)	R (>8)



Where Did This Bug Come from?

- **Pt0: Patient with treatment at a hospital in India (no ERCP performed at UCLA):**
  - **58 yo male, cerebellar stroke and decompressive craniectomy in India in mid-2014**
  - **Several procedures at UCLA including bronchoscopy**
  - **CRE was isolated from tracheal suction, on the same day CRE was isolated from Pt1**

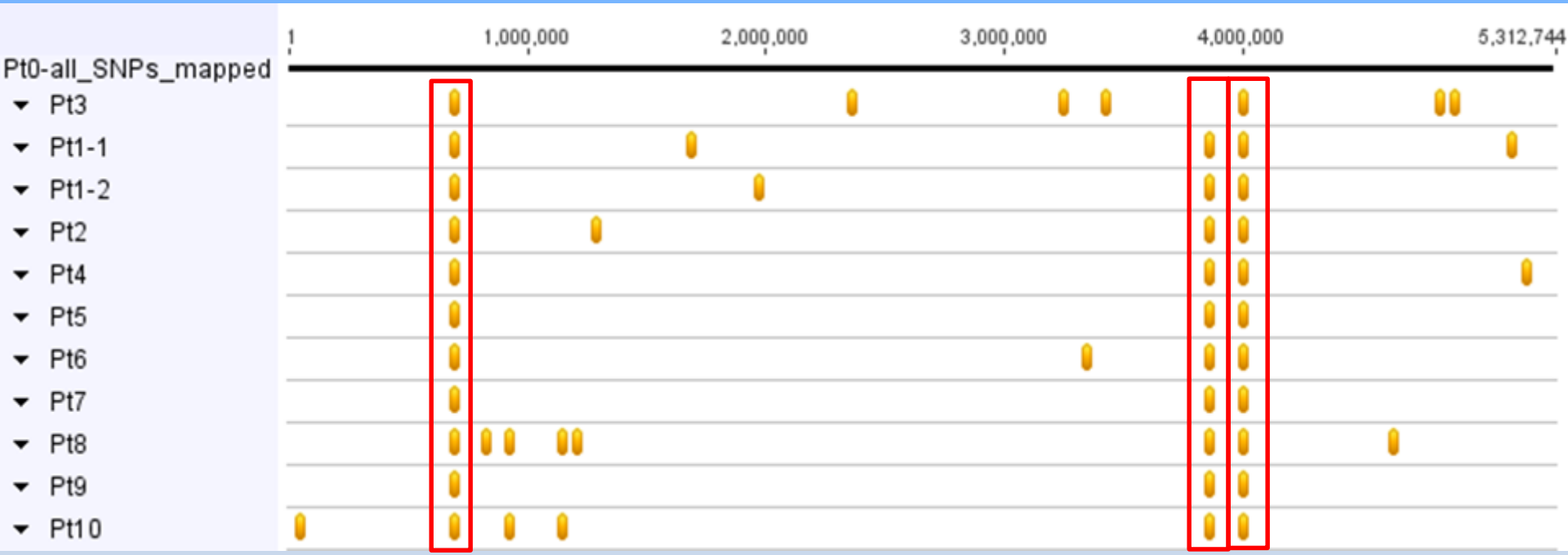
WGS Confirmed the Relatedness of the Outbreak CRE



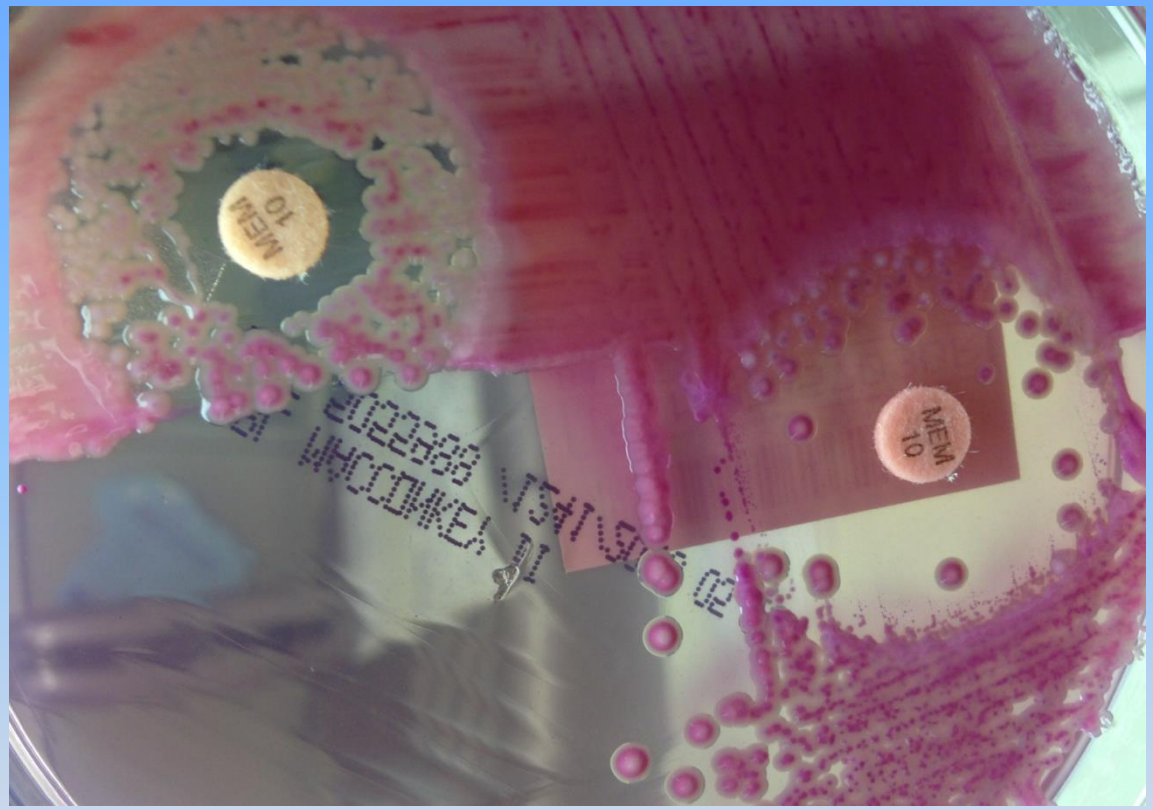
Carbapenem Resistant *K. pneumoniae* SNP Phylogenetic Tree

WGS Confirmed the Relatedness of the Outbreak CRE

SNP analysis of Outbreak isolates



Post-Outbreak OXA-232 CRE Surveillance Program

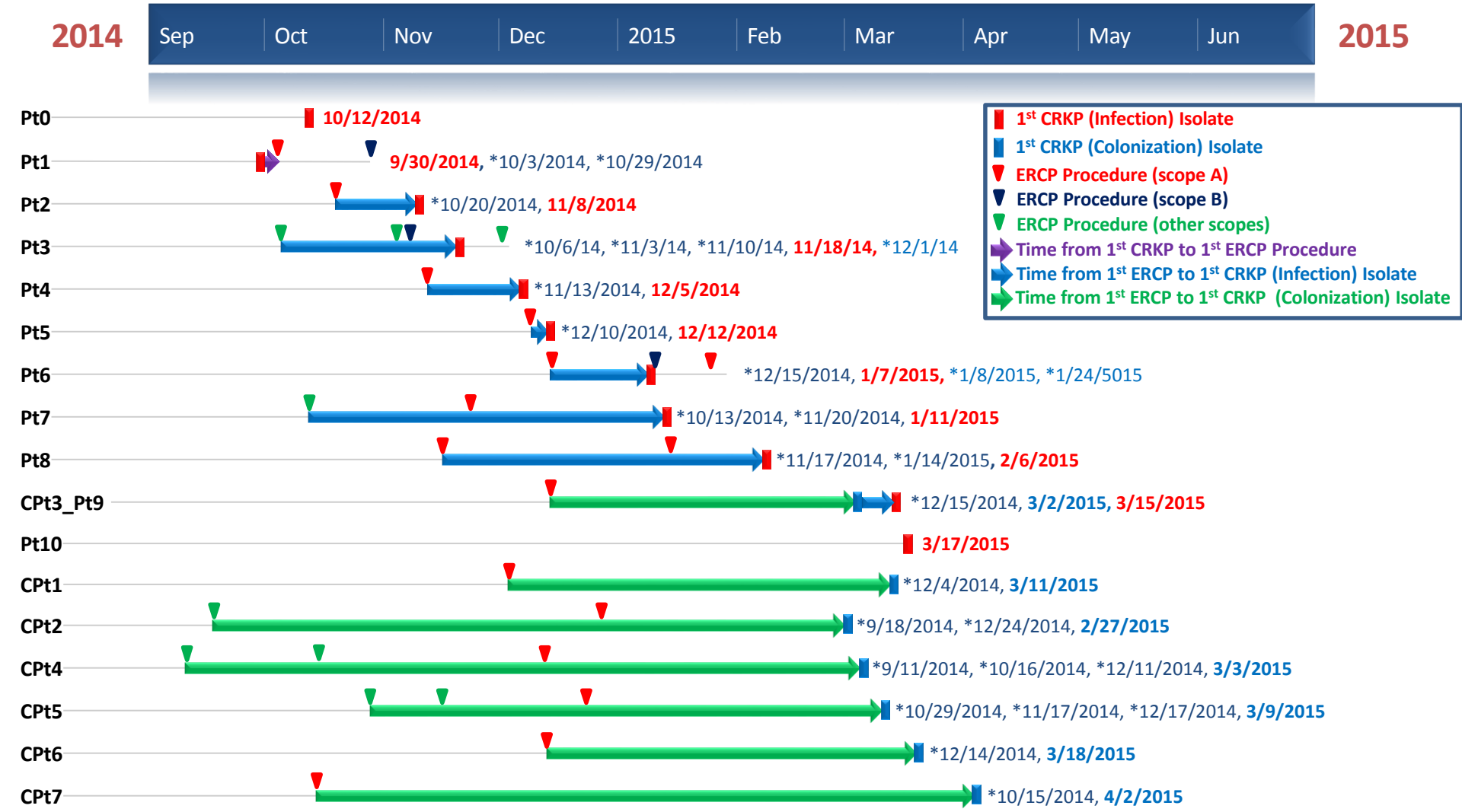


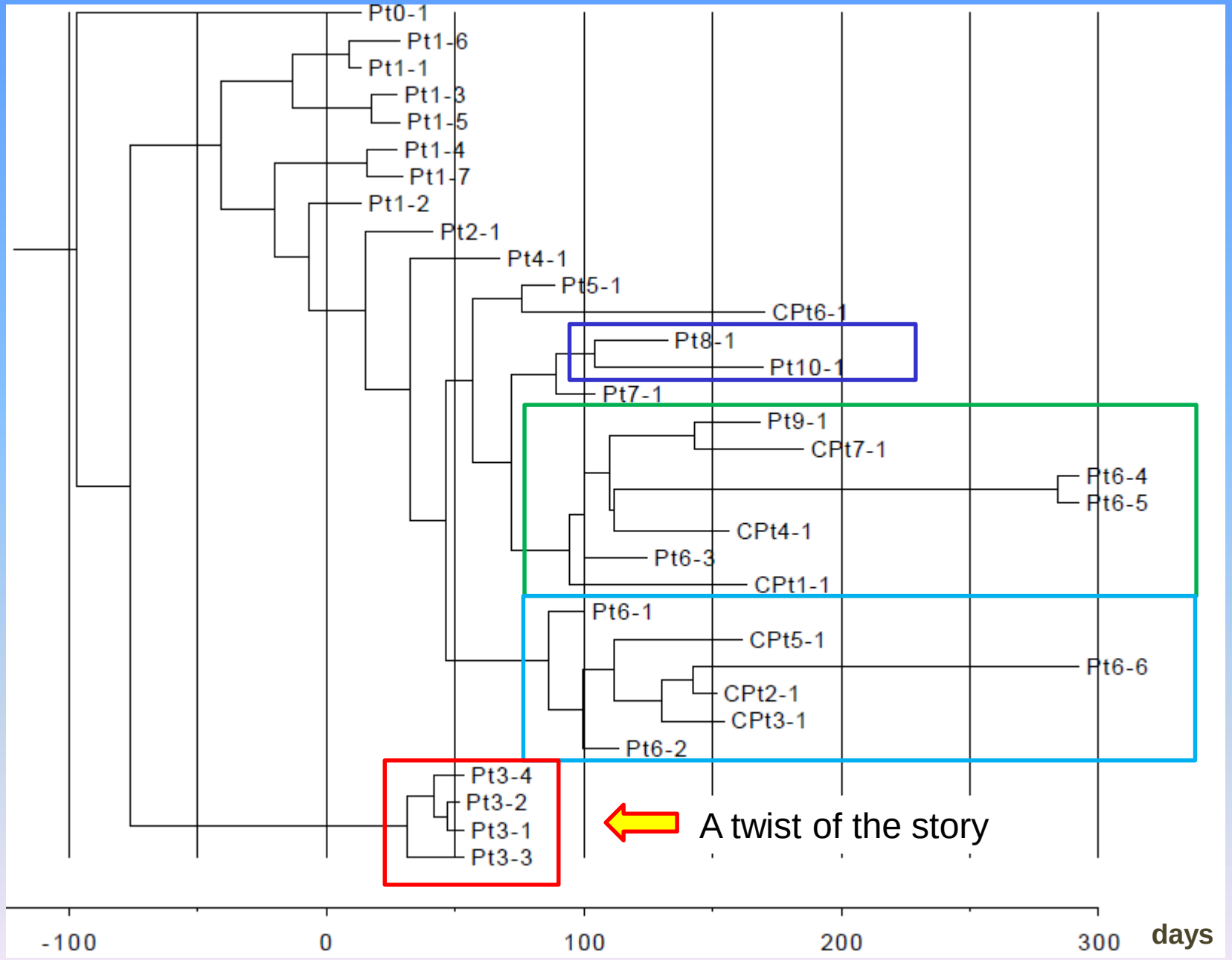
- Self-collect rectal swab
- 179 patients exposed to ERCP during outbreak
- 149 returned swabs

- Cut-off zone size = 28mm
- MALDI-TOF → MIC → PCR → WGS

Post-Outbreak Surveillance & Continuous Screening for OXA-232 CRE

- 7 patients found to be colonized (all from one implicated scope)
  - 4.3% of all returned rectal swabs
  - 7.1% of those exposed to the implicated scope
- 1 colonized patient subsequently developed a clinical infections (splenic abscess)
- 1 patient acquired CRKP infection (UTI) from non-ERCP route after the outbreak
- 3 months after the outbreak, no more new OXA-232 CRE case was found. Overall CRE rate went down 80% due to stricter IP!


2014
Sep
Oct
Nov
Dec
2015
Feb
Mar
Apr
May
Jun
2015
1st CRKP (Infection) Isolate
1st CRKP (Colonization) Isolate
ERCP Procedure (scope A)
ERCP Procedure (scope B)
ERCP Procedure (other scopes)
Time from 1st CRKP to 1st ERCP Procedure
Time from 1st ERCP to 1st CRKP (Infection) Isolate
Time from 1st ERCP to 1st CRKP (Colonization) Isolate
Pt0 10/12/2014
Pt1 9/30/2014, *10/3/2014, *10/29/2014
Pt2 *10/20/2014, 11/8/2014
Pt3 *10/6/14, *11/3/14, *11/10/14, 11/18/14, *12/1/14
Pt4 *11/13/2014, 12/5/2014
Pt5 *12/10/2014, 12/12/2014
Pt6 *12/15/2014, 1/7/2015, *1/8/2015, *1/24/5015
Pt7 *10/13/2014, *11/20/2014, 1/11/2015
Pt8 *11/17/2014, *1/14/2015, 2/6/2015
CPt3_Pt9 *12/15/2014, 3/2/2015, 3/15/2015
Pt10 3/17/2015
CPt1 *12/4/2014, 3/11/2015
CPt2 *9/18/2014, *12/24/2014, 2/27/2015
CPt4 *9/11/2014, *10/16/2014, *12/11/2014, 3/3/2015
CPt5 *10/29/2014, *11/17/2014, *12/17/2014, 3/9/2015
CPt6 *12/14/2014, 3/18/2015
CPt7 *10/15/2014, 4/2/2015



Timed SNV phylogenetic tree of the outbreak CRKP isolates

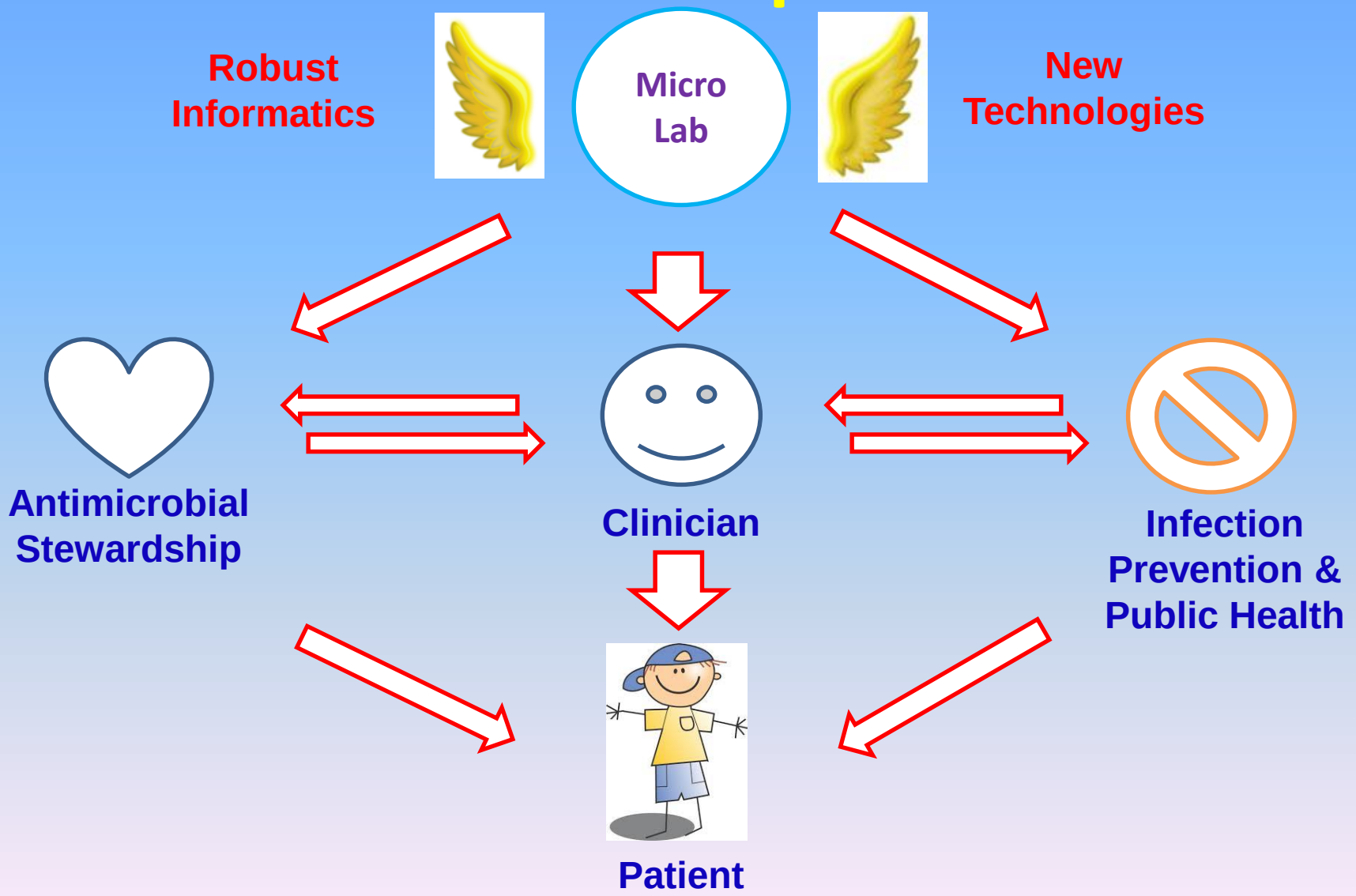
Rep. Lieu's New Superbug Legislation

The DEVICE Act (Disclosure; and Encouragement of Verification, Innovation, Cleaning, and Efficiency)

The Preventing Superbugs and Protecting Patients Act

"Antibiotic-resistant bacteria are a major threat to public health. I am proud to introduce these pieces of legislation today in response to the numerous superbug outbreaks happening in hospitals across the nation. Patients and hospitals deserve to know that the medical devices being used on patients can be properly cleaned and are designed effectively. Patients should not be worried that undergoing a routine medical procedure could lead to them becoming infected with a deadly superbug. What happened to the patients and families at UCLA Medical Center and hospitals across the country should not happen again." -- Congressman Ted W. Lieu (D | Los Angeles County)

The Role of Clinical Microbiology Lab: Never Such Important!



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Thank you! Questions?