

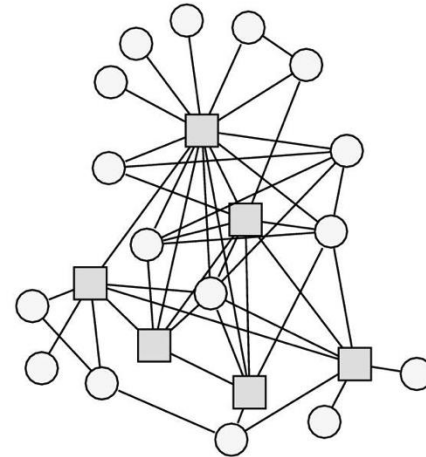
Genomics and Metagenomics

New tools for tracking and detecting resistant bacteria

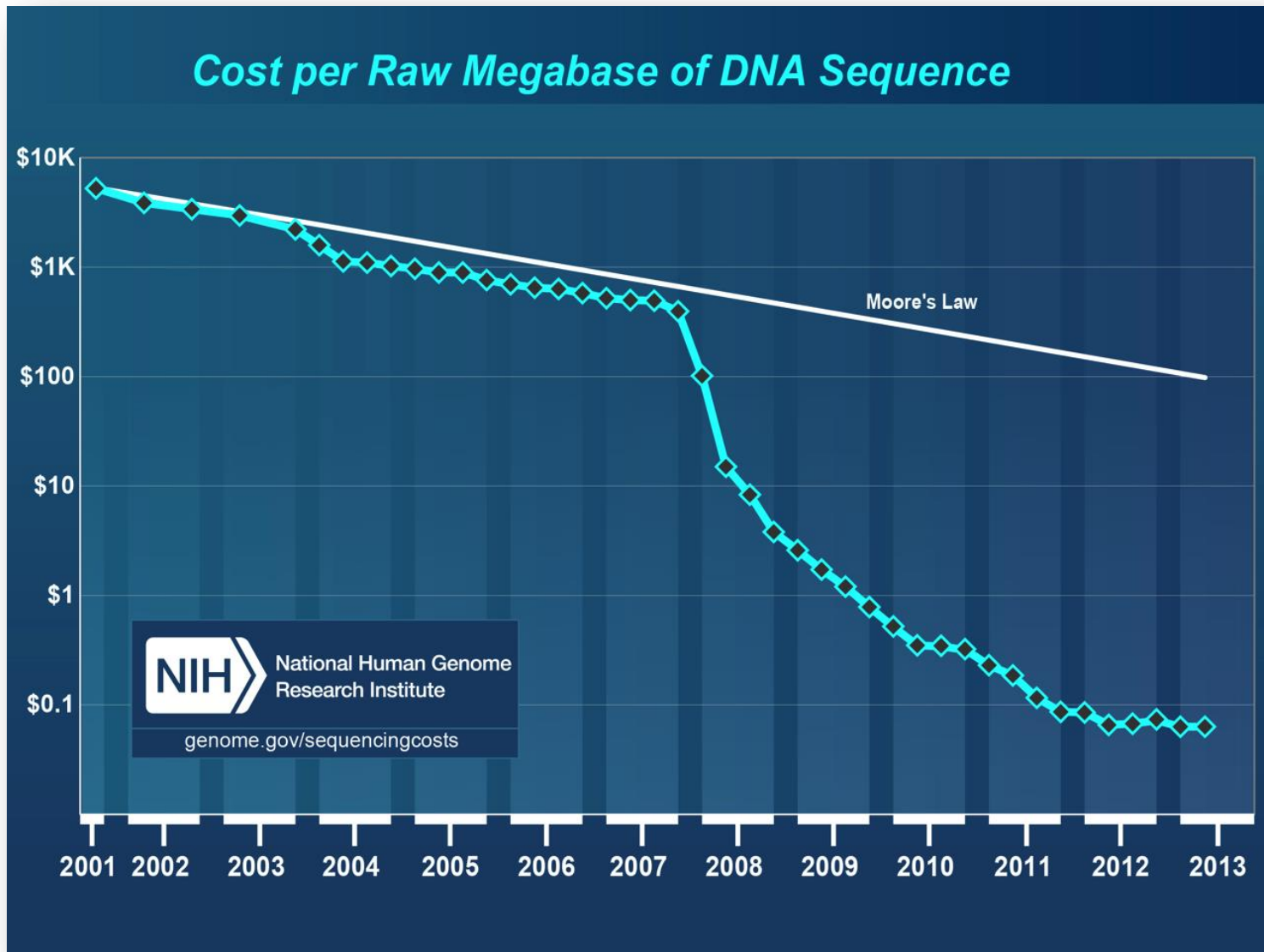
Professor Mark Pallen

Problem #1: Lack of medical intelligence

- ▶ Pathogens pop up all over the place, often without any obvious logic
 - ▶ Hard to target resources
 - ▶ Leads to “whack-a-mole” approach to infection control
- ▶ Careful scrutiny of “time and place” data can help
 - ▶ But still often leads to a “furball” of potential interactions between cases



A New Opportunity: High-Throughput Sequencing



ge·no·mic ep·i·de·mi·ol·o·gy

(jē' nōmik ,epi ,dēmē' äləjē/)

n. reading whole genome sequences from outbreak germs to track person-to-person spread of an infectious disease.



REMEMBER THE OLD GAME OF “TELEPHONE?”



TACGTAGTACGTAACTGCGACGTCTCTGATGCTAGT
AATGATGCTCGTTAGCGTTAGTCGTAATCGTGATGC
TGTACGTACCGTACGTACGTAGCTGATCTACGTATC
GTATCGTCGATCGTAGCTAGCTGCTACGTATCGTCG
ATCGTAGCTGTAGCTA



TACGTAGTACGTA ACTGCGACGTCTCTGATGCTAGT
AATGATGCTCGTTAGCGTTAGTCGTAATCGTGATGC
TGTACGTAGCGTACGTAAGCTGATCTACGTATC
GTATCGTCGATCGTAGCTAGCTGCTACGTATCGTCG
ATCGTAGCTGTAGCTA



TACGTAGTACGTA ACTGCGACGTCTCTGATGCTAGT
AATGATGCTCGTTAGCGTTAGTCGTAATCGTGATGC
TGTACGTAGCGTACGTA GCTGAACTACGTATC
GTATCGTCGATCGTAGCTAGCTGCTACGTATCGTCG
ATCGTAGCTGTAGCTA



TACGTAGTACGTA ACTGCGACGTCTCTGATGCTAGT
AATGATGCTCGTTAGCGTTAGTCGTAATCGTGATGC
TGTACGTAGCGTACGTACGTAGCTGA ACTACGTATC
GTATCGTCGATCGTATCTAGCTGCTACGTATCGTCG
ATCGTAGCTGTAGCTA

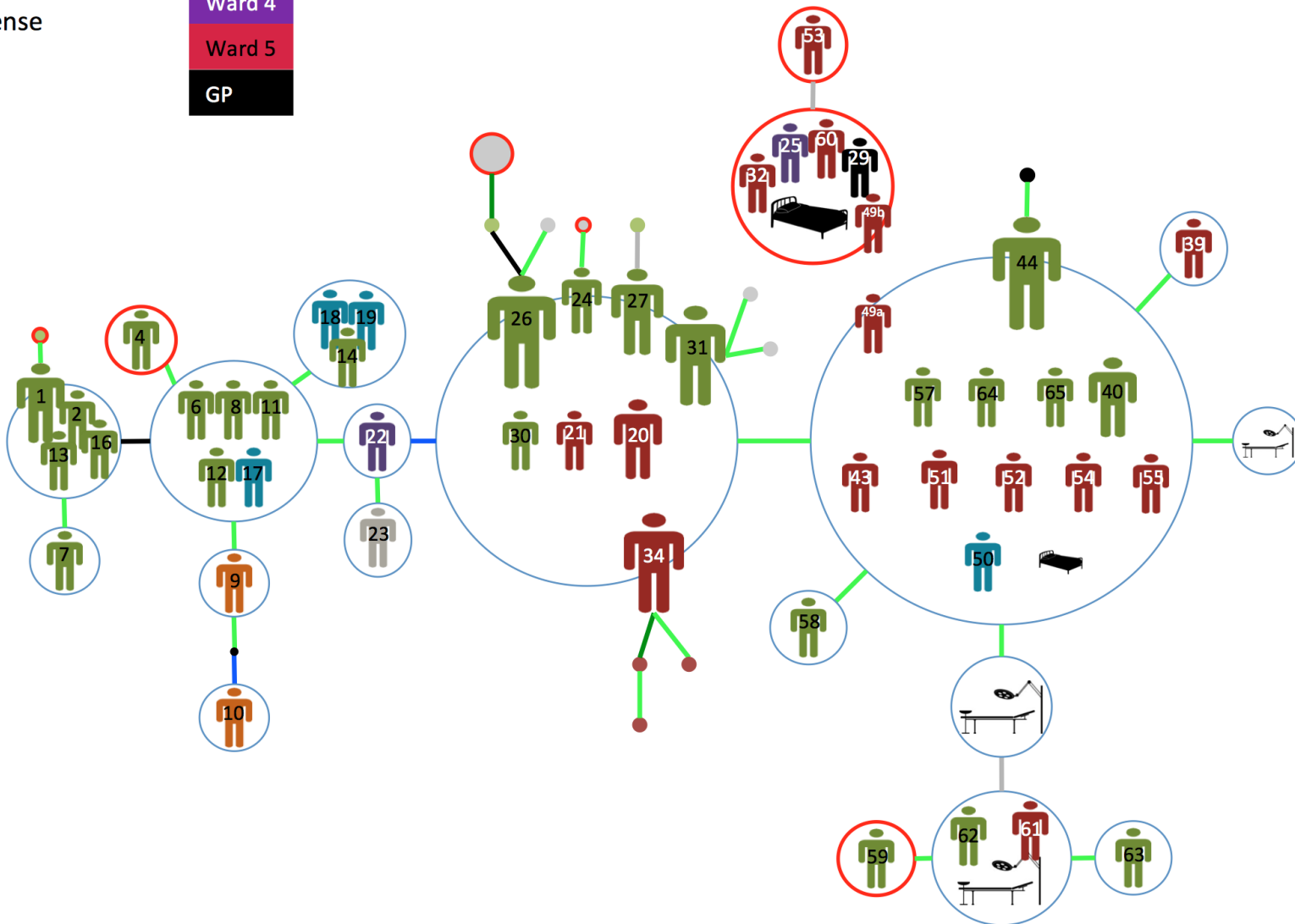
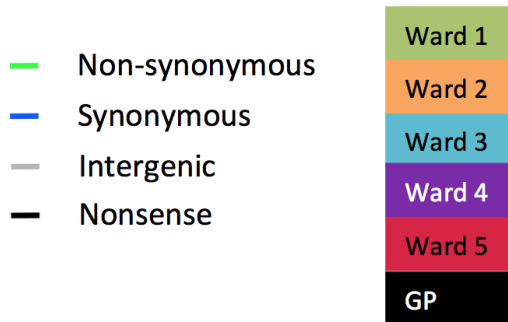


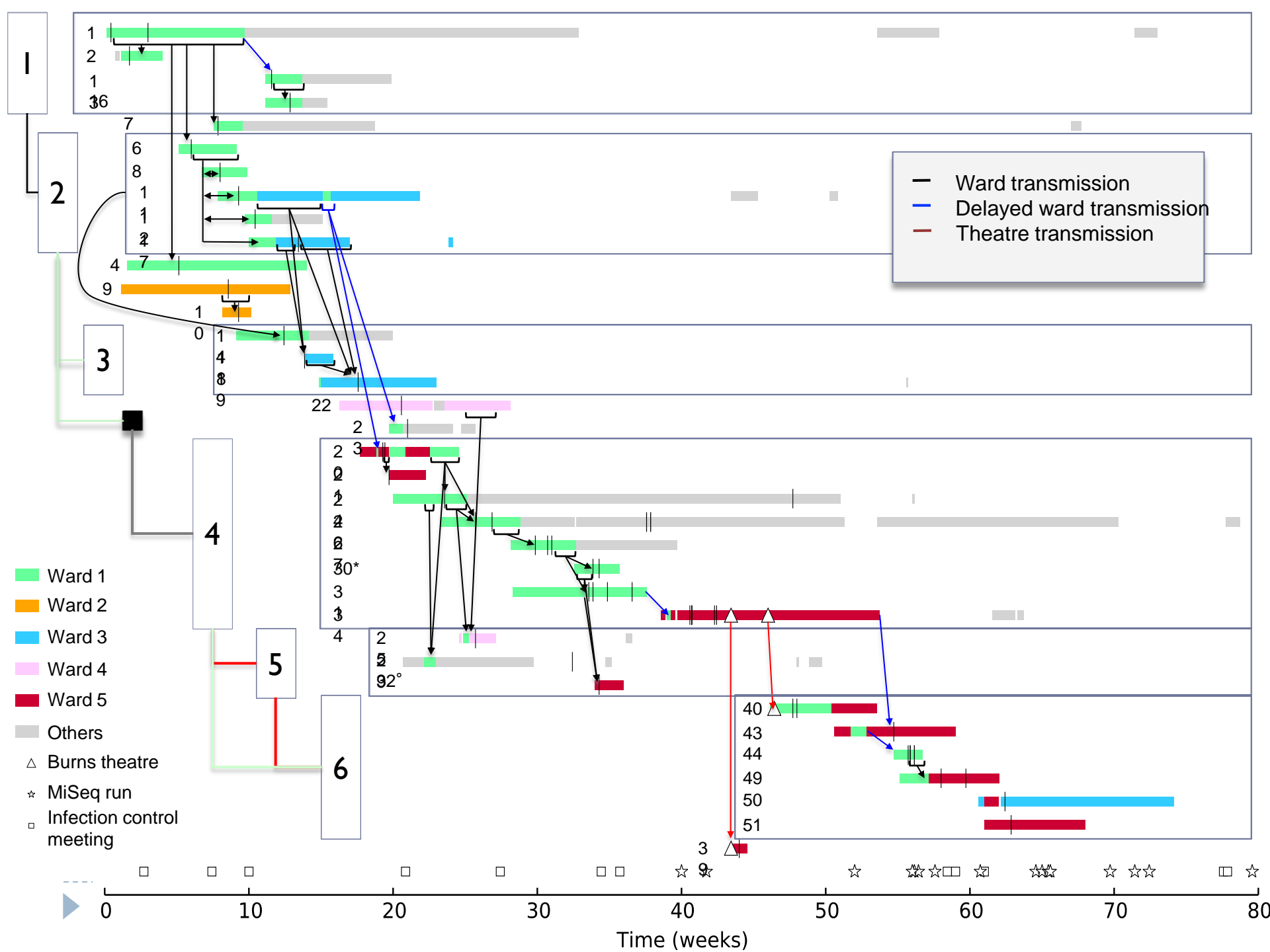
Case study: *Acinetobacter baumannii*

- ▶ **Multi-drug resistant bacterium, associated with**
 - ▶ wound and bloodstream infections and ventilator-associated pneumonia
 - ▶ returning military personnel from Iraq and Afghanistan
- ▶ **Causes outbreaks**
 - ▶ mode of spread and transmission chains uncertain
 - ▶ hinders optimal management of outbreaks and rational design of policies



91 isolates from patients and environment genome-sequenced including multiples from same patient (different time and body sites)





Problem #2

19th C techniques used in 21st C

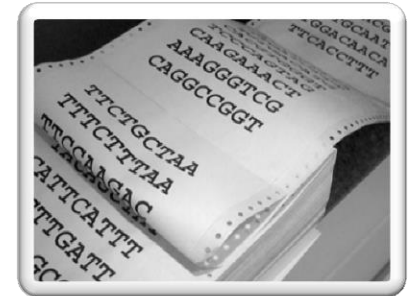
Gram, C. 1884. Ueber die isolirte Färbung der Schizomyceten in Schnitt- und Trockenpräparaten. *Fortschritte der Medicin*, Vol. 2, pages 185–189.

Koch, Robert. 1881. Zur Untersuchung von pathogenen Organismen. 1881. *Mittheilungen aus dem Kaiserlichen Gesundheitsamte*, Vol. 1, pages 1–48.



Shotgun Metagenomics: direct sequencing of DNA extracted from a sample without culture, amplification or capture: includes genomes from all the organisms in the sample

Diagnostic Metagenomics: application of metagenomics to human or animal samples to detect and characterise pathogens



Just sequence the sh*t!



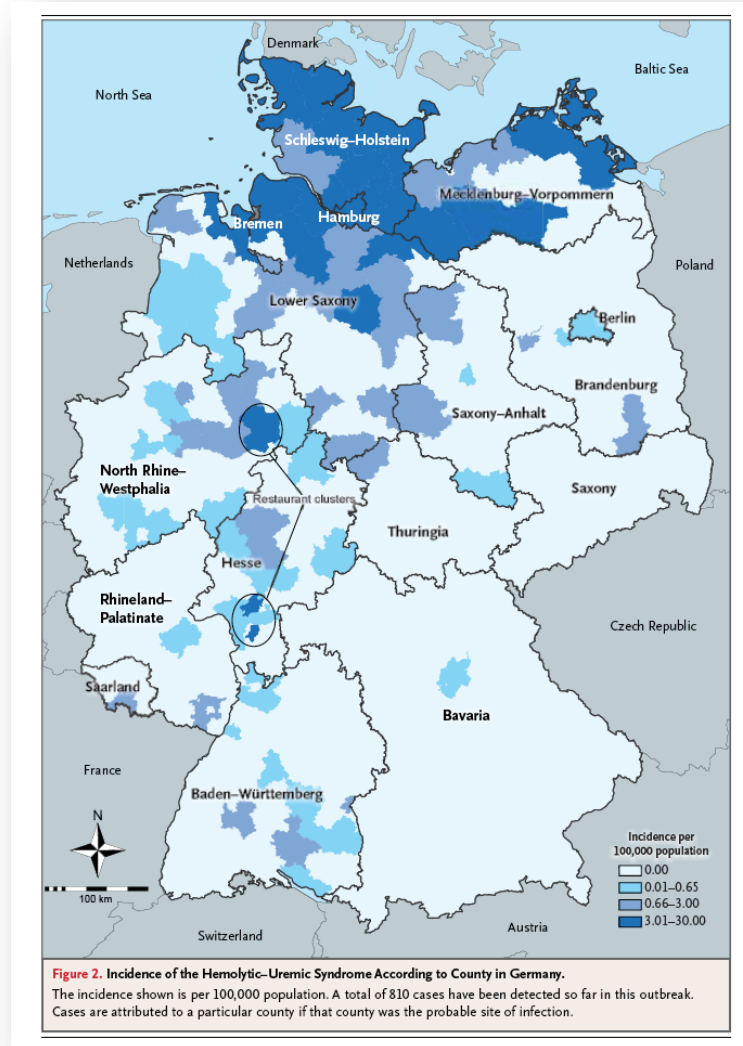
Birmingham Science City

ideasforlife



Diagnostic metagenomics: Example 1

- ▶ German *E. coli* “sproutbreak”
- ▶ May-June 2011
- ▶ >4000 cases
- ▶ >40 deaths

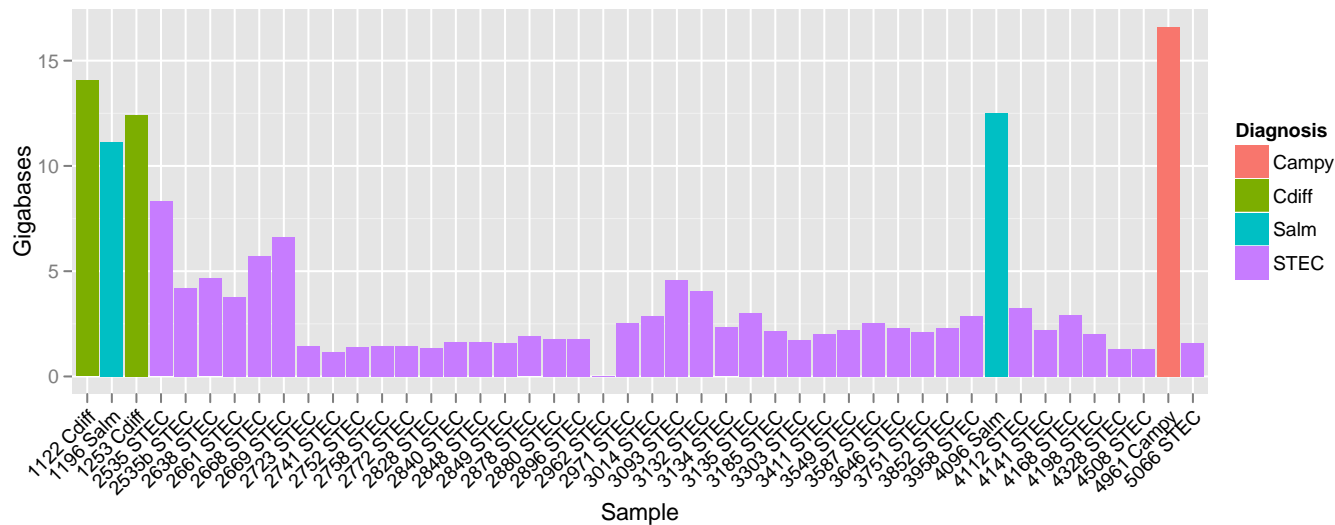


Proof of principle

- ▶ Found *E. coli* sequences in most outbreak samples
- ▶ Found expected pathogens in non-*E. coli* samples
- ▶ Found “unknown unknowns”



NEW HiSeq 2500



Diagnostic Metagenomics: Example 2

- ▶ In 1994, a crypt was discovered in Vác, Hungary, containing 242 bodies, many naturally mummified
- ▶ Included the remains of Terézia Hausmann, who died on 25 December 1797, aged 28 years



Vác museum: *Memento Mori*



Metagenomic diagnosis of 200-year-old TB

- ▶ DNA from lung tissue sequenced
- ▶ 8% of sequences aligned with the *Mycobacterium tuberculosis* reference strain H37Rv (32-X coverage)
- ▶ First glimpse into the epidemiology of tuberculosis at time of “peak TB”
 - ▶ Two strains detected
 - ▶ Both related to, but distinct from, strains circulating in Europe and North America during last century, including recent outbreak strain in Germany



Conclusions

- ▶ Genomic and metagenomic approaches can augment conventional microbiological and epidemiological investigations
- ▶ Genomic epidemiology can help unravel sources and routes of transmission
- ▶ Diagnostic metagenomics can identify bacterial pathogens in samples, including “unknown unknowns”

Caveats

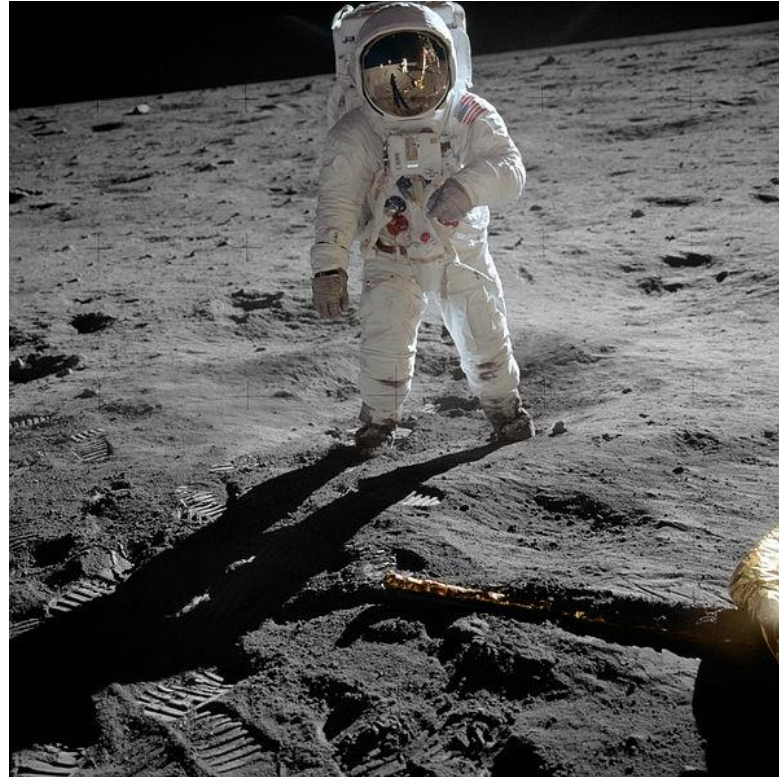
- ▶ Our studies were mostly retrospective
- ▶ Metagenome sequencing is still orders of magnitude too expensive and difficult for routine use
 - ▶ AT THE MOMENT...
- ▶ Genome sequence may not always predict how organism behaves



From Kitty Hawk to the Moon...



1903



1969



Acknowledgements



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