"All-Time Top" Infection Control Literature part 3

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Topics

1. Antimicrobial Resistance
2. Key Epidemiologic Risk Factors
3. Five General Control Measures
4. Surgical Site Infection Control
5. Device-associated Infection Control
6. Major Outbreaks
7. Quality Improvement
8. Statistics and Modeling
9. Molecular Advances
10. The Microbiome

More Robust Statistical Analyses and Mathematical Models

"All models are wrong, but some are useful"

George Box, *Robustness in the Strategy of Scientific Model Building*, RL Launer and GN Wilkinson (editors) 1979, p202

Vancomycin-resistant enterococci in intensive-care hospital settings: Transmission dynamics, persistence, and the impact of infection control programs

(nosocomial infections/mathematical models)

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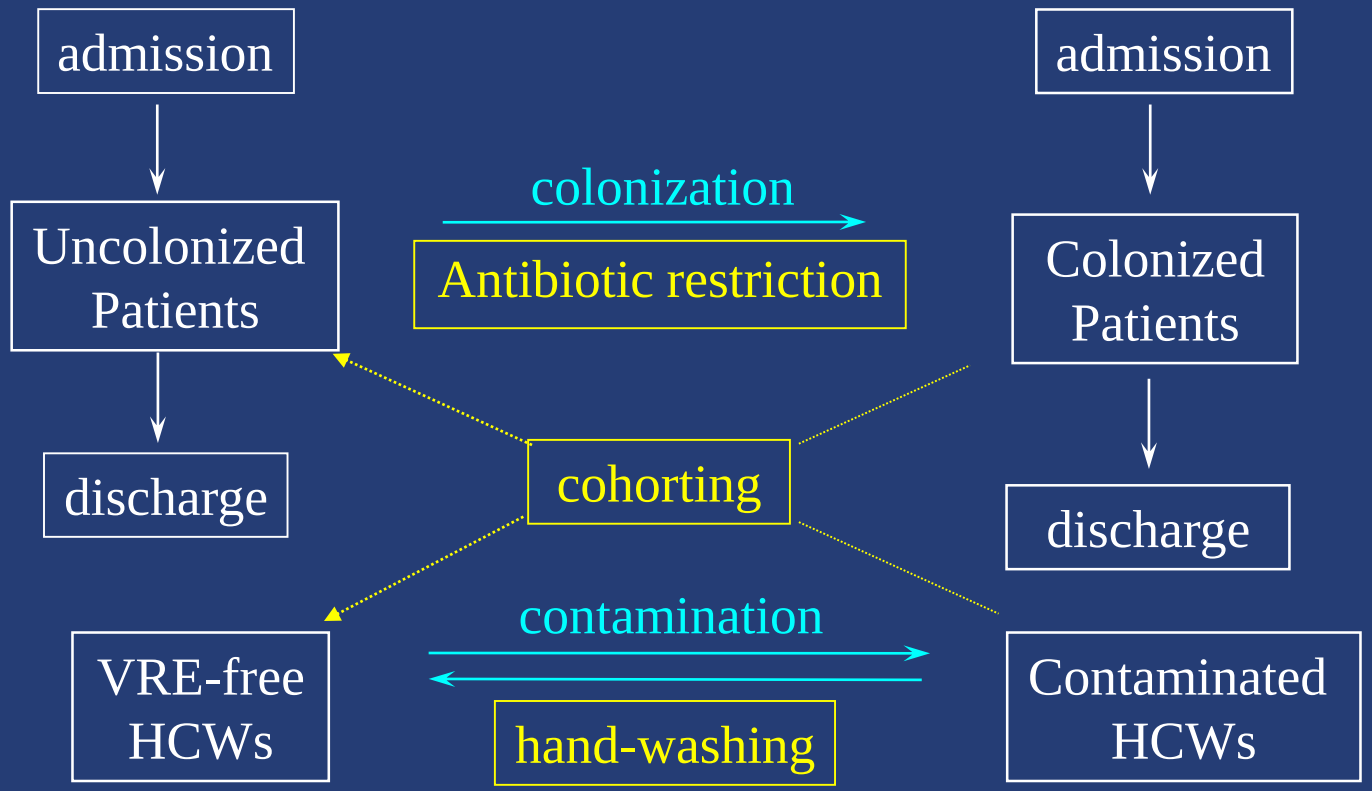
Theoretical framework for transmission/control of VRE in endemic setting



Austin et al, *PNAS* 1999; 96:6908-13

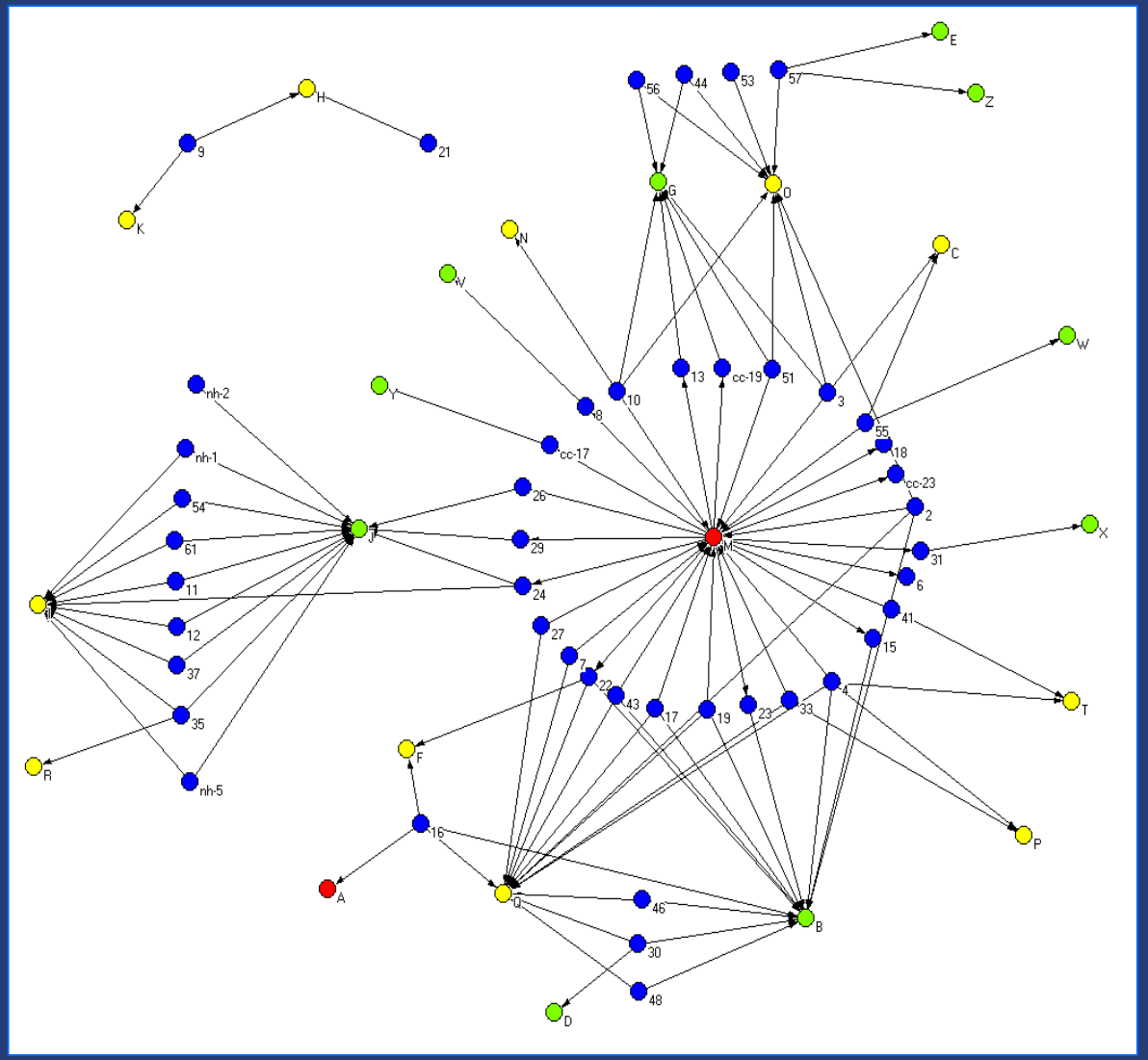
Social Network Analysis & Regional Control

Social Network depiction of LTACH, Nursing Home, & Hospital spread of KPC (Carbapenem-resistant *Klebsiella pneumoniae)*

Legend

- LTACH
- Nursing Home
- Acute Hospital
- Patient

LTACH, Long term acute care hospital; MDRO, Multi-drug resistant organism.



Won et al, *Clin Infect Dis* 2011; 53(6):532-40

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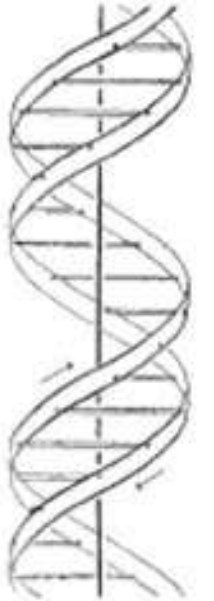
MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

WE wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.

A structure for nucleic acid has already been proposed by Pauling and Corey[1]. They kindly made their manuscript available to us in advance of publication. Their model consists of three inter-twined chains, with the phosphates near the fibre axis, and the bases on the outside. In our opinion, this structure is unsatisfactory for two reasons: (1) We believe that the material which gives the X-ray diagrams is the salt, not the free acid. Without the acidic hydrogen atoms it is not clear what forces would hold the structure together, especially as the negatively charged phosphates near the axis will repel each other. (2) Some of the van der Waals distances appear to be too small.

Another three-chain structure has also been suggested by Fraser (in the press). In his model the phosphates are on the outside and the bases on the inside, linked together by hydrogen bonds. This structure as described is rather ill-defined, and for this reason we shall not comment on it.



This figure is purely diagrammatic. The two ribbons symbolize the two phosphate–sugar chains, and the horizontal rods the pairs of bases holding the chains together. The vertical line marks the fibre axis

We wish to put forward a radically different structure for the salt of deoxyribose nucleic acid. This structure has two helical chains each coiled round the same axis (see diagram). We have made the usual chemical assumptions, namely, that each chain consists of phosphate di-ester groups joining β-D-deoxy-ribofuranose residues with 3′,5′ linkages. The two chains (but not their bases) are related by a dyad perpendicular to the fibre axis. Both chains follow right-handed helices, but owing to the dyad the sequences of the atoms in the two chains run in opposite directions. Each chain loosely resembles Furberg's[2] model No. 1; that is, the bases are on the inside of the helix and the phosphates on the outside. The configuration of the sugar and the atoms near it is close to Furberg's 'standard configuration', the sugar being roughly perpendicular to the attached base. There

Watson & Crick, *Nature* 1953; (171)4356:737-8

How to Select and Interpret Molecular Strain Typing Methods for Epidemiological Studies of Bacterial Infections: A Review for Healthcare Epidemiologists

Fred C. Tenover, PhD; Robert D. Arbeit, MD; Richard V. Goering, PhD;
the Molecular Typing Working Group of the Society for Healthcare Epidemiology of America

ABSTRACT

Strain typing is an integral part of epidemiological investigations of nosocomial infections. Methods for distinguishing among bacterial strains have improved dramatically over the last 5 years, due mainly to the introduction of molecular technology. Although not all molecular techniques are equally effective for typing all organisms, pulsed-field gel electrophoresis is the technique currently favored for most nosocomial pathogens. Criteria to aid epidemiologists in interpreting results have been published. Nucleic acid amplification-based typing methods also are applicable to many organisms and can be completed within a single day, but interpretive criteria still are under debate. Strain typing cannot be used to replace a sound epidemiological investigation, but serves as a useful adjunct to such investigations (*Infect Control Hosp Epidemiol* 1997;18:426-439).

Tenover et al, *Infect Control Hosp Epidemiol* 1997; 18(6):426-39

Whole Genome Sequencing of MRSA

Rapid Whole-Genome Sequencing for Investigation of a Neonatal MRSA Outbreak

Claudio U. Köser, B.A., Matthew T.G. Holden, Ph.D., Matthew J. Ellington, D.Phil., Edward J.P. Cartwright, M.B., B.S., Nicholas M. Brown, M.D., Amanda L. Ogilvy-Stuart, F.R.C.P., Li Yang Hsu, M.R.C.P., Claire Chewapreecha, B.A., Nicholas J. Croucher, M.A., Simon R. Harris, Ph.D., Mandy Sanders, B.Sc., Mark C. Enright, Ph.D., Gordon Dougan, Ph.D., Stephen D. Bentley, Ph.D., Julian Parkhill, Ph.D., Louise J. Fraser, Ph.D., Jason R. Betley, Ph.D., Ole B. Schulz-Trieglaff, Ph.D., Geoffrey P. Smith, Ph.D., and Sharon J. Peacock, Ph.D., F.R.C.P.

CONCLUSIONS

Whole-genome sequencing can provide clinically relevant data within a time frame that can influence patient care. The need for automated data interpretation and the provision of clinically meaningful reports represent hurdles to clinical implementation. (Funded by the U.K. Clinical Research Collaboration Translational Infection Research Initiative and others.)

We constructed a phylogenetic tree by comparing single-nucleotide polymorphisms (SNPs) in the core genome to a reference genome (an epidemic MRSA clone, EMRSA-15 [sequence type 22]). This revealed a distinct cluster of outbreak isolates and clear separation between these and the nonoutbreak isolates. A previously missed transmission event was detected between two patients with bacteremia who were not part of the outbreak. We created an artificial "resistome" of antibiotic-resistance genes and demonstrated concordance between it and the results of phenotypic susceptibility testing; we also created a "toxome" consisting of toxin genes. One outbreak isolate had a hypermutator phenotype with a higher number of SNPs than the other outbreak isolates, highlighting the difficulty of imposing a simple threshold for the number of SNPs between isolates to decide whether they are part of a recent transmission chain.

CONCLUSIONS

Whole-genome sequencing can provide clinically relevant data within a time frame that can influence patient care. The need for automated data interpretation and the provision of clinically meaningful reports represent hurdles to clinical implementation. (Funded by the U.K. Clinical Research Collaboration Translational Infection Research Initiative and others.)

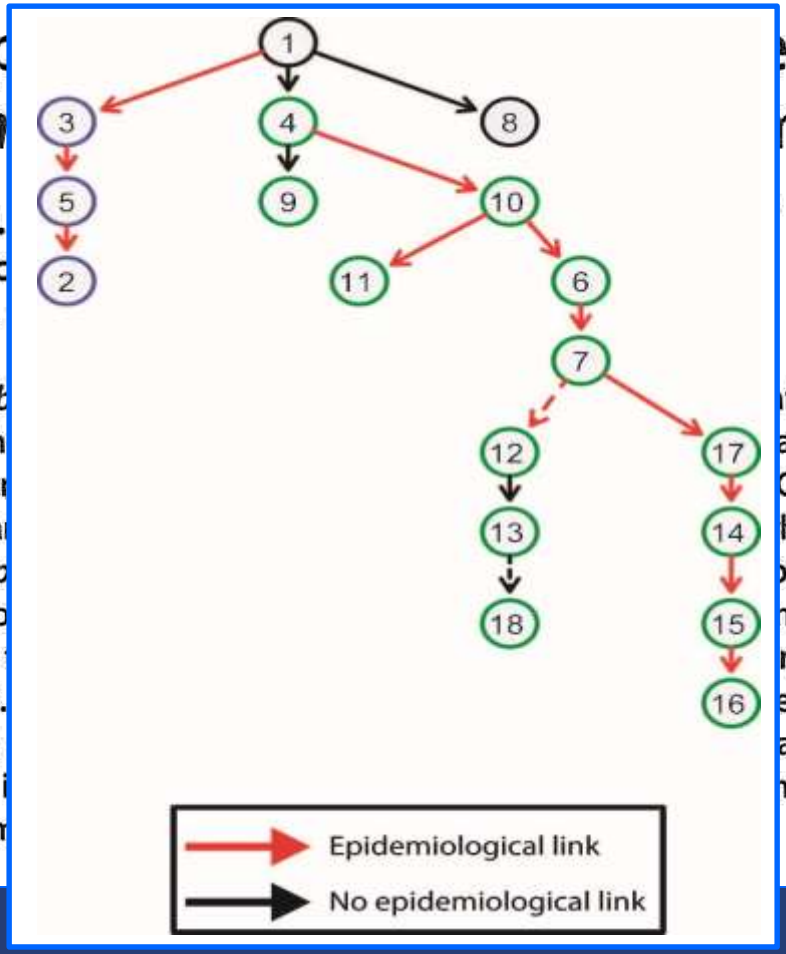
Köser et al, *N Engl J Med* 2012; 366(24):2267-75

Putative map of *K. pneumoniae* Transmission During Outbreak

Tracking a Hosp … enem-Resistant *Klebsiella pneun* … ne Sequencing

Evan S. Snitkin,[1] Adrian M. … NISC Comparative Sequenc … Tara N. Palmore,[2]* Julia A. …

The Gram-negative bacteria *Kleb* … fections, primarily among immunocompromised patients. Th … as left few treatment options, making infection containment c… Clinical Center experienced an outbreak of carbapenem-resista… hom died. Whole-genome sequencing was performed on *K. p* … reak progressed despite early implementation of infection co… iological analysis traced the outbreak to three independent … rged 3 weeks before the next case became clinically apparent. … e for unexpected transmission routes, with subsequent mining … ations for these transmissions. Our analysis demonstrates that i… yield actionable insights and facilitate the control of nosocom…



Snitkin et al, *Sci Transl Med* 2012;
http://stm.sciencemag.org/content/4/148/148ra116.full.html

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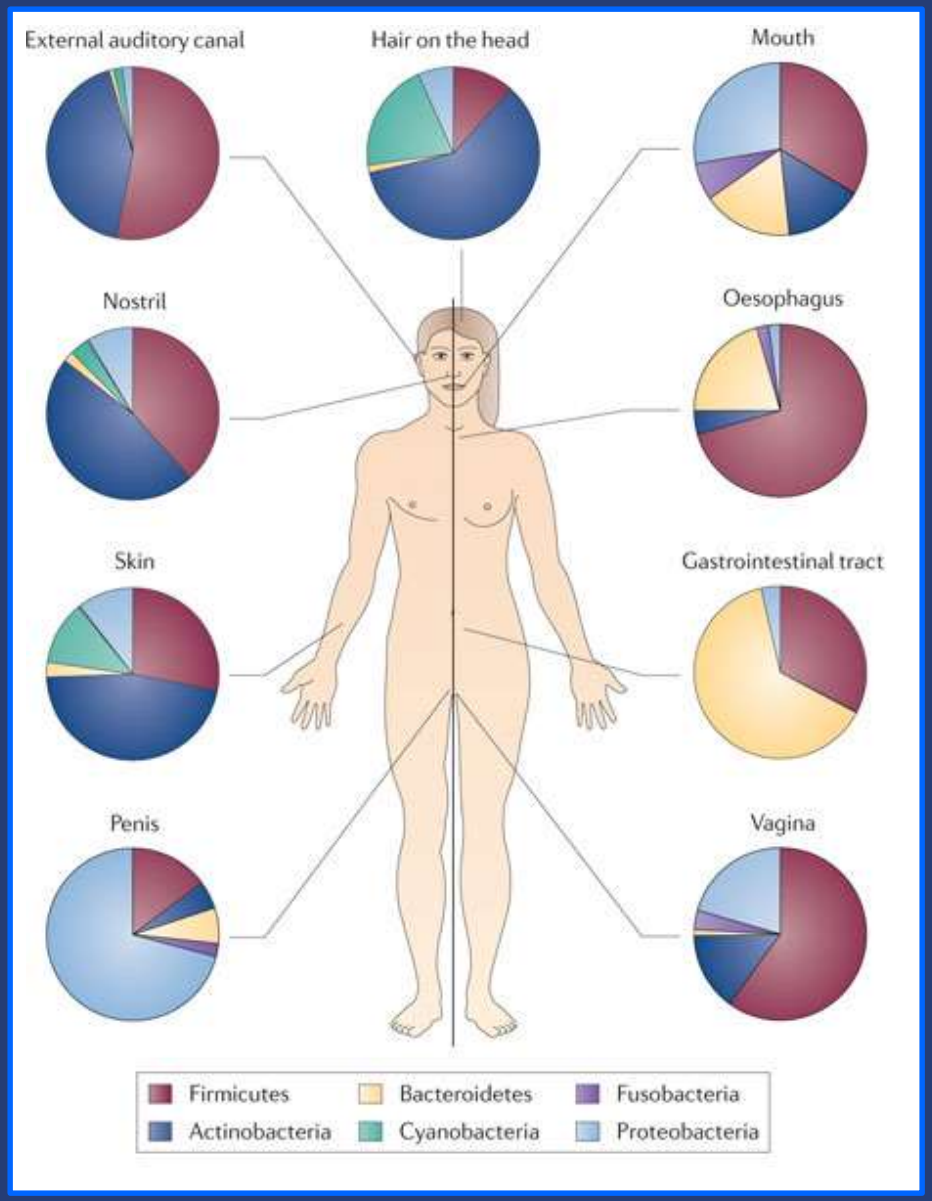
NIH Human Microbiome Project



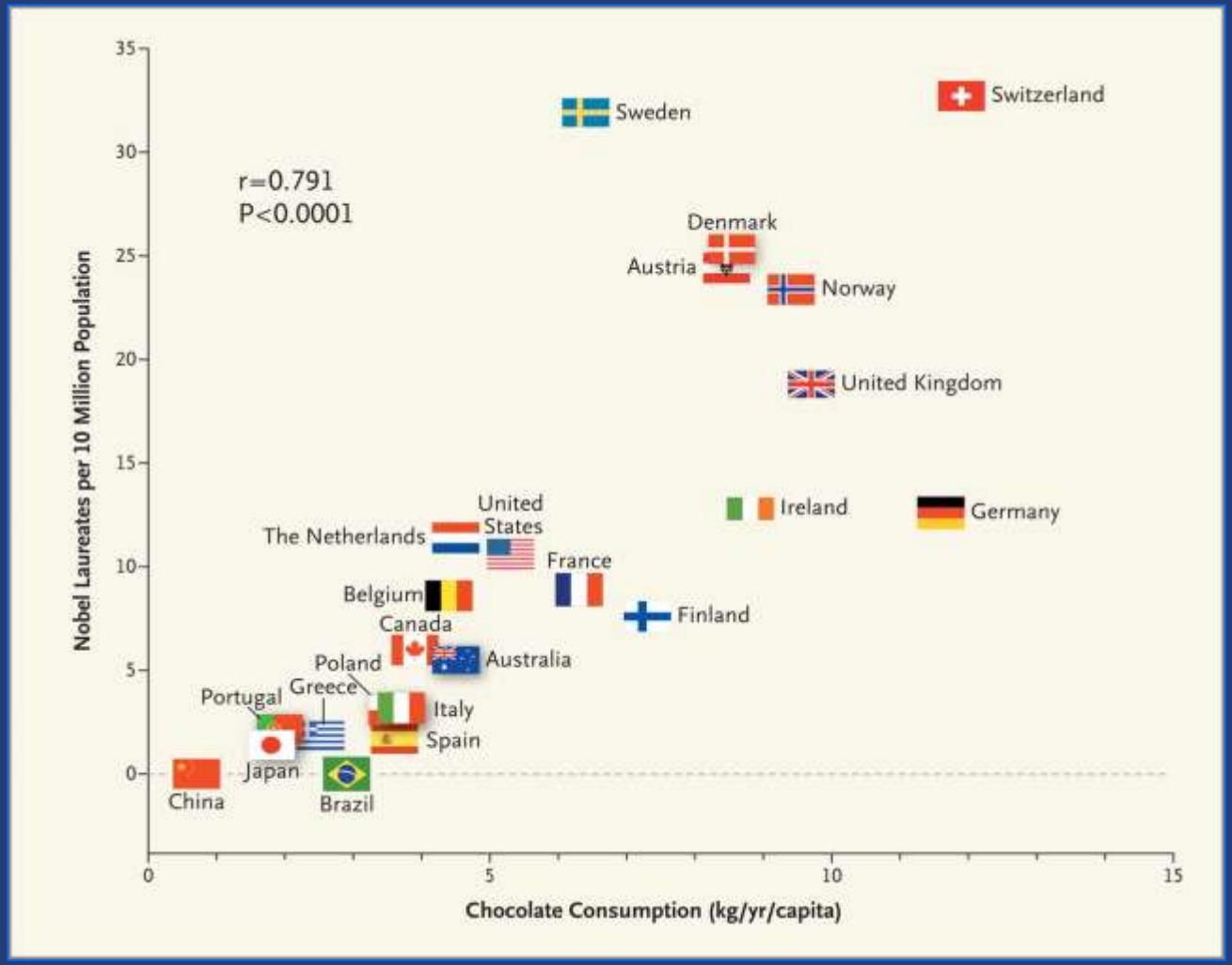
WE ARE WHAT WE EAT?

- Gut Microbiomes of Malawian Twins Discordant for Kwashiorkor, *Science* 2013; 339:548-54
- Antibiotics Treat Malnutrition? *N Engl J Med* 2013; 368:425-35
- Intestinal Metabolism and Cardiac Risk, *N Engl J Med* 2013; 368:1575-84
- Gut Microbiota in Diabetes, *Nature* 2012; 490:55-60
- Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*, *N Engl J Med* 2013; 368:407-15

Spor, Koren, Ley, *Nature Rev Microbiol* 2011; 9:279

Some Things Are Good to Eat

Correlation between Countries' Annual Per Capita Chocolate Consumption and the Number of Nobel Laureates Per 10 Million Population



Messerli, *N Engl J Med* 2012; 367(16):1562-4

The Microbiome & Treatment

Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

Els van Nood, M.D., Anne Vrieze, M.D., Max Nieuwdorp, M.D., Ph.D., Susana Fuentes, Ph.D., Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D., Caroline E. Visser, M.D., Ph.D., Ed J. Kuijper, M.D., Ph.D., Joep F.W.M. Bartelsman, M.D., Jan G.P. Tijssen, Ph.D., Peter Speelman, M.D., Ph.D., Marcel G.W. Dijkgraaf, Ph.D., and Josbert J. Keller, M.D., Ph.D.

ABSTRACT

BACKGROUND

Recurrent *Clostridium difficile* infection is difficult to treat, and failure rates for antibiotic therapy are high. We studied the effect of duodenal infusion of donor feces in patients with recurrent *C. difficile* infection.

METHODS

We randomly assigned patients to receive one of three therapies: an initial vancomycin regimen (500 mg orally four times per day for 4 days), followed by bowel lavage and subsequent infusion of a solution of donor feces through a nasoduodenal tube; a standard vancomycin regimen (500 mg orally four times per day for 14 days); or a standard vancomycin regimen with bowel lavage. The primary end point was the resolution of diarrhea associated with *C. difficile* infection without relapse after 10 weeks.

RESULTS

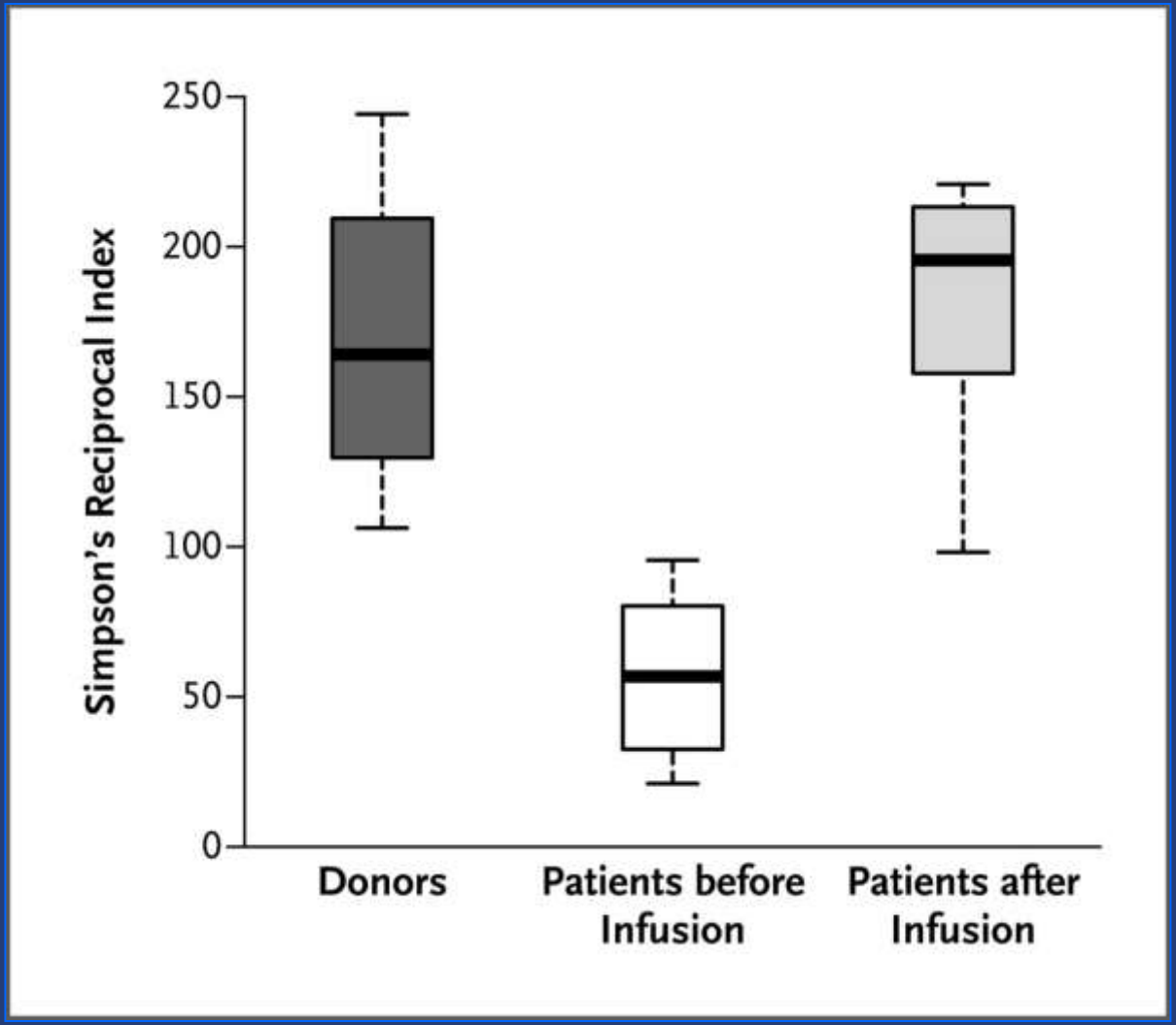
The study was stopped after an interim analysis. Of 16 patients in the infusion group, 13 (81%) had resolution of *C. difficile*–associated diarrhea after the first infusion. The 3 remaining patients received a second infusion with feces from a different donor, with resolution in 2 patients. Resolution of *C. difficile* infection occurred in 4 of 13 patients (31%) receiving vancomycin alone and in 3 of 13 patients (23%) receiving vancomycin with bowel lavage ($P<0.001$ for both comparisons with the infusion group). No significant differences in adverse events among the three study groups were observed except for mild diarrhea and abdominal cramping in the infusion group on the infusion day. After donor-feces infusion, patients showed increased fecal bacterial diversity, similar to that in healthy donors, with an increase in Bacteroidetes species and clostridium clusters IV and XIVa and a decrease in Proteobacteria species.

CONCLUSIONS

The infusion of donor feces was significantly more effective for the treatment of recurrent *C. difficile* infection than the use of vancomycin. (Funded by the Netherlands Organization for Health Research and Development and the Netherlands Organization for Scientific Research; Netherlands Trial Register number, NTR1177.)

Van Nood et al, *N Engl J Med* 2013; 368(5):407-15

Microbiota Diversity in Patients before and after Infusion of Donor Feces, as Compared with Diversity in Healthy Donors



Van Nood et al, *N Engl J Med* 2013; 368(5):407-15

Using a dog's superior olfactory sensitivity to identify *Clostridium difficile* in stools and patients: proof of principle study

OPEN ACCESS

Marije K Bomers *consultant*[1], *psychologist*[2], Merk C van Vee
M Smulders *professor*[1]

[1]Department of Internal Medicine, VU Univers
Research, Animal Behaviour and Cognition,
Amsterdam, Netherlands; [4]Department of Me

Abstract

Objective To investigate whether a dog's su
can be used to detect *Clostridium difficile* in s
patients.

Design Proof of principle study, using a case-control design

(specificity 98%, 95% to 99%).

Cliff (the dog) correctly identified 25 of 30 cases (sensitivity 83%) and 265 of 270 controls (specificity 98%)

Bomers et al, *BMJ* 2012; 345:e7396-7404

Control of the Microbiome & MDROs?

Intestinal Microbiota Containing *Barnesiella* Species Cures Vancomycin-Resistant *Enterococcus faecium* Colonization

Carles Ubeda,[a,e,f] Vanni Bucci,[b] Silvia Caballero,[a,e] Ana Djukovic,[f] Nora C. Toussaint,[a,e] Michele Equinda,[a,e] Lauren Lipuma,[a,c,e] Lilan Ling,[a,e] Asia Gobourne,[a,c,e] Daniel No,[a,c,e] Ying Taur,[a,c] Robert R. Jenq,[d] Marcel R. M. van den Brink,[d] Joao B. Xavier,[b,c] Eric G. Pamer[a,c,e]

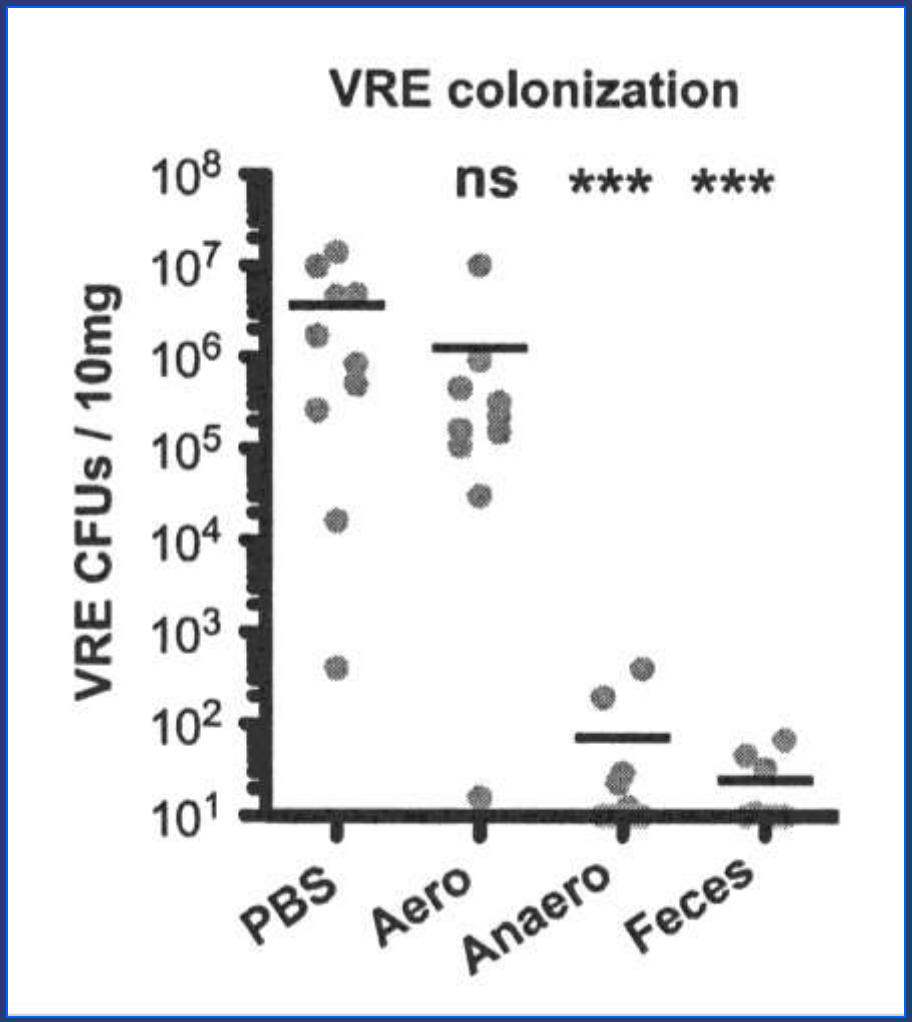
Infectious Diseases Service, Department of Medicine,[a] Computational Biology Center,[b] Lucille Castori Center for Microbes, Inflammation and Cancer,[c] and Bone Marrow Transplant Service, Department of Medicine,[d] Memorial Sloan-Kettering Cancer Center, New York, New York, USA; Immunology Program, Sloan-Kettering Institute, New York, New York, USA[e]; Departamento de Genómica y Salud, Centro Superior de Investigación en Salud Pública, Valencia, Spain[f]

Bacteria causing infections in hospitalized patients are increasingly antibiotic resistant. Classical infection control practices are only partially effective at preventing spread of antibiotic-resistant bacteria within hospitals. Because the density of intestinal colonization by the highly antibiotic-resistant bacterium vancomycin-resistant *Enterococcus* (VRE) can exceed 10^9 organisms per gram of feces, even optimally implemented hygiene protocols often fail. Decreasing the density of intestinal colonization, therefore, represents an important approach to limit VRE transmission. We demonstrate that reintroduction of a diverse intestinal microbiota to densely VRE-colonized mice eliminates VRE from the intestinal tract. While oxygen-tolerant members of the microbiota are ineffective at eliminating VRE, administration of obligate anaerobic commensal bacteria to mice results in a billionfold reduction in the density of intestinal VRE colonization. 16S rRNA gene sequence analysis of intestinal bacterial populations isolated from mice that cleared VRE following microbiota reconstitution revealed that recolonization with a microbiota that contains *Barnesiella* correlates with VRE elimination. Characterization of the fecal microbiota of patients undergoing allogeneic hematopoietic stem cell transplantation demonstrated that intestinal colonization with *Barnesiella* confers resistance to intestinal domination and bloodstream infection with VRE. Our studies indicate that obligate anaerobic bacteria belonging to the *Barnesiella* genus enable clearance of intestinal VRE colonization and may provide novel approaches to prevent the spread of highly antibiotic-resistant bacteria.

MDROs, Multi-drug resistant organisms

Ubeda et al, *Infect Immun* 2013; 81(3):965-73

Commensal Anaerobic Bacteria Suppress VRE Colonization in Antibiotic-treated Mice



Mice were infected with 108 VRE CFU after 1 week of ampicillin treatment. One day after infection, ampicillin treatment was stopped. Mice were orally gavaged for 3 consecutive days, starting 1 day after antibiotic cessation, with PBS, a suspension of fecal pellets from untreated mice (feces), or an aerobic (aero) or anaerobic (anaero) culture of fecal microbiota from untreated mice. Numbers of VRE CFU in the fecal pellets of infected mice were analyzed 5 weeks after infection (*n* 8 to 10). Limit of detection, 10 CFU/10 mg. ***, significantly different (*P* <0.001) from the PBS group; ns, not significant.

Ubeda et al, *Infect Immun* 2013; 81(3):965-73

What's Missing?

- Did I overlook key studies?
- Science in progress but not yet classic?
  - Antimicrobial Stewardship
  - Environmental Interventions
  - Others?