Mikrobiyom çağında tıbbi mikrobiyoloji

fütüristik bir deneme

William Brownrigg’e göre dünya

(John Waller, Mikrobun Keşfi, Tubitak Yayınları, 2013)

- Kızın yüzü kabarıp şişmişti (…) şişlik buruna ve yanaklarına yayılmıştı. Bu durum büyük bir ağrıya neden oluyordu (...) Hasta altı gün içinde yedi kez hacamat edilmiş, her defasında hastadan büyük miktarda kan alınmıştı, bu yüzden de kendini sık sık halsiz hissediyordu.

http://wunderkammer.ki.se/images/facial-erysipelas-or-st-anthony-s-fire

https://en.wikipedia.org/wiki/William_Brownrigg

Etiyoloji?

- Hastanın ateşinin nedeni olarak onun “*narin yapısını*”, *vücudunda biriken* *“kusurlu sıvılar*”ı ve “*havaların aşırı derecede nemli, yağışlı ve günbatısından esen rüzgarlar yüzünden soğuk*” olmasını gösteriyordu...

http://wunderkammer.ki.se/images/facial-erysipelas-or-st-anthony-s-fire

Tıbbın kilometretaşları - Son 500 Yıl (NEJM)

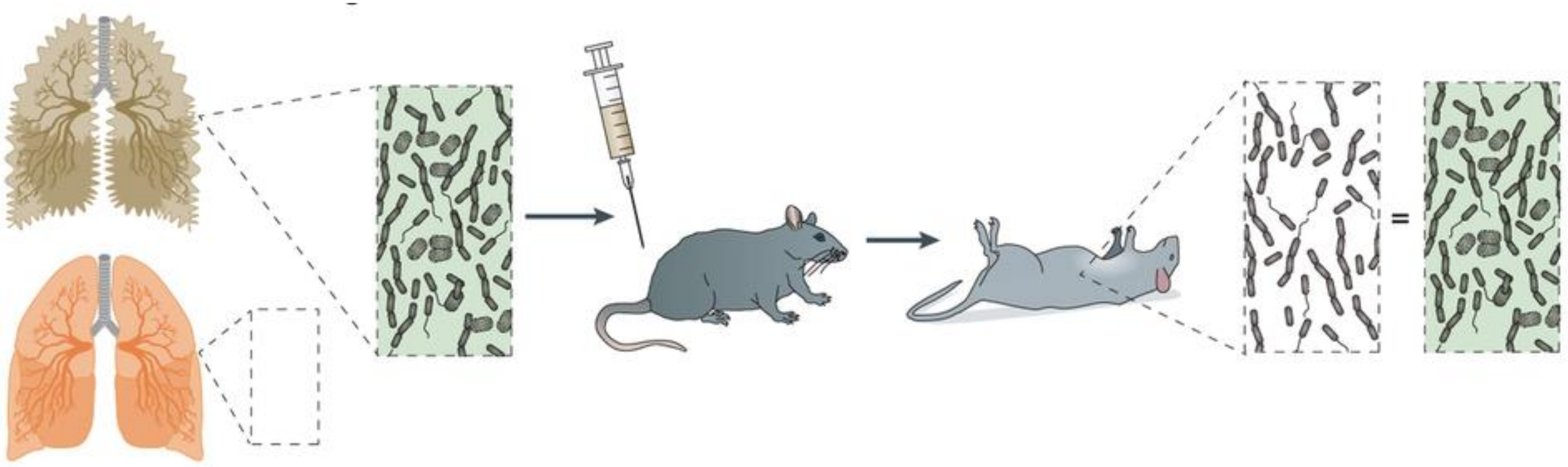
Medical Milestones - The Past 500 Years

- İnsan anatomisi ve fizyolojisinin anlaşılması
- Hücre ve alt birimlerinin keşfi
- Yaşamın kimyasal temellerinin anlaşılması
- İstatistiğin tıbba uygulanması
- Anestezinin geliştirilmesi
- Mikrop kuramı
- Kalıtım ve genetiğin anlaşılması
- Bağışıklık sisteminin anlaşılması
- Vücut görüntülemenin gelişimi
- Antimikrobik ajanların keşfi
- Moleküler farmakoterapinin gelişimi

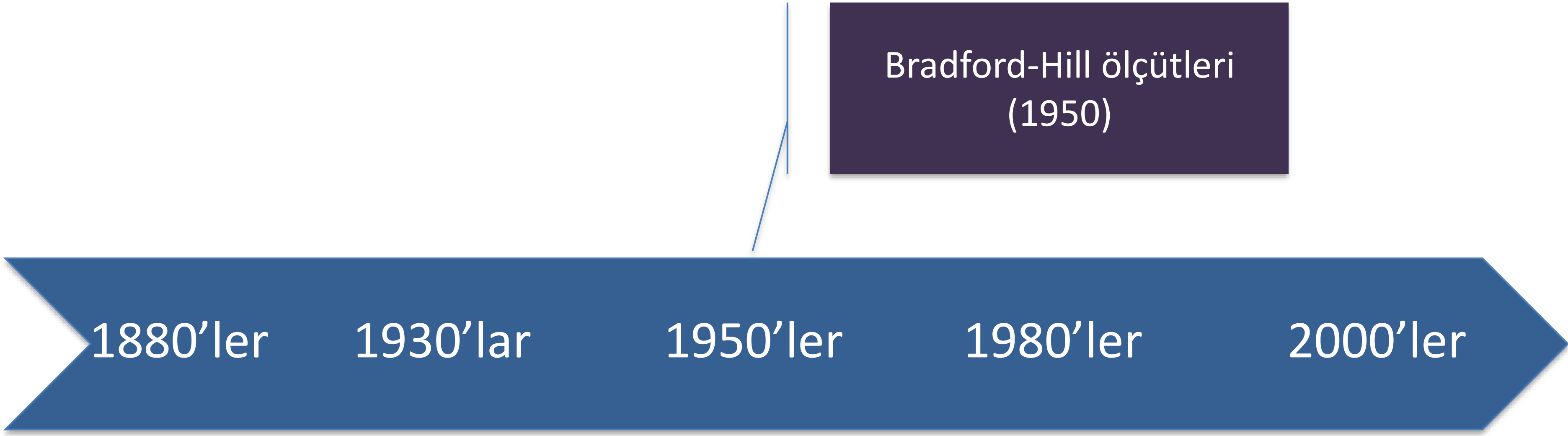
Koch önermelerinin *evrimi*

Henle-Koch ölçütleri
(mikrop kuramı)

1880’ler 1930’lar 1950’ler 1980’ler 2000’ler

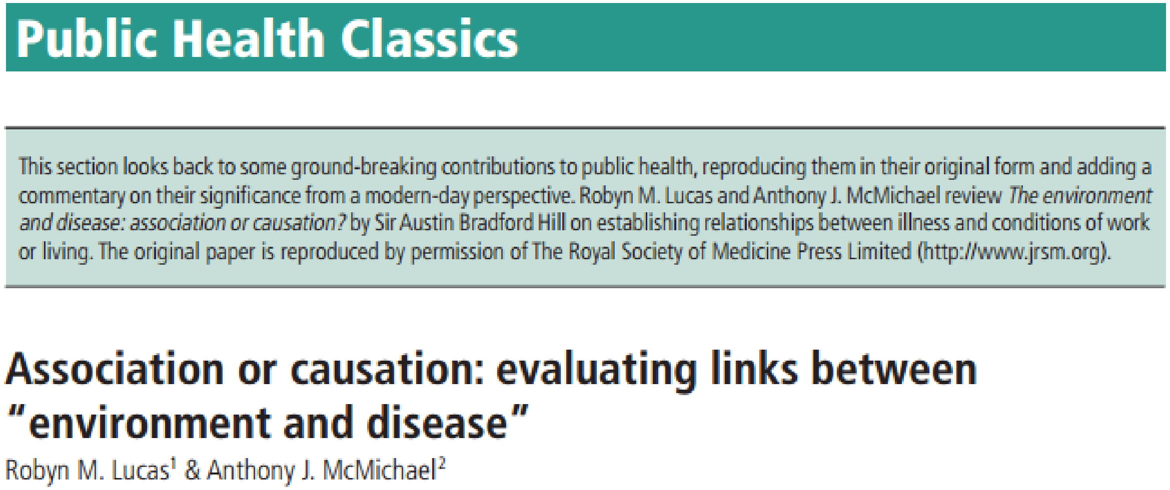


Koch önermelerinin *evrimi*



Bradford-Hill ölçütleri
(1950)

1880'ler 1930'lar 1950'ler 1980'ler 2000'ler



Public Health Classics

This section looks back to some ground-breaking contributions to public health, reproducing them in their original form and adding a commentary on their significance from a modern-day perspective. Robyn M. Lucas and Anthony J. McMichael review *The environment and disease: association or causation?* by Sir Austin Bradford Hill on establishing relationships between illness and conditions of work or living. The original paper is reproduced by permission of The Royal Society of Medicine Press Limited (http://www.jrsm.org).

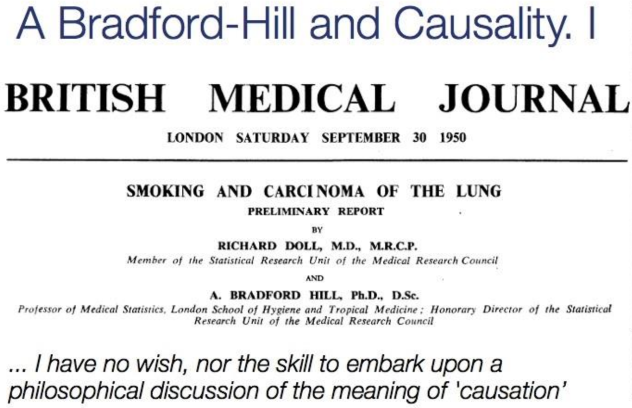
Association or causation: evaluating links between "environment and disease"

Robyn M. Lucas[1] & Anthony J. McMichael[2]

Emerging Themes in Epidemiology 2005, 2:11

Bradford Hill ölçütleri

- İlişkinin gücü
- Yinelenen gözlemler
- Özgüllük
- Zamansallık
- Deneysel kanıt
- Biyolojik gradyan (doza bağlı sonuç)
- Akla yatkınlık
- Tutarlık
- Benzeşim



A Bradford-Hill and Causality. I

BRITISH MEDICAL JOURNAL

LONDON SATURDAY SEPTEMBER 30 1950

SMOKING AND CARCINOMA OF THE LUNG

PRELIMINARY REPORT

BY

RICHARD DOLL, M.D., M.R.C.P.

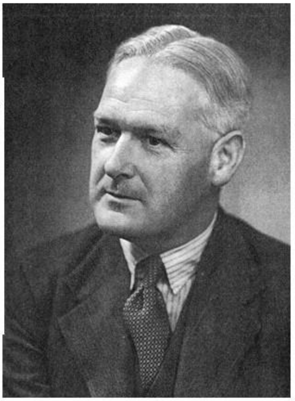
Member of the Statistical Research Unit of the Medical Research Council

AND

A. BRADFORD HILL, Ph.D., D.Sc.

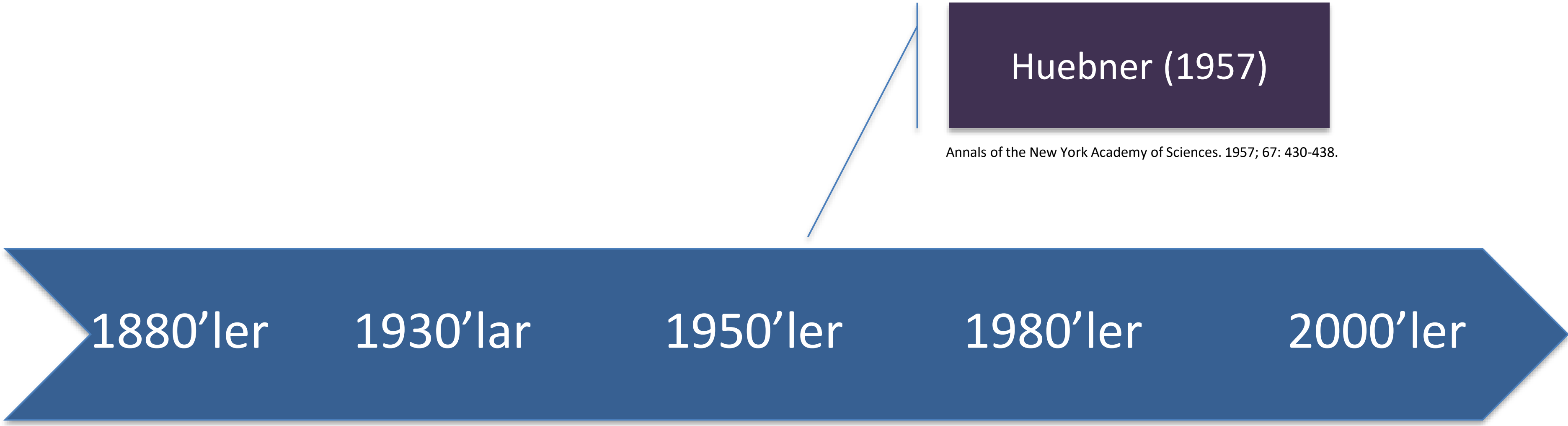
Professor of Medical Statistics, London School of Hygiene and Tropical Medicine; Honorary Director of the Statistical Research Unit of the Medical Research Council

... I have no wish, nor the skill to embark upon a philosophical discussion of the meaning of 'causation'



Emerging Themes in Epidemiology 2005, 2:11

Koch önermelerinin *evrimi*



Huebner (1957)

Annals of the New York Academy of Sciences. 1957; 67: 430-438.

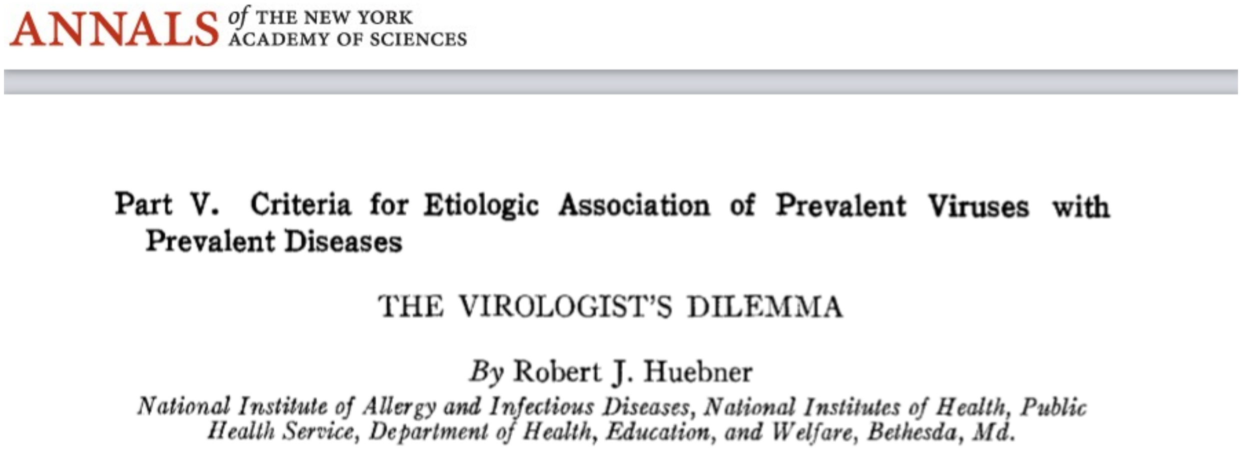
1880’ler

1930’lar

1950’ler

1980’ler

2000’ler



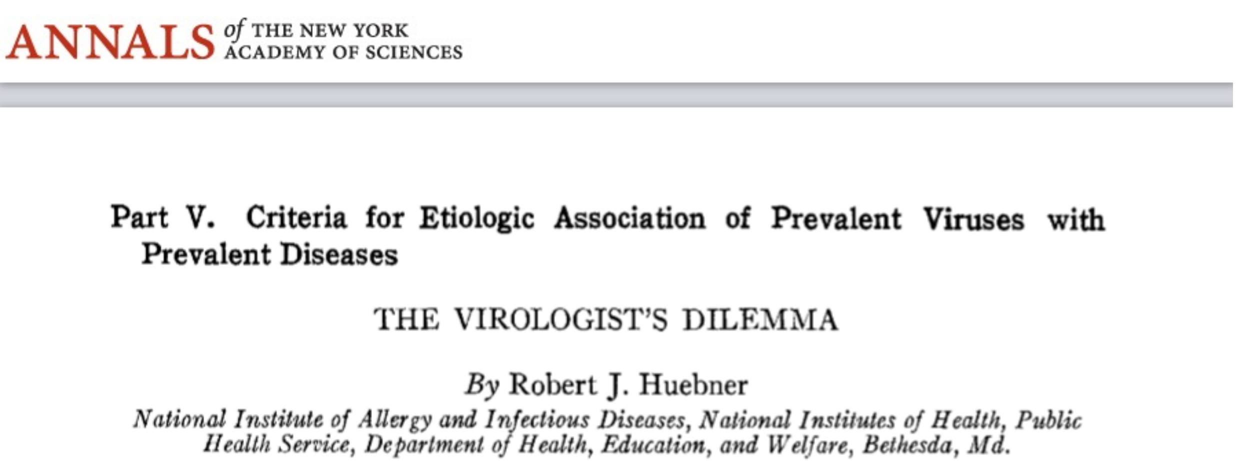
ANNALS *of* THE NEW YORK ACADEMY OF SCIENCES

Part V. Criteria for Etiologic Association of Prevalent Viruses with Prevalent Diseases

THE VIROLOGIST’S DILEMMA

By Robert J. Huebner

National Institute of Allergy and Infectious Diseases, National Institutes of Health, Public Health Service, Department of Health, Education, and Welfare, Bethesda, Md.



ANNALS of THE NEW YORK ACADEMY OF SCIENCES

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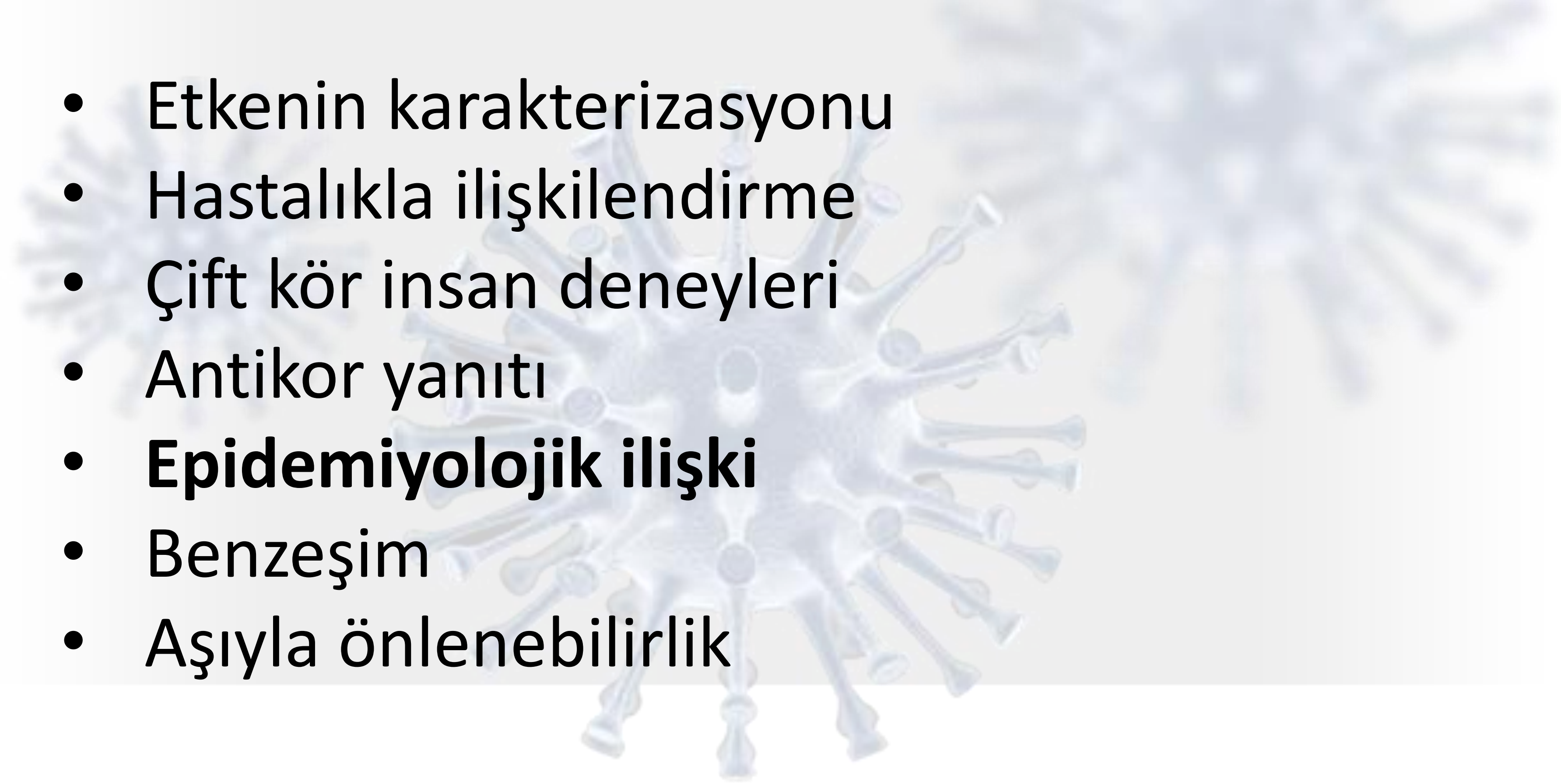
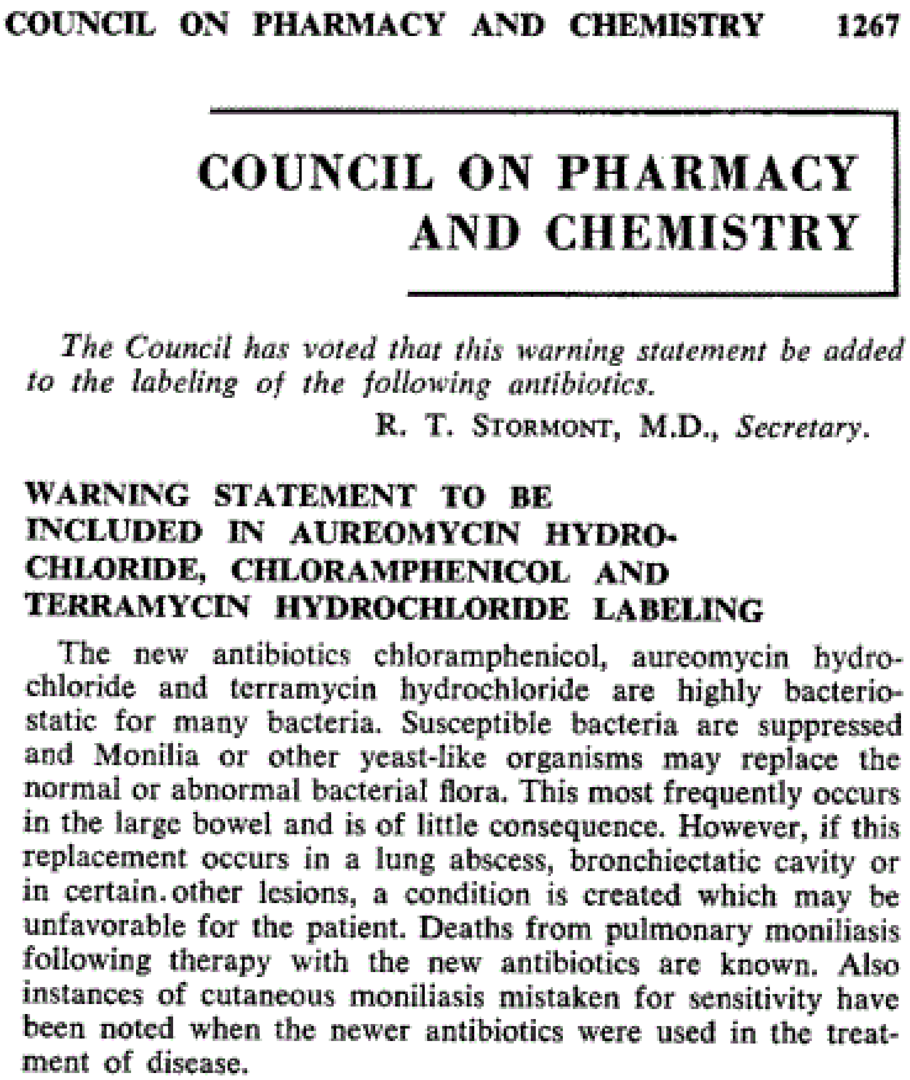


- Etkenin karakterizasyonu
- Hastalıkla ilişkilendirme
- Çift kör insan deneyleri
- Antikor yanıtı
- **Epidemiyolojik ilişki**
- Benzeşim
- Aşıyla önlenebilirlik

Annals of the New York Academy of Sciences. 1957; 67: 430-438.

1950+ yıllar: *konak faktörü?*



COUNCIL ON PHARMACY AND CHEMISTRY 1267

COUNCIL ON PHARMACY AND CHEMISTRY

The Council has voted that this warning statement be added to the labeling of the following antibiotics.

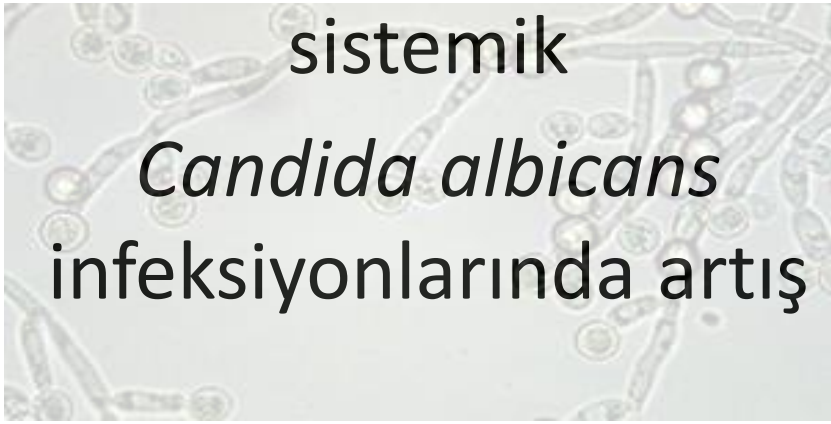
R. T. Stormont, M.D., *Secretary.*

WARNING STATEMENT TO BE INCLUDED IN AUREOMYCIN HYDROCHLORIDE, CHLORAMPHENICOL AND TERRAMYCIN HYDROCHLORIDE LABELING

The new antibiotics chloramphenicol, aureomycin hydrochloride and terramycin hydrochloride are highly bacteriostatic for many bacteria. Susceptible bacteria are suppressed and Monilia or other yeast-like organisms may replace the normal or abnormal bacterial flora. This most frequently occurs in the large bowel and is of little consequence. However, if this replacement occurs in a lung abscess, bronchiectatic cavity or in certain other lesions, a condition is created which may be unfavorable for the patient. Deaths from pulmonary moniliasis following therapy with the new antibiotics are known. Also instances of cutaneous moniliasis mistaken for sensitivity have been noted when the newer antibiotics were used in the treatment of disease.

JAMA. 1951;145(16):1267. doi:10.1001/jama.1951.02920340045014

Antibiyotik ve kortikosteroidlerin yaygın kullanımı

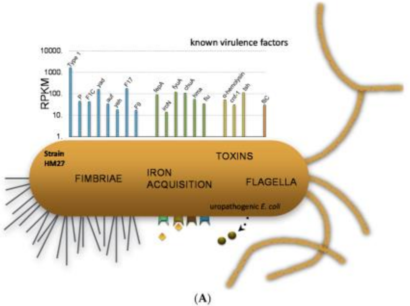


sistemik

Candida albicans

infeksiyonlarında artış

Koch önermelerinin *evrimi*



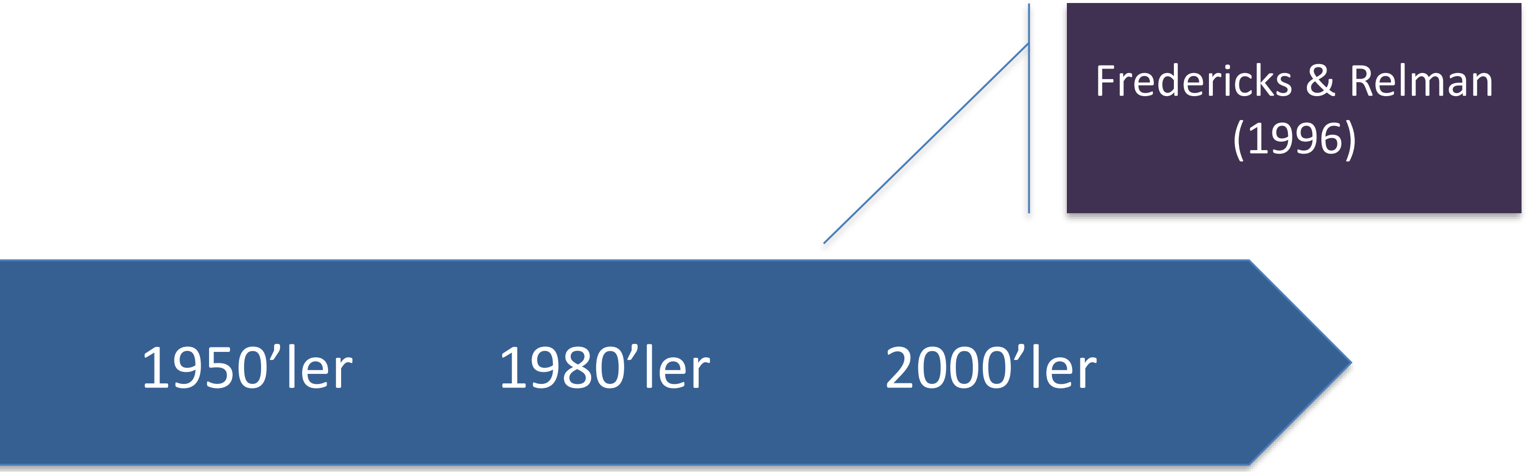
Falkow
(1988)

1880'ler 1930'lar 1950'ler 1980'ler 2000'ler

- Patojenik türler ve patojenik suşlar
- **Virülans genleri (patojenlerde olmalı, diğerlerinde olmamalı)**
- Bu genlerin spesifik inaktivasyonu virülansın azalmasını ya da ortadan kalkmasını sağlamalı
- Genlerin işlevleri geri kazandırıldığında suş patojen hale gelmeli

Clin Infect Dis. (July-August 1988) 10 (Supplement 2): S274-S276

Koch önermelerinin *evrimi*

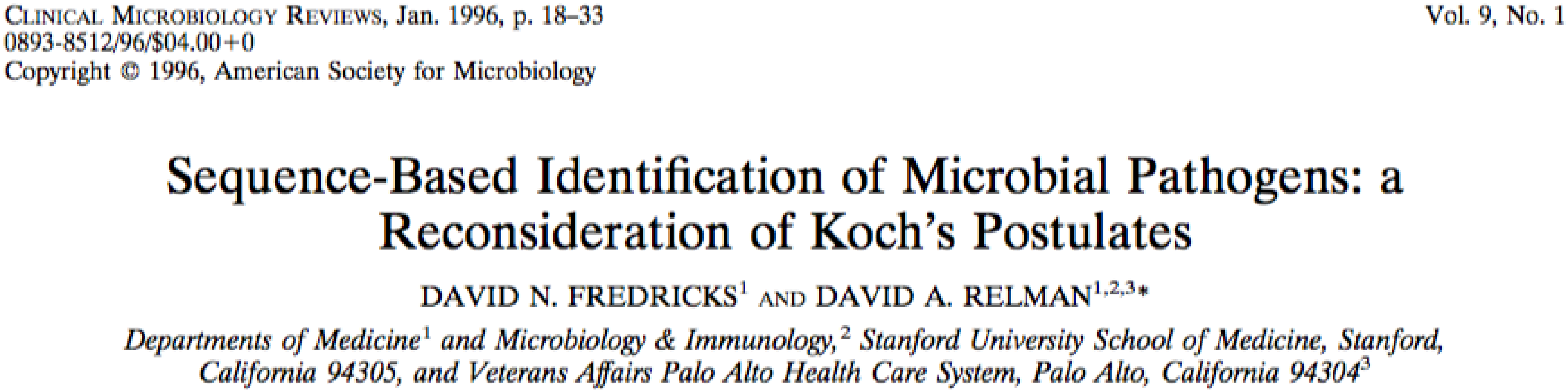


Fredericks & Relman (1996)

1950'ler

1980'ler

2000'ler



CLINICAL MICROBIOLOGY REVIEWS, Jan. 1996, p. 18–33
0893-8512/96/$04.00+0
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Vol. 9, No. 1

Sequence-Based Identification of Microbial Pathogens: a Reconsideration of Koch's Postulates

DAVID N. FREDRICKS[1] AND DAVID A. RELMAN[1,2,3]*

Departments of Medicine[1] and Microbiology & Immunology,[2] Stanford University School of Medicine, Stanford, California 94305, and Veterans Affairs Palo Alto Health Care System, Palo Alto, California 94304[3]

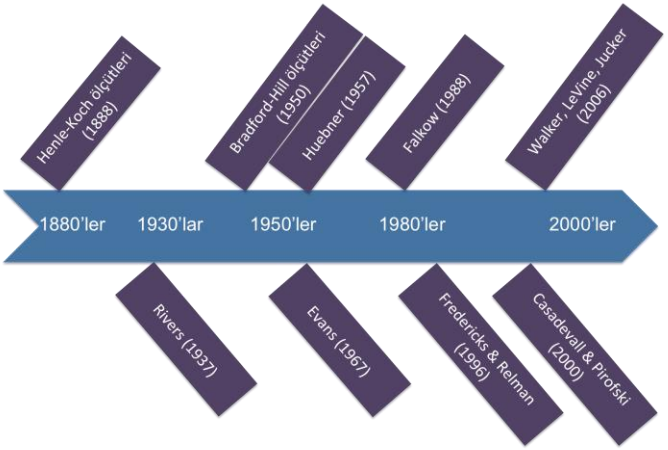
Fredricks-Relman ölçütleri

- Hastalananların çoğunda etkenin nükleik asit dizisi patolojinin olduğu organlarda/dokularda bulunmalıdır.
- İyileşme ile birlikte kopya sayısı azalmalı/saptanamamalı
- Diziler hastalıktan önce saptanıyor ya da kopya sayısı hastalığın şiddeti ile korelasyon gösteriyorsa nedensellik olasılığı yüksektir.
- Diziye atfedilen özellikler ilgili mikroorganizmanın bilinen özellikleri ile uyuşmalıdır.
- Patolojinin olduğu dokularda etken saptanabilmeli
- Yinelenebilir kanıtlar

Clin Microbiol Rev 1996, 9: 18-33

Koch önermelerinin *evrimi*

20. yüzyıl sonlarında egemen paradigma



Henle-Koch ölçütleri (1888)

Rivers (1937)

Bradford-Hill ölçütleri (1950)

Huebner (1957)

Evans (1967)

Falkow (1988)

Fredericks & Relman (1996)

Casadevall & Pirofski (2000)

Walker, LeVine, Jucker (2006)

1880'ler

1930'lar

1950'ler

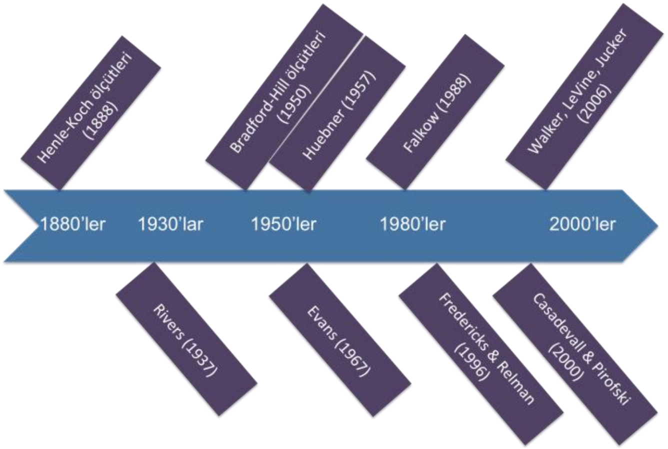
1980'ler

2000'ler

- "Mikrop-merkezli" görüş egemen

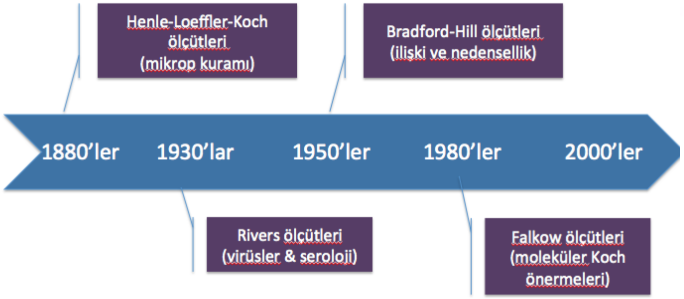
Koch önermelerinin *evrimi*

20. yüzyıl sonlarında egemen paradigmalar



- "Patojen" ve "patojen olmayan" mikroplar
- Bir hastalık bir patojen
- İmmunosüpresyon ve fırsatçı patojenler
- Virülans genleri sadece patojenlerde
- Antibiyotik sağaltımı
- Mikroçevre ve "normal flora" ???

Yeni yüzyılda yeni paradigmalar...

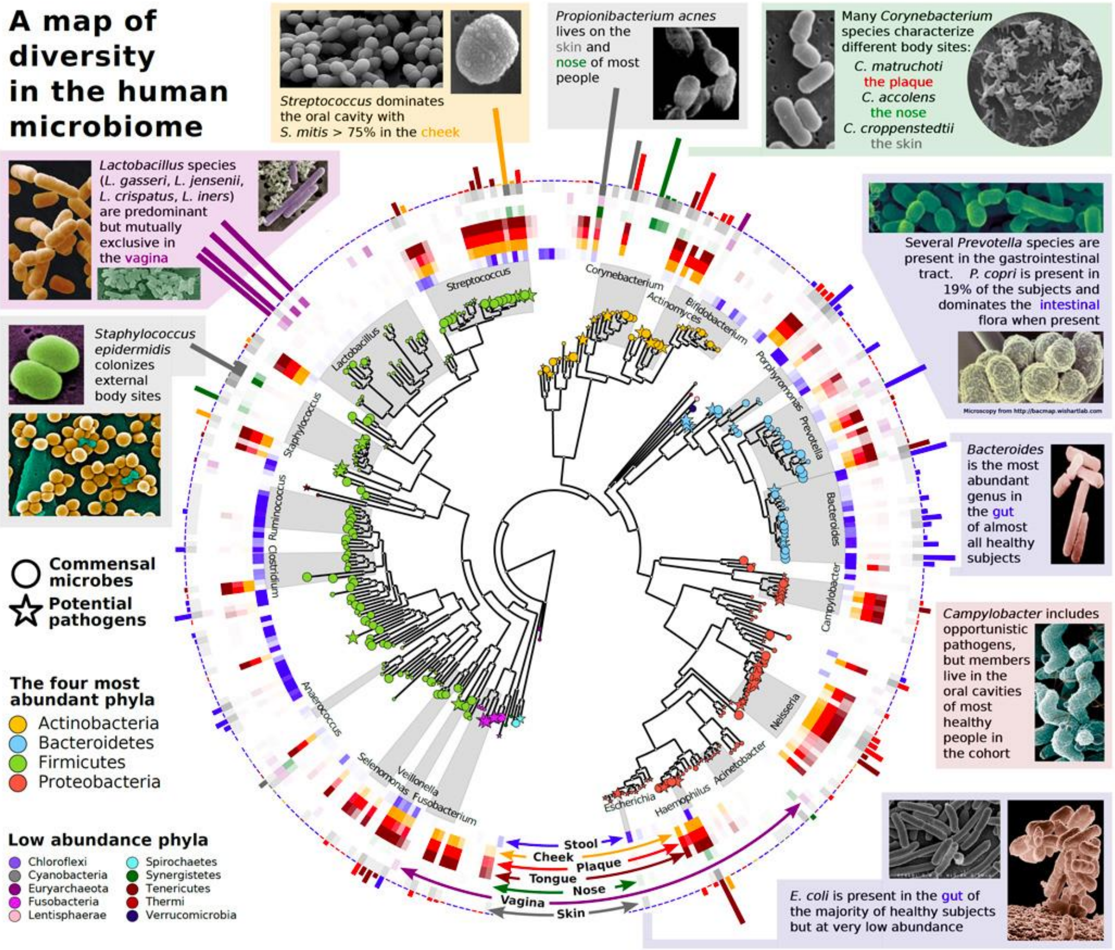


Henle-Loeffler-Koch ölçütleri (mikrop kuramı)

Rivers ölçütleri (virüsler & seroloji)

Bradford-Hill ölçütleri (ilişki ve nedensellik)

Falkow ölçütleri (moleküler Koch önermeleri)


A map of diversity in the human microbiome

Streptococcus dominates the oral cavity with *S. mitis* > 75% in the cheek

Propionibacterium acnes lives on the skin and nose of most people

Many *Corynebacterium* species characterize different body sites:
C. matruchoti the plaque
C. accolens the nose
C. croppenstedtii the skin

Lactobacillus species (*L. gasseri*, *L. jensenii*, *L. crispatus*, *L. iners*) are predominant but mutually exclusive in the vagina

Several *Prevotella* species are present in the gastrointestinal tract. *P. copri* is present in 19% of the subjects and dominates the intestinal flora when present

Microscopy from http://bacmap.wishartlab.com

Staphylococcus epidermidis colonizes external body sites

Bacteroides is the most abundant genus in the gut of almost all healthy subjects

Campylobacter includes opportunistic pathogens, but members live in the oral cavities of most healthy people in the cohort

E. coli is present in the gut of the majority of healthy subjects but at very low abundance

○ Commensal microbes
☆ Potential pathogens

The four most abundant phyla
- ● Actinobacteria
- ● Bacteroidetes
- ● Firmicutes
- ● Proteobacteria

Low abundance phyla
- ● Chloroflexi
- ● Cyanobacteria
- ● Euryarchaeota
- ● Fusobacteria
- ● Lentisphaerae
- ● Spirochaetes
- ● Synergistetes
- ● Tenericutes
- ● Thermi
- ● Verrucomicrobia

Meta HIT

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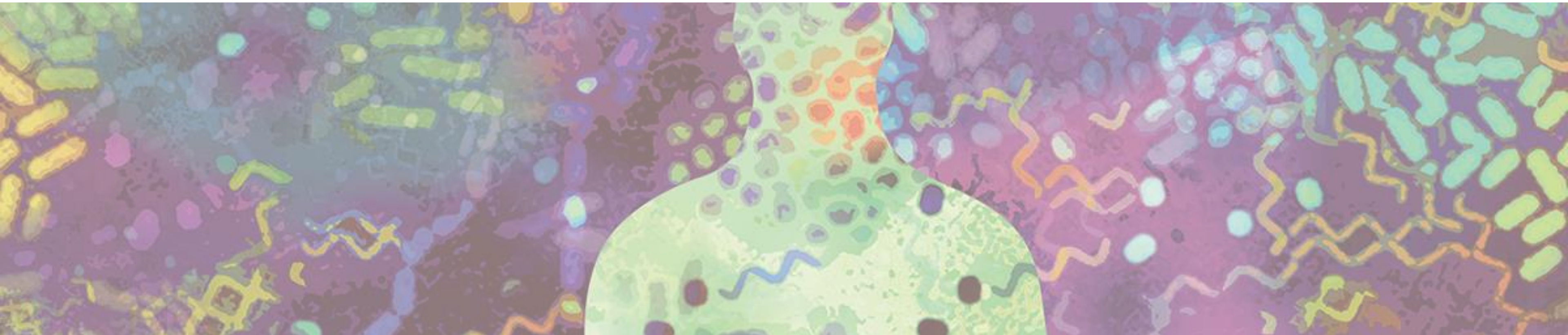
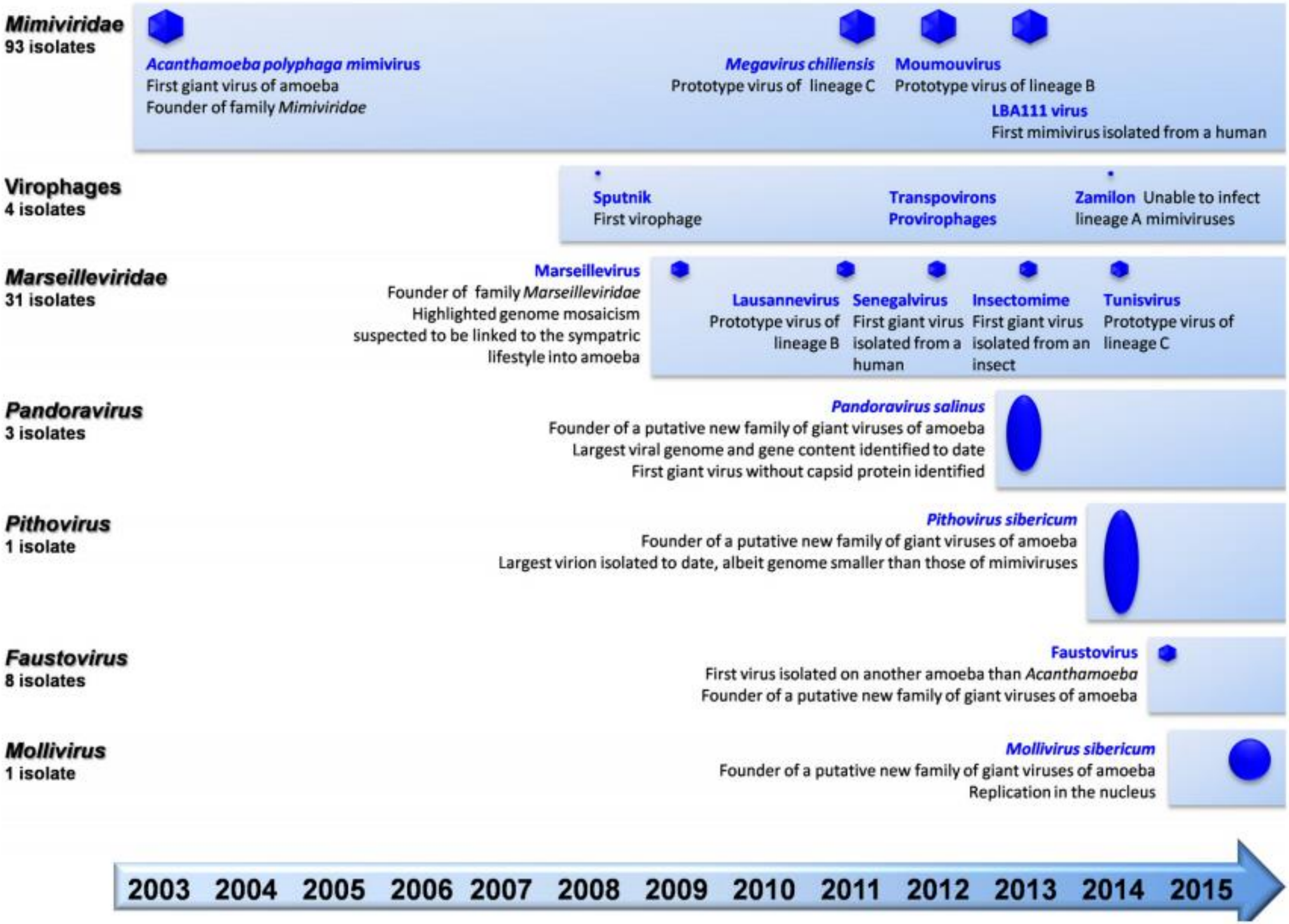
NIH HUMAN
MICROBIOME
PROJECT

yeni yaşam formları, yeni türler…





Mimiviridae
93 isolates

Acanthamoeba polyphaga mimivirus
First giant virus of amoeba
Founder of family *Mimiviridae*

Megavirus chiliensis
Prototype virus of lineage C

Moumouvirus
Prototype virus of lineage B

LBA111 virus
First mimivirus isolated from a human

Virophages
4 isolates

Sputnik
First virophage

Transpovirons
Provirophages

Zamilon Unable to infect lineage A mimiviruses

Marseilleviridae
31 isolates

Marseillevirus
Founder of family *Marseilleviridae*
Highlighted genome mosaicism suspected to be linked to the sympatric lifestyle into amoeba

Lausannevirus
Prototype virus of lineage B

Senegalvirus
First giant virus isolated from a human

Insectomime
First giant virus isolated from an insect

Tunisvirus
Prototype virus of lineage C

Pandoravirus
3 isolates

Pandoravirus salinus
Founder of a putative new family of giant viruses of amoeba
Largest viral genome and gene content identified to date
First giant virus without capsid protein identified

Pithovirus
1 isolate

Pithovirus sibericum
Founder of a putative new family of giant viruses of amoeba
Largest virion isolated to date, albeit genome smaller than those of mimiviruses

Faustovirus
8 isolates

Faustovirus
First virus isolated on another amoeba than *Acanthamoeba*
Founder of a putative new family of giant viruses of amoeba

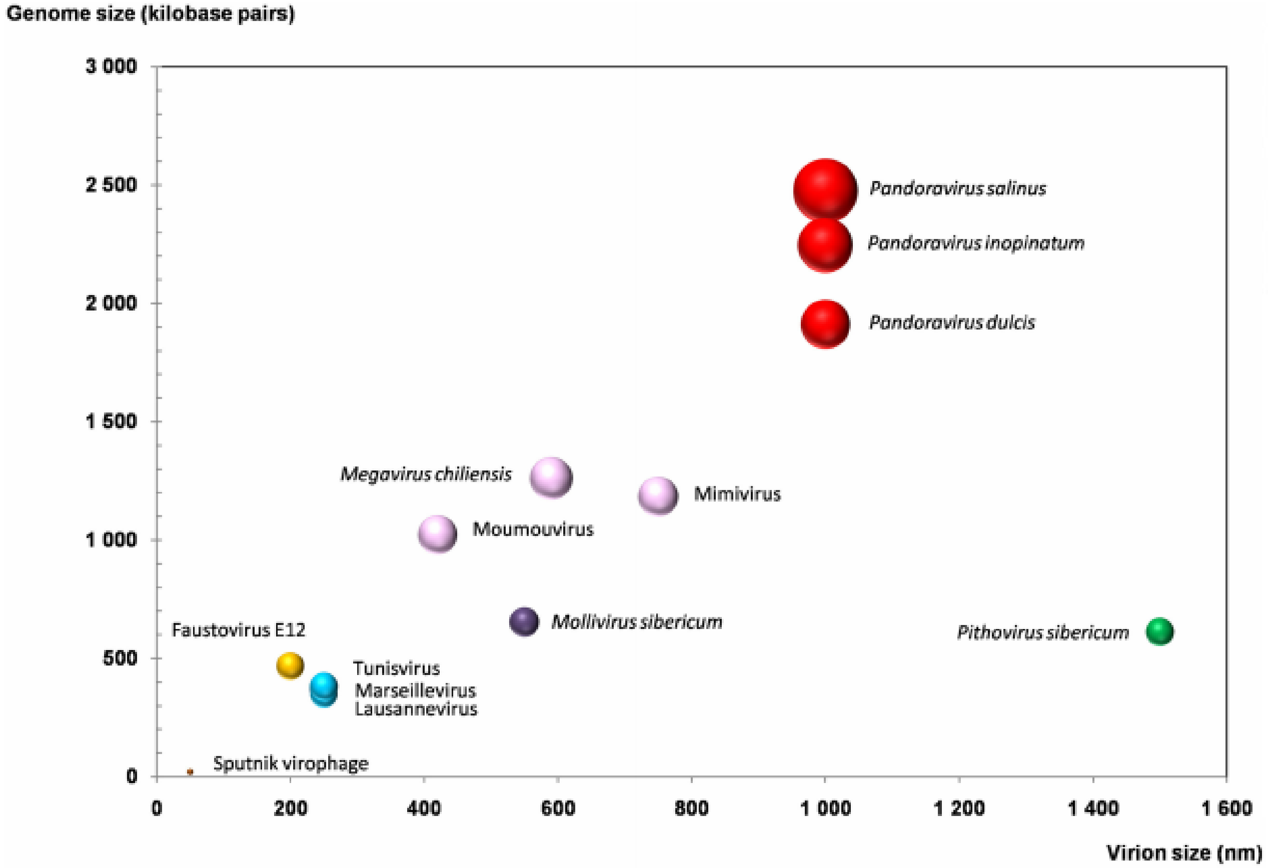
Mollivirus
1 isolate

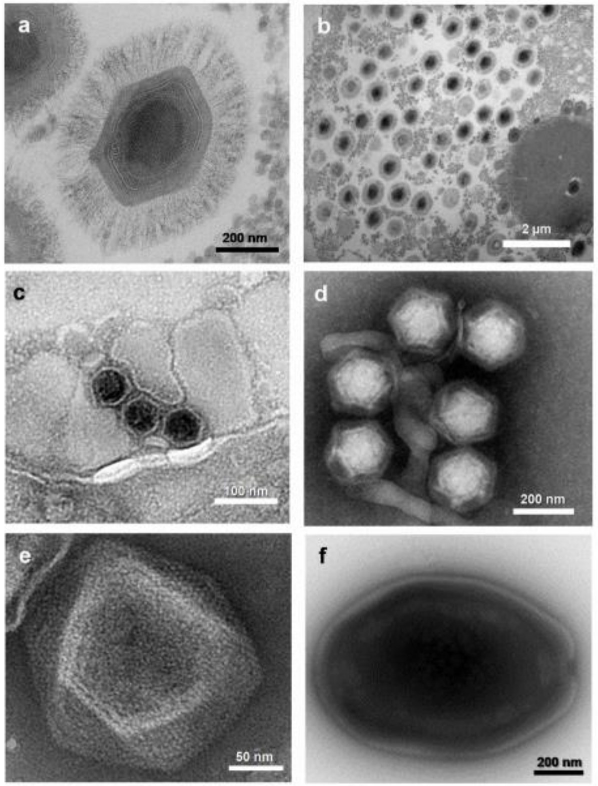
Mollivirus sibericum
Founder of a putative new family of giant viruses of amoeba
Replication in the nucleus

2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015

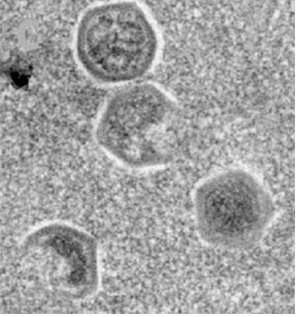
Aherfi S, Colson P, La Scola B and Raoult D (2016) Giant Viruses of Amoebas: An Update. Front. Microbiol. 7:349. doi: 10.3389/fmicb.2016.00349

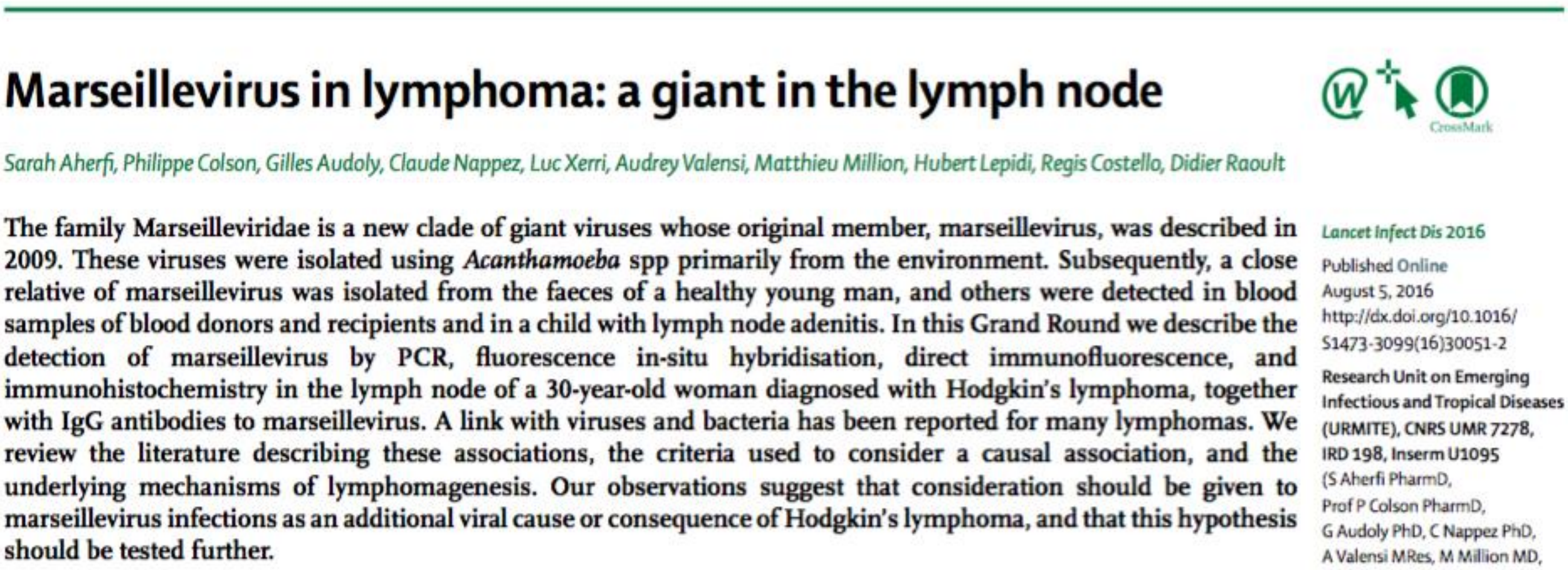
Megavirales…





Aherfi S, Colson P, La Scola B and Raoult D (2016) Giant Viruses of Amoebas: An Update. Front. Microbiol. 7:349. doi: 10.3389/fmicb.2016.00349





Marseillevirus in lymphoma: a giant in the lymph node

Sarah Aherfi, Philippe Colson, Gilles Audoly, Claude Nappez, Luc Xerri, Audrey Valensi, Matthieu Million, Hubert Lepidi, Regis Costello, Didier Raoult

The family Marseilleviridae is a new clade of giant viruses whose original member, marseillevirus, was described in 2009. These viruses were isolated using *Acanthamoeba* spp primarily from the environment. Subsequently, a close relative of marseillevirus was isolated from the faeces of a healthy young man, and others were detected in blood samples of blood donors and recipients and in a child with lymph node adenitis. In this Grand Round we describe the detection of marseillevirus by PCR, fluorescence in-situ hybridisation, direct immunofluorescence, and immunohistochemistry in the lymph node of a 30-year-old woman diagnosed with Hodgkin's lymphoma, together with IgG antibodies to marseillevirus. A link with viruses and bacteria has been reported for many lymphomas. We review the literature describing these associations, the criteria used to consider a causal association, and the underlying mechanisms of lymphomagenesis. Our observations suggest that consideration should be given to marseillevirus infections as an additional viral cause or consequence of Hodgkin's lymphoma, and that this hypothesis should be tested further.

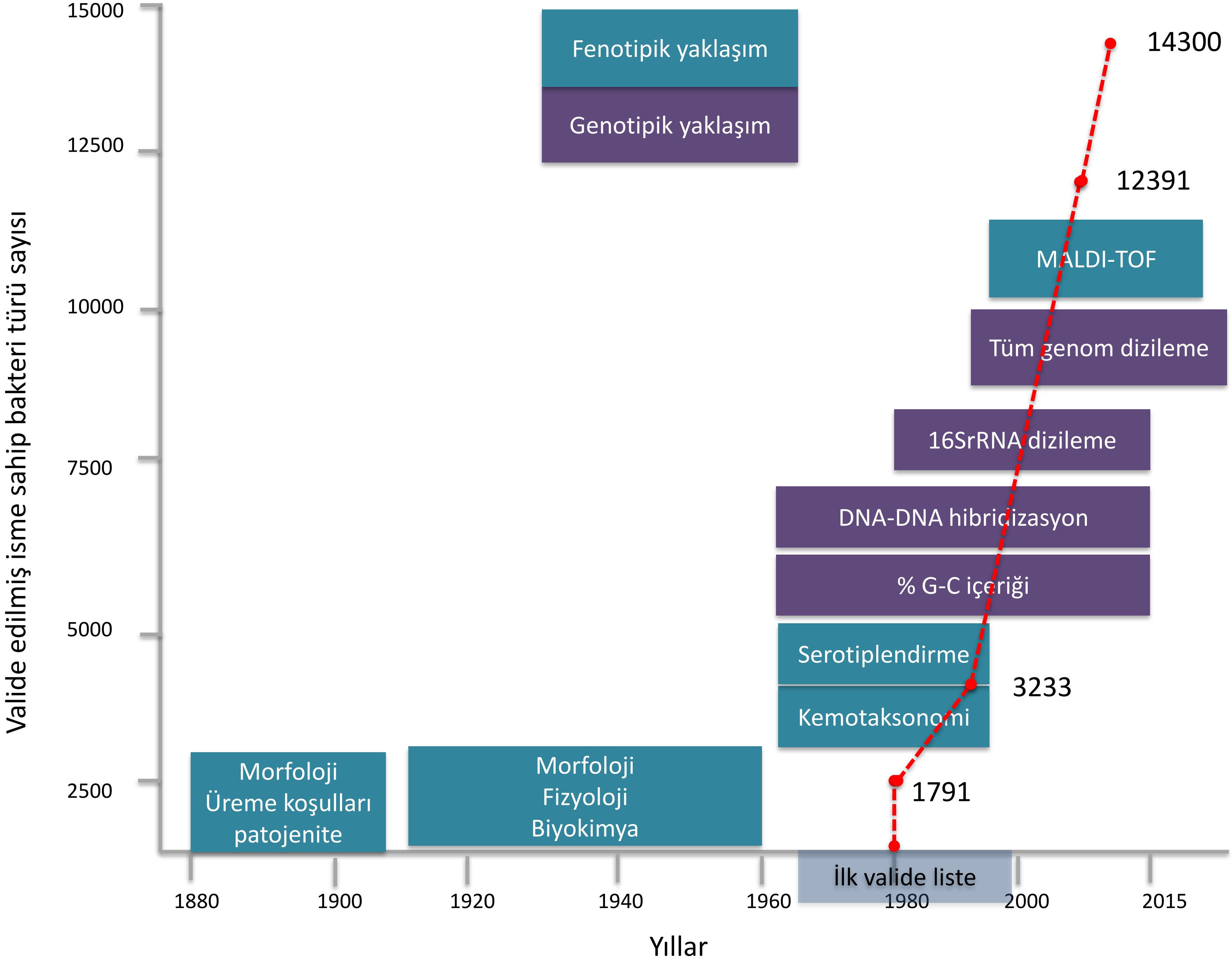
Lancet Infect Dis 2016

Published Online
August 5, 2016

http://dx.doi.org/10.1016/S1473-3099(16)30051-2

Research Unit on Emerging Infectious and Tropical Diseases (URMITE), CNRS UMR 7278, IRD 198, Inserm U1095 (S Aherfi PharmD, Prof P Colson PharmD, G Audoly PhD, C Nappez PhD, A Valensi MRes, M Million MD,

underlying mechanisms of lymphomagenesis. Our observations suggest that consideration should be given to marseillevirus infections as an additional viral cause or consequence of Hodgkin's lymphoma, and that this hypothesis should be tested further.



Lancet Infect Dis 2015; 15: 1211–19 uyarlanarak yeniden çizilmiştir

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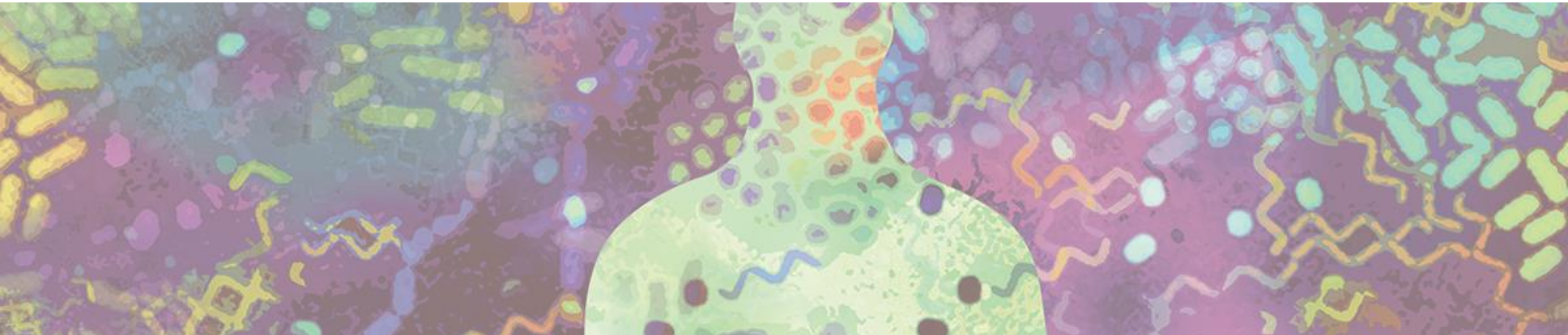
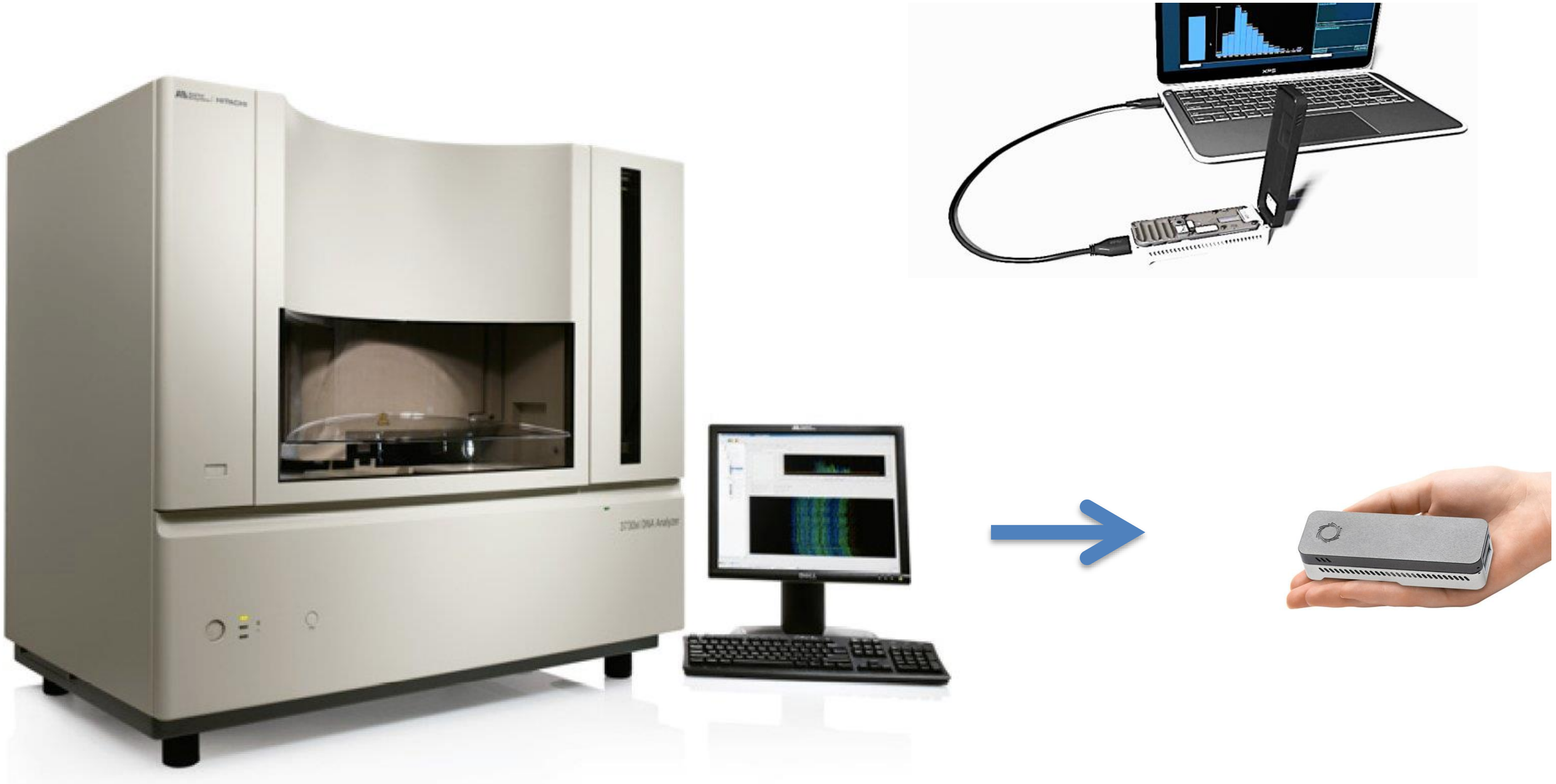
yeni teknolojiler…



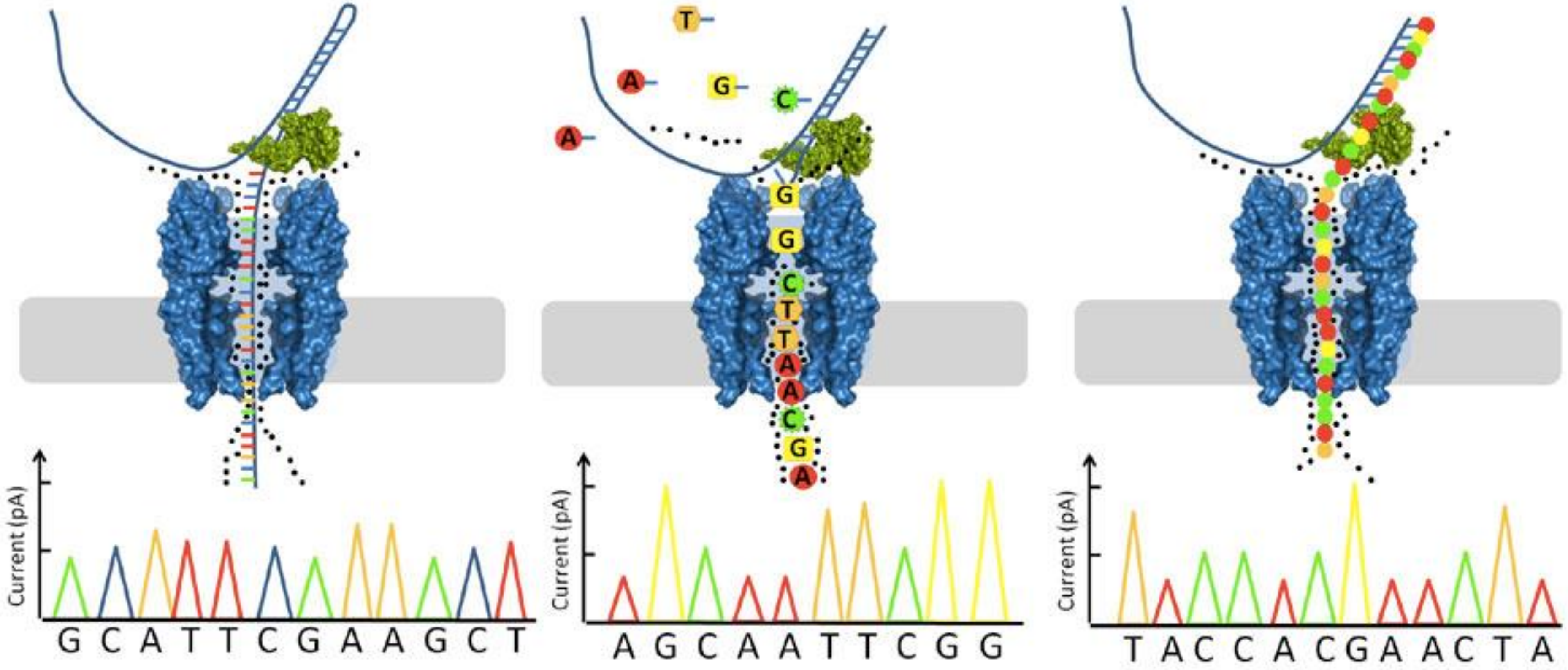

HITACHI
3730xl DNA Analyzer

Nanopore Sequencing Technologies

A) Oxford Nanopore Technologies

B) Genia Technology

C) Stratos Genomics



Semiconductivity based measuremets of current flow changes are translated into DNA sequence information

https://www.nextgenerationsequencing.info/ngs-products/ngs-technologies

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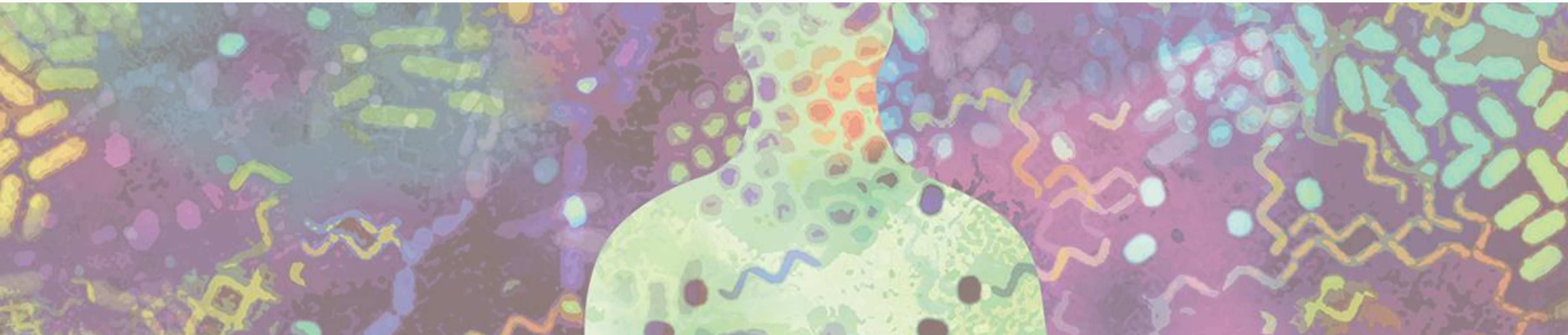
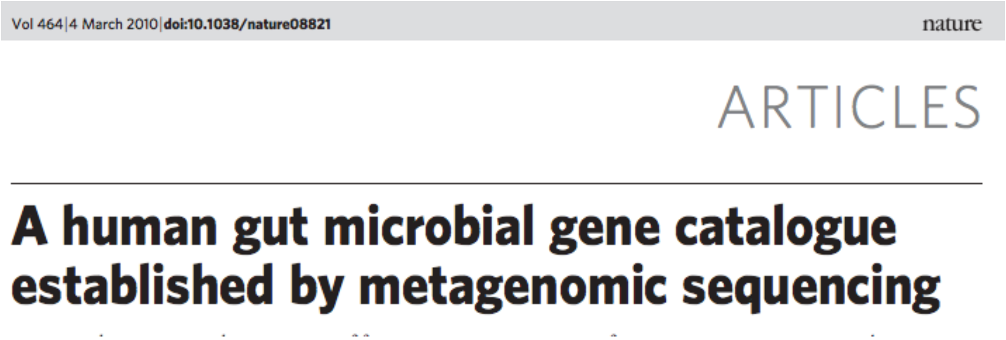
Mikrobiyom projeleri...



Meta HIT

2010



Vol 464 | 4 March 2010 | doi:10.1038/nature08821

nature

ARTICLES

A human gut microbial gene catalogue established by metagenomic sequencing

HMP

NIH HUMAN MICROBIOME PROJECT

2012

ARTICLE

doi:10.1038/nature11209

A framework for human microbiome research

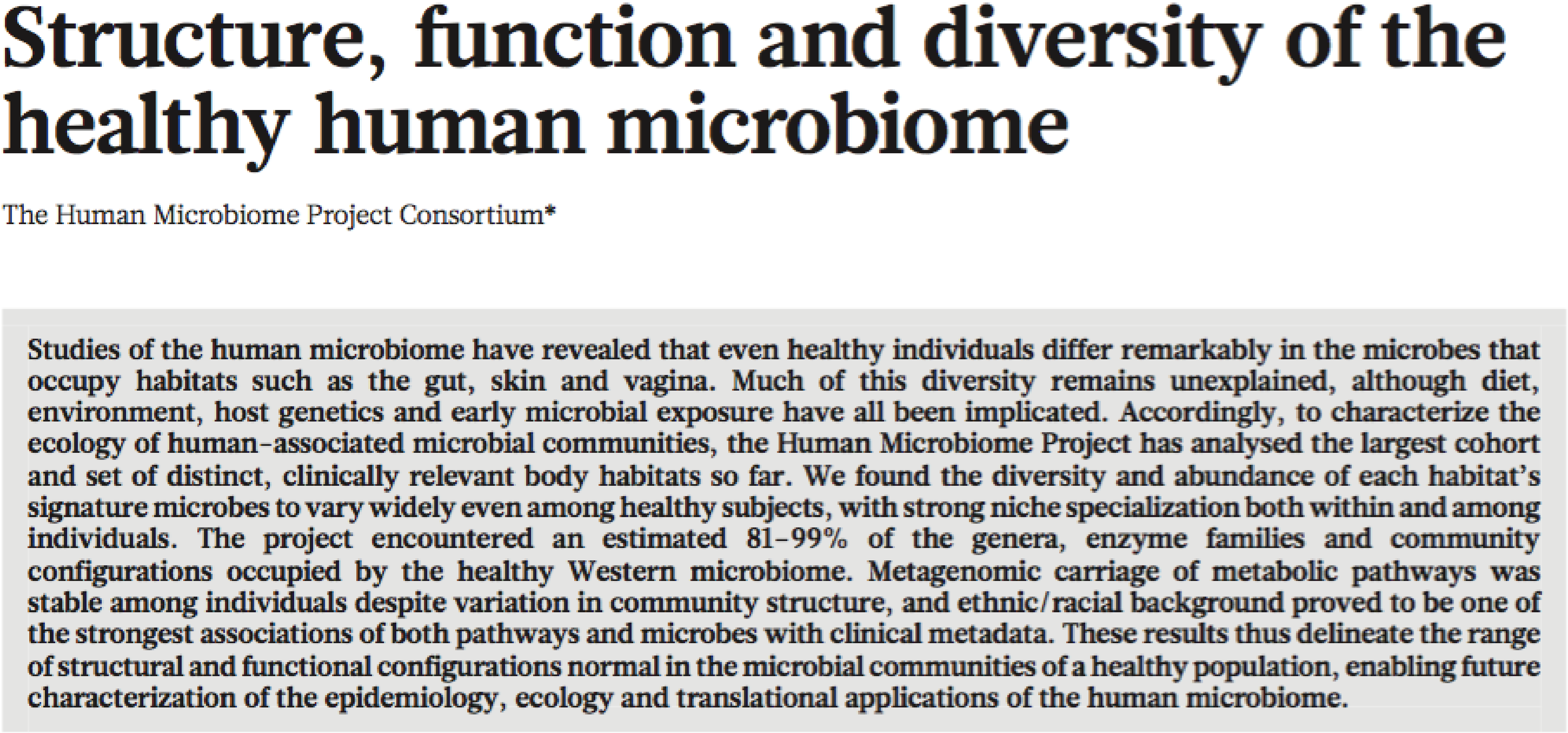
The Human Microbiome Project Consortium*

An integrated catalog of reference genes in the human gut microbiome

Junhua Li, Huijue Jia, Xianghang Cai, Huanzi Zhong, Qiang Feng, Shinichi Sunagawa, Manimozhiyan Arumugam, Jens Roat Kultima, Edi Prifti, Trine Nielsen, Agnieszka Sierakowska Juncker, Chaysavanh Manichanh, Bing Chen, Wenwei Zhang, Florence Levenez, Juan Wang, Xun Xu, Liang Xiao, Suisha Liang, Dongya Zhang, Zhaoxi Zhang, Weineng Chen, Hailong Zhao, Jumana Yousuf Al-Aama, Sherif Edris + *et al.*

- 1250 insan barsak mikrobiyom verisi
- 9.8 milyon gen
- Her bir örnekte ortalama 762,665 gen. Bunların ortalama 469’u örneğe özgü.

Nature Biotechnology 32, 834–841 (2014) doi:10.1038/nbt.2942



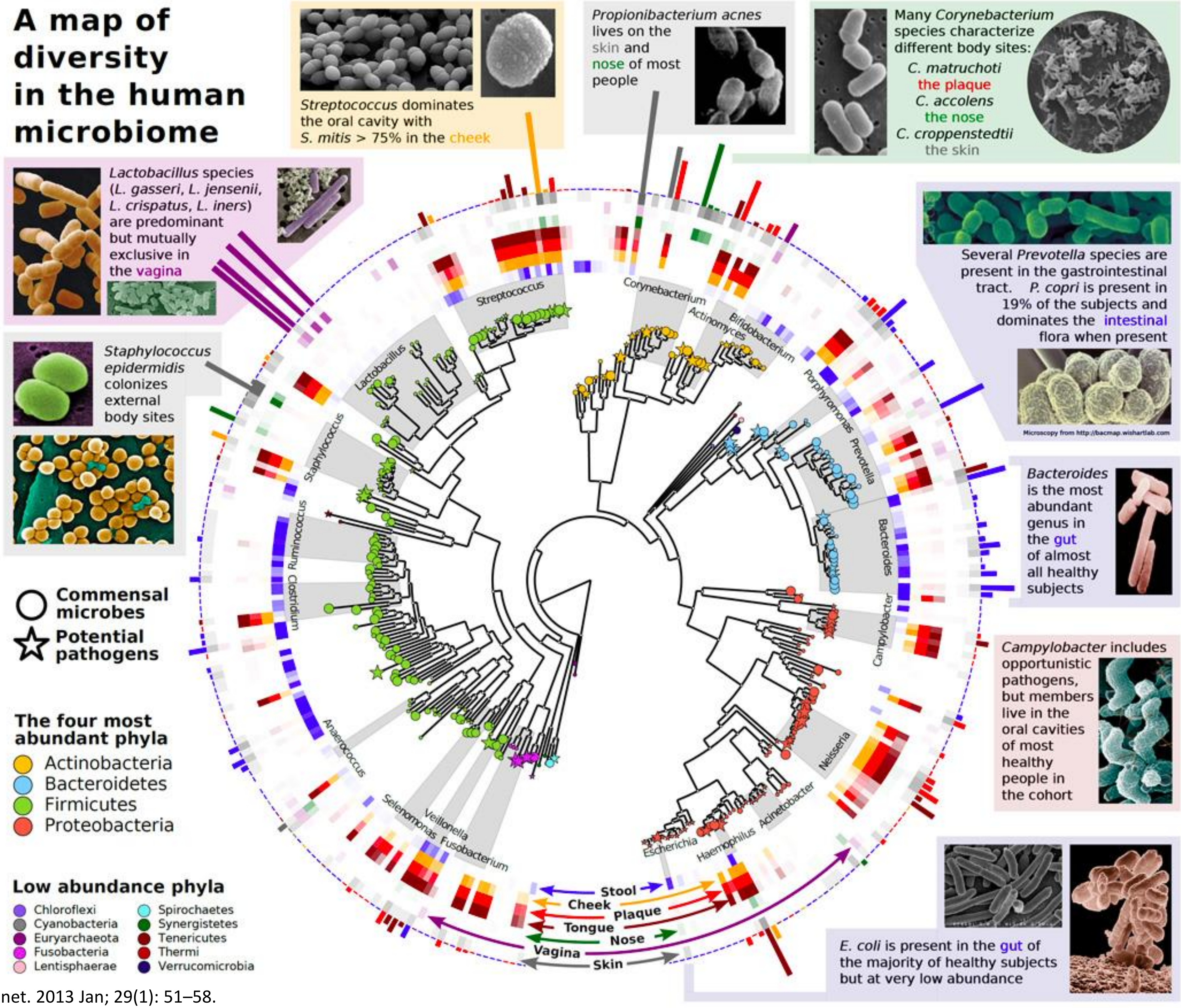
Structure, function and diversity of the healthy human microbiome

The Human Microbiome Project Consortium*

Studies of the human microbiome have revealed that even healthy individuals differ remarkably in the microbes that occupy habitats such as the gut, skin and vagina. Much of this diversity remains unexplained, although diet, environment, host genetics and early microbial exposure have all been implicated. Accordingly, to characterize the ecology of human-associated microbial communities, the Human Microbiome Project has analysed the largest cohort and set of distinct, clinically relevant body habitats so far. We found the diversity and abundance of each habitat's signature microbes to vary widely even among healthy subjects, with strong niche specialization both within and among individuals. The project encountered an estimated 81–99% of the genera, enzyme families and community configurations occupied by the healthy Western microbiome. Metagenomic carriage of metabolic pathways was stable among individuals despite variation in community structure, and ethnic/racial background proved to be one of the strongest associations of both pathways and microbes with clinical metadata. These results thus delineate the range of structural and functional configurations normal in the microbial communities of a healthy population, enabling future characterization of the epidemiology, ecology and translational applications of the human microbiome.

14 JUNE 2012 | VOL 486 | NATURE | 207

A map of diversity in the human microbiome



Streptococcus dominates the oral cavity with *S. mitis* > 75% in the cheek

Propionibacterium acnes lives on the skin and nose of most people

Many *Corynebacterium* species characterize different body sites:
C. matruchoti the plaque
C. accolens the nose
C. croppenstedtii the skin

Lactobacillus species (*L. gasseri*, *L. jensenii*, *L. crispatus*, *L. iners*) are predominant but mutually exclusive in the vagina

Several *Prevotella* species are present in the gastrointestinal tract. *P. copri* is present in 19% of the subjects and dominates the intestinal flora when present

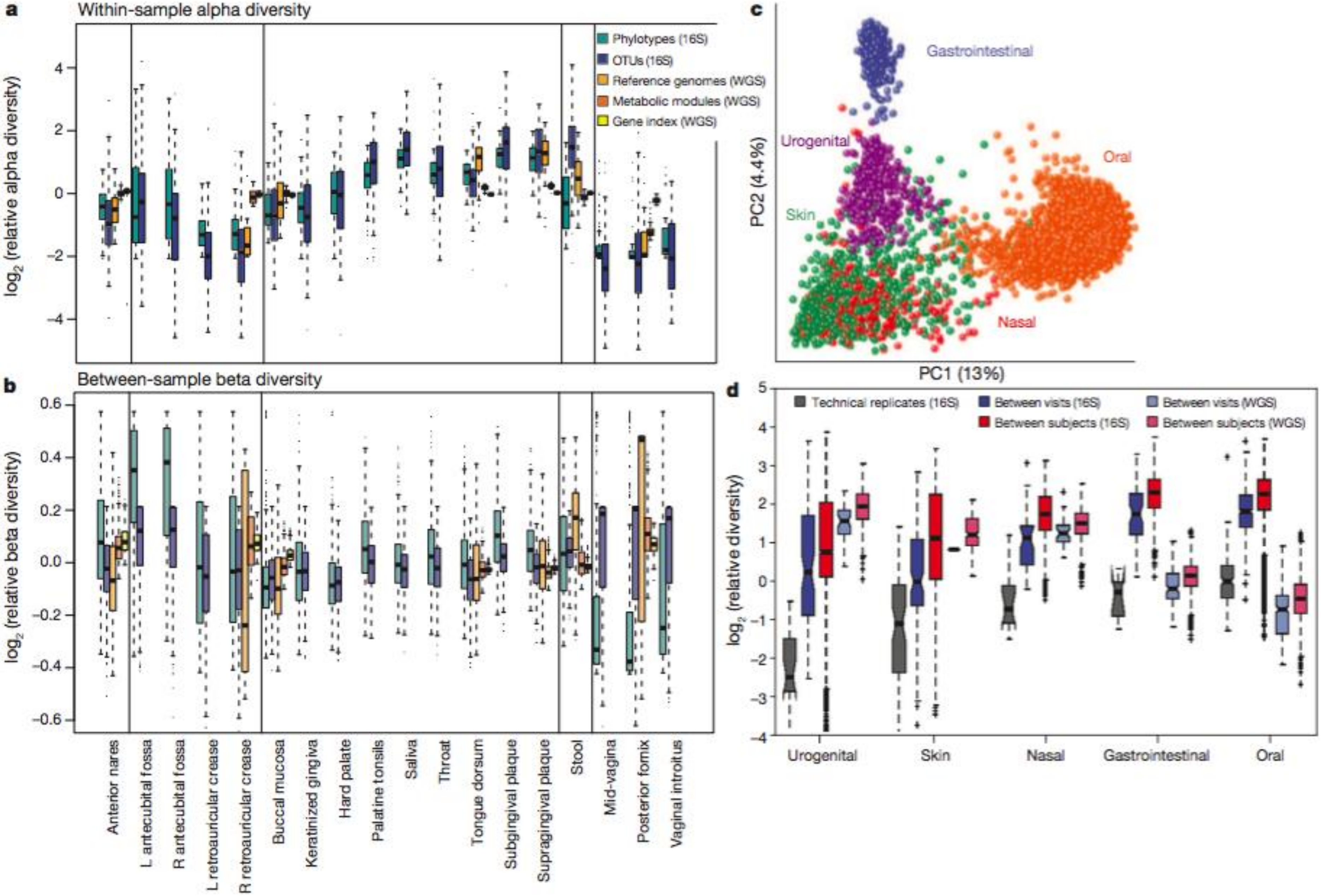
Staphylococcus epidermidis colonizes external body sites

Bacteroides is the most abundant genus in the gut of almost all healthy subjects

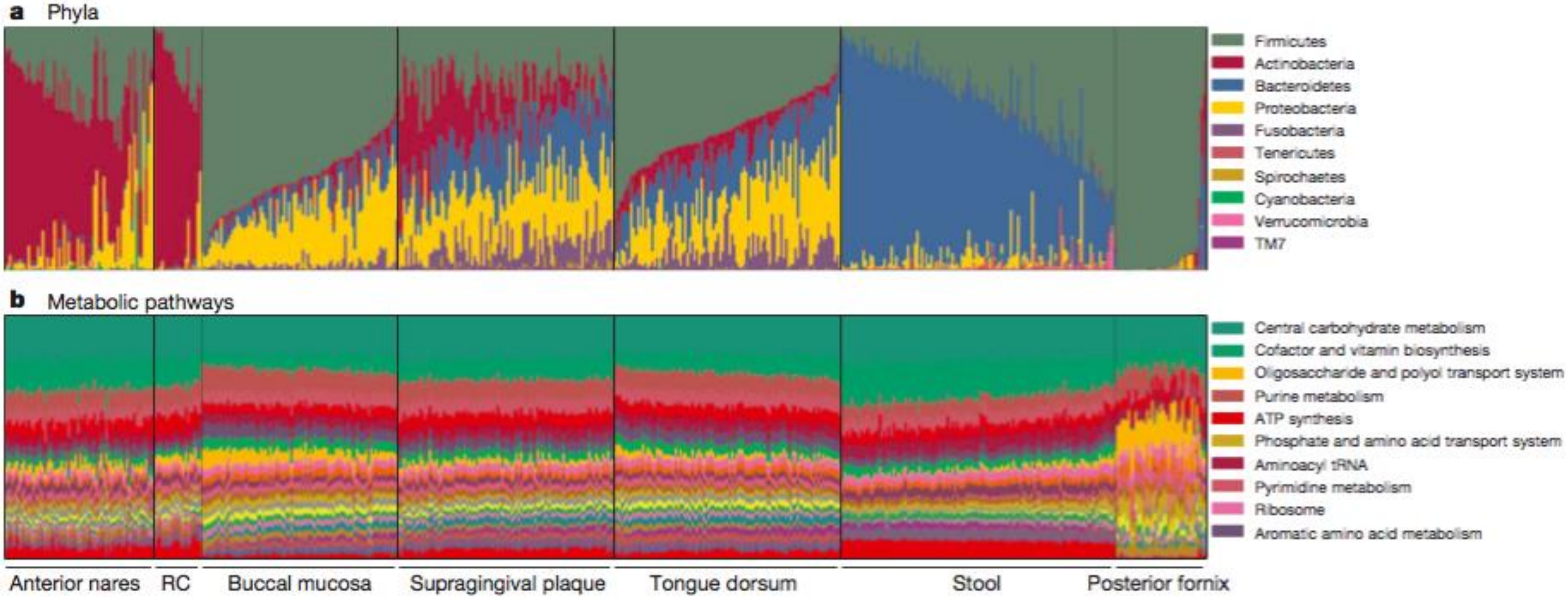
Campylobacter includes opportunistic pathogens, but members live in the oral cavities of most healthy people in the cohort

E. coli is present in the gut of the majority of healthy subjects but at very low abundance

Trends Genet. 2013 Jan; 29(1): 51–58.


a
Within-sample alpha diversity
Phylotypes (16S)
OTUs (16S)
Reference genomes (WGS)
Metabolic modules (WGS)
Gene index (WGS)
log$_2$ (relative alpha diversity)
4
2
0
−2
−4
b
Between-sample beta diversity
log$_2$ (relative beta diversity)
0.6
0.4
0.2
0.0
−0.2
−0.4
−0.6
Anterior nares
L antecubital fossa
R antecubital fossa
L retroauricular crease
R retroauricular crease
Buccal mucosa
Keratinized gingiva
Hard palate
Palatine tonsils
Saliva
Throat
Tongue dorsum
Subgingival plaque
Supragingival plaque
Stool
Mid-vagina
Posterior fornix
Vaginal introitus
c
Gastrointestinal
Urogenital
Oral
Skin
Nasal
PC2 (4.4%)
PC1 (13%)
d
Technical replicates (16S)
Between visits (16S)
Between subjects (16S)
Between visits (WGS)
Between subjects (WGS)
log$_2$ (relative diversity)
5
4
3
2
1
0
−1
−2
−3
−4
Urogenital
Skin
Nasal
Gastrointestinal
Oral

Metabolik işlevler korunuyor…

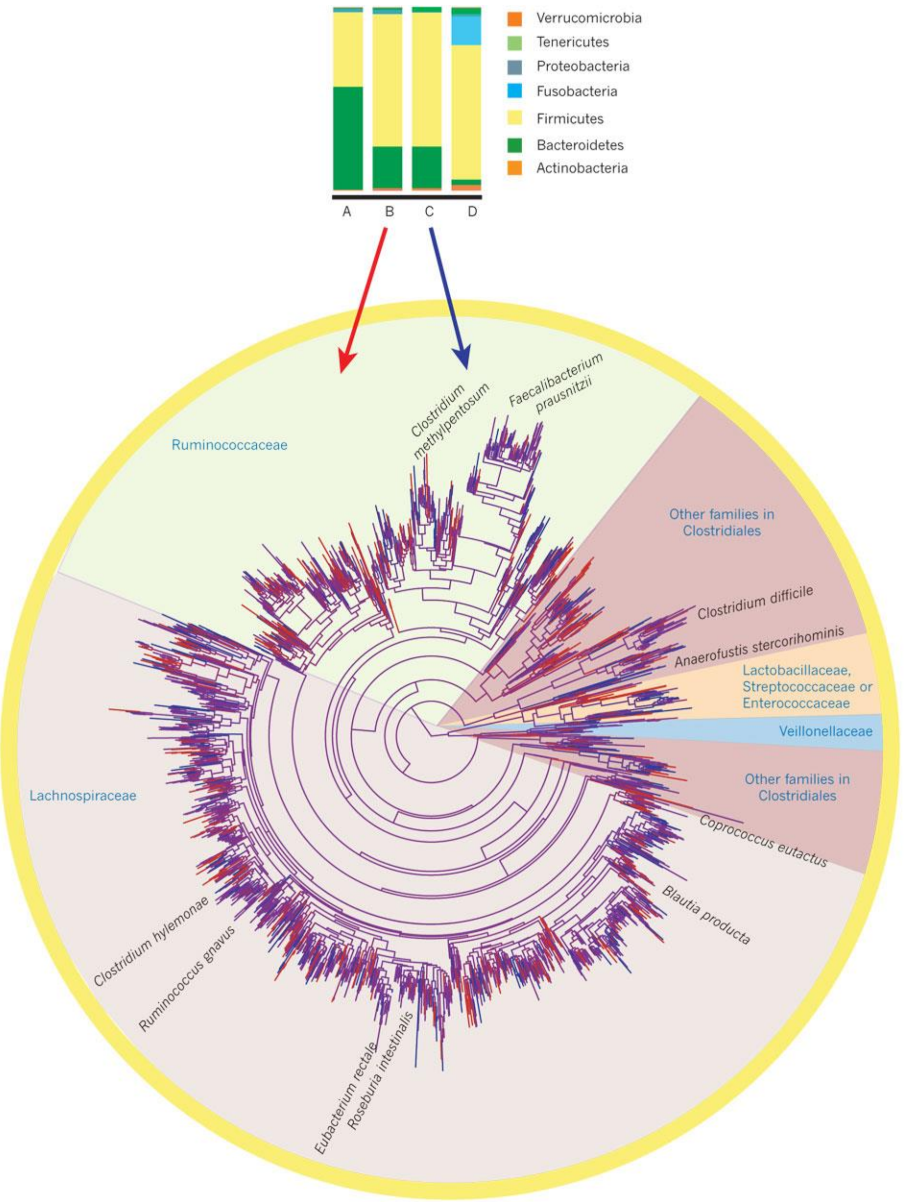


14 JUNE 2012 | VOL 486 | NATURE | 207

Çekirdek barsak mikrobiyotası?

- Bilinen 100 prokaryot bölümünden (phylum) **yedisi** barsakta bulunur.
  - Firmicutes
  - Bacteriodetes
  - Actinobacteria
  - Proteobacteria
  - Verrucomicrobia
  - Tenericutes
  - Fusobacteria

%80-90



Frontiers in Microbiology 2014; doi: 10.3389/fmicb.2014.00587

Nature 489, 220–230 (13 September 2012) doi:10.1038/nature11550

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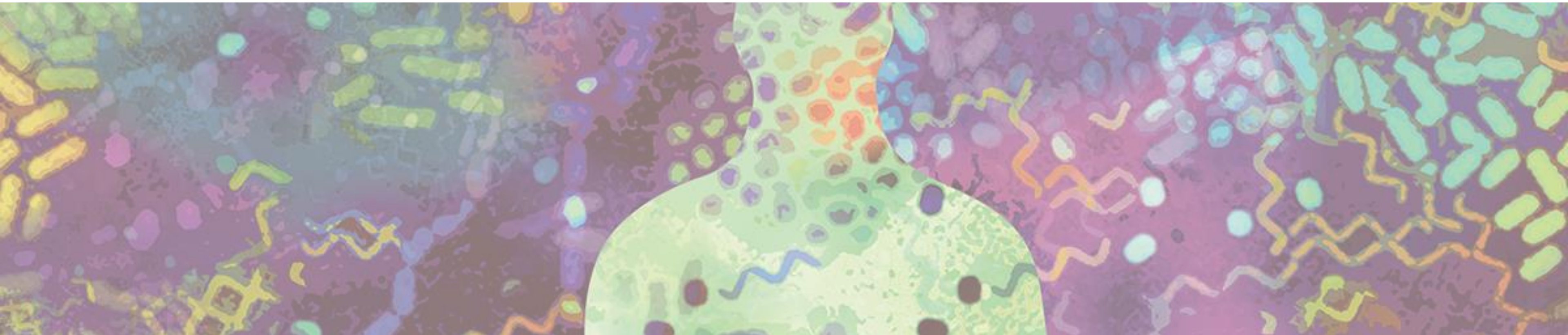
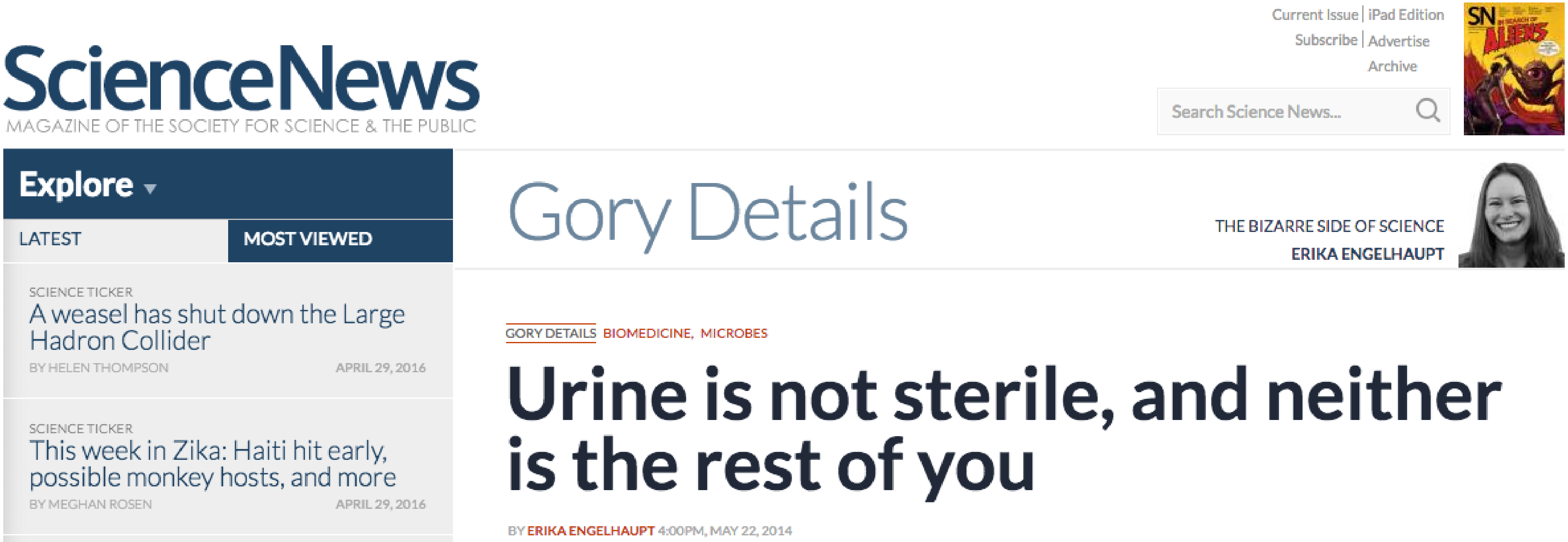
Steril sanıyorduk...





SCIENCE TICKER
A weasel has shut down the Large Hadron Collider
BY HELEN THOMPSON APRIL 29, 2016

SCIENCE TICKER
This week in Zika: Haiti hit early, possible monkey hosts, and more
BY MEGHAN ROSEN APRIL 29, 2016

Gory Details

THE BIZARRE SIDE OF SCIENCE
ERIKA ENGELHAUPT

GORY DETAILS BIOMEDICINE, MICROBES

Urine is not sterile, and neither is the rest of you

BY ERIKA ENGELHAUPT 4:00PM, MAY 22, 2014

Urine Is Not Sterile: Use of Enhanced Urine Culture Techniques To Detect Resident Bacterial Flora in the Adult Female Bladder

Evann E. Hilt,[a] Kathleen McKinley,[b] Meghan M. Pearce,[c] Amy B. Rosenfeld,[d] Michael J. Zilliox,[d] Elizabeth R. Mueller,[e] Linda Brubaker,[e] Xiaowu Gai,[d] Alan J. Wolfe,[a,c] Paul C. Schreckenberger[a,b]

Infectious Disease and Immunology Institute,[a] Department of Pathology,[b] Department of Microbiology and Immunology,[c] Department of Molecular Pharmacology and Therapeutics,[d] and Departments of Obstetrics & Gynecology and Urology,[e] Stritch School of Medicine Loyola University Chicago, Maywood, Illinois, USA

J Clin Microbiol 2014; 52:871 –876..

pathogens

MDPI

Review

Deliberate Establishment of Asymptomatic Bacteriuria—A Novel Strategy to Prevent Recurrent UTI

Björn Wullt * and Catharina Svanborg

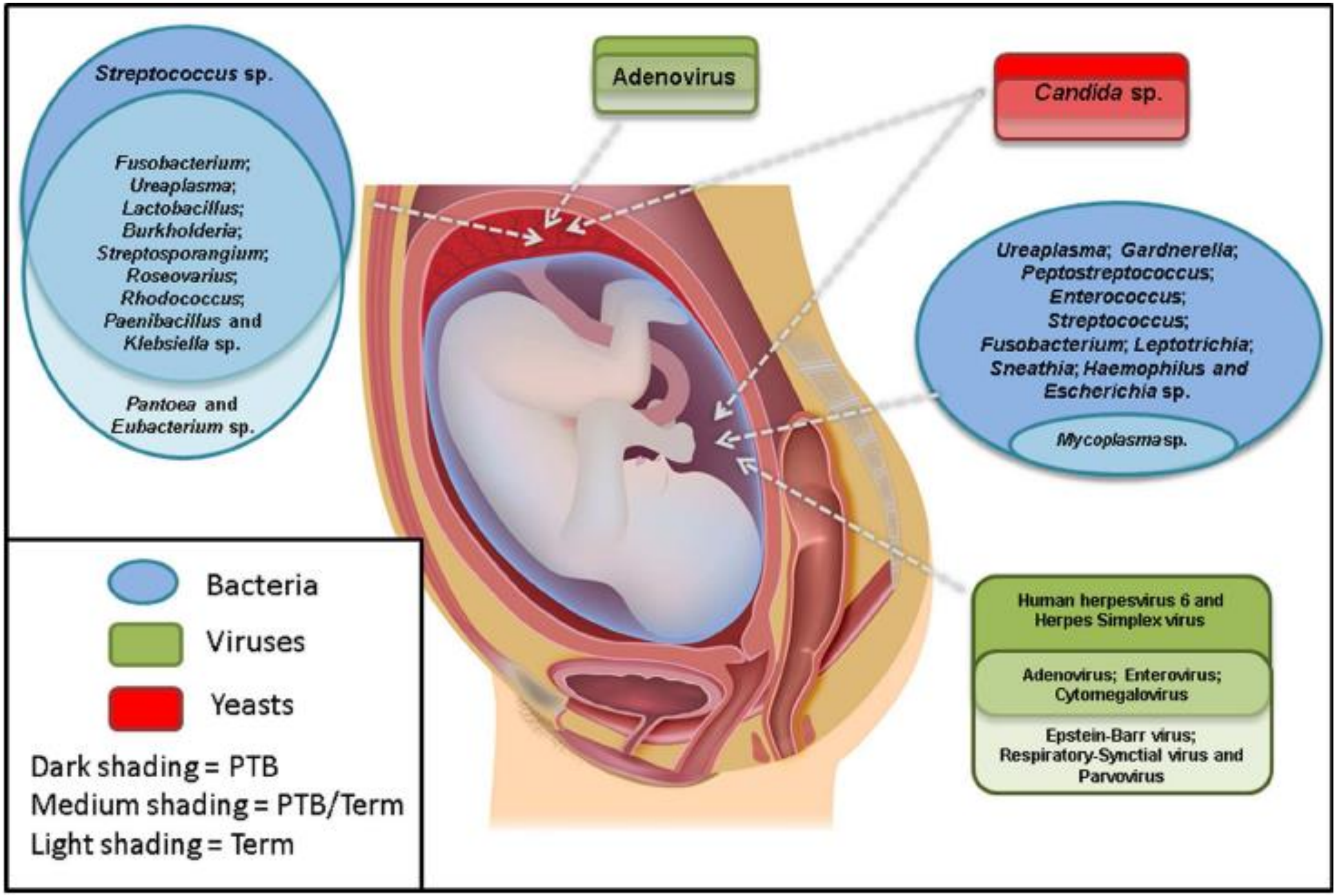
Department of Microbiology, Immunology and Glycobiology (MIG), Institute of Laboratory Medicine, Lund University, 221 00 Lund, Sweden; catharina.svanborg@med.lu.se
* Correspondence: bjorn.wullt@med.lu.se

Academic Editor: Lawrence S. Young
Received: 12 November 2015; Accepted: 21 July 2016; Published: 29 July 2016

Abstract: We have established a novel strategy to reduce the risk for recurrent urinary tract infection (UTI), where rapidly increasing antibiotic resistance poses a major threat. Epidemiologic studies have demonstrated that asymptomatic bacteriuria (ABU) protects the host against symptomatic infections with more virulent strains. To mimic this protective effect, we deliberately establish ABU in UTI-prone patients, who are refractory to conventional therapy. The patients are inoculated with *Escherichia coli* (*E. coli*) 83972, now widely used as a prototype ABU strain. Therapeutic efficacy has been demonstrated in a placebo-controlled trial, supporting the feasibility of using *E. coli* 83972 as a tool to prevent recurrent UTI and, potentially, to outcompete antibiotic-resistant strains from the human urinary tract. In addition, the human inoculation protocol offers unique opportunities to study host-parasite interaction in vivo in the human urinary tract. Here, we review the clinical evidence for protection using this approach as well as some molecular insights into the pathogenesis of UTI that have been gained during these studies.

Exploring preterm birth as a polymicrobial disease: an overview of the uterine microbiome

Matthew S. Payne and Sara Bayatibojakhi*



Front Immunol 2014;5: 595

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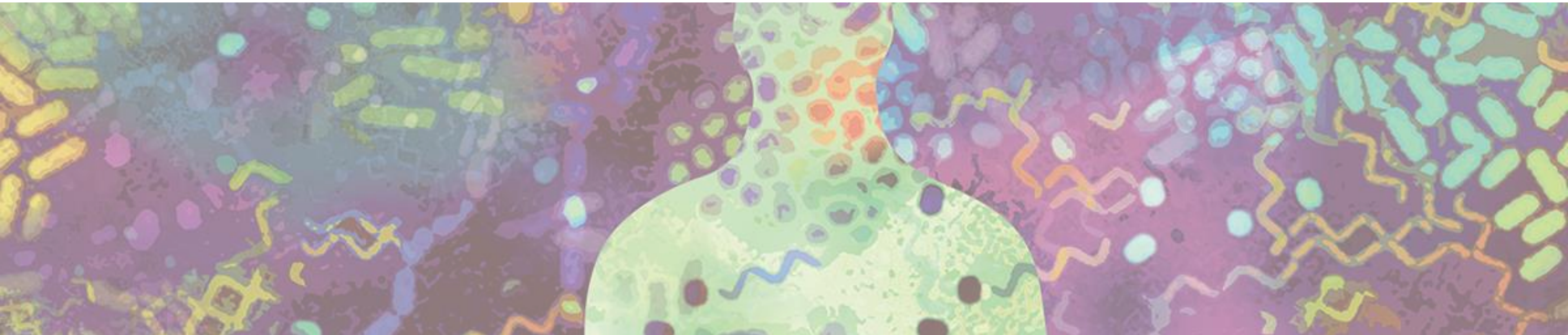
PROJECT

Mikrobiyota: *yeni organımız*?



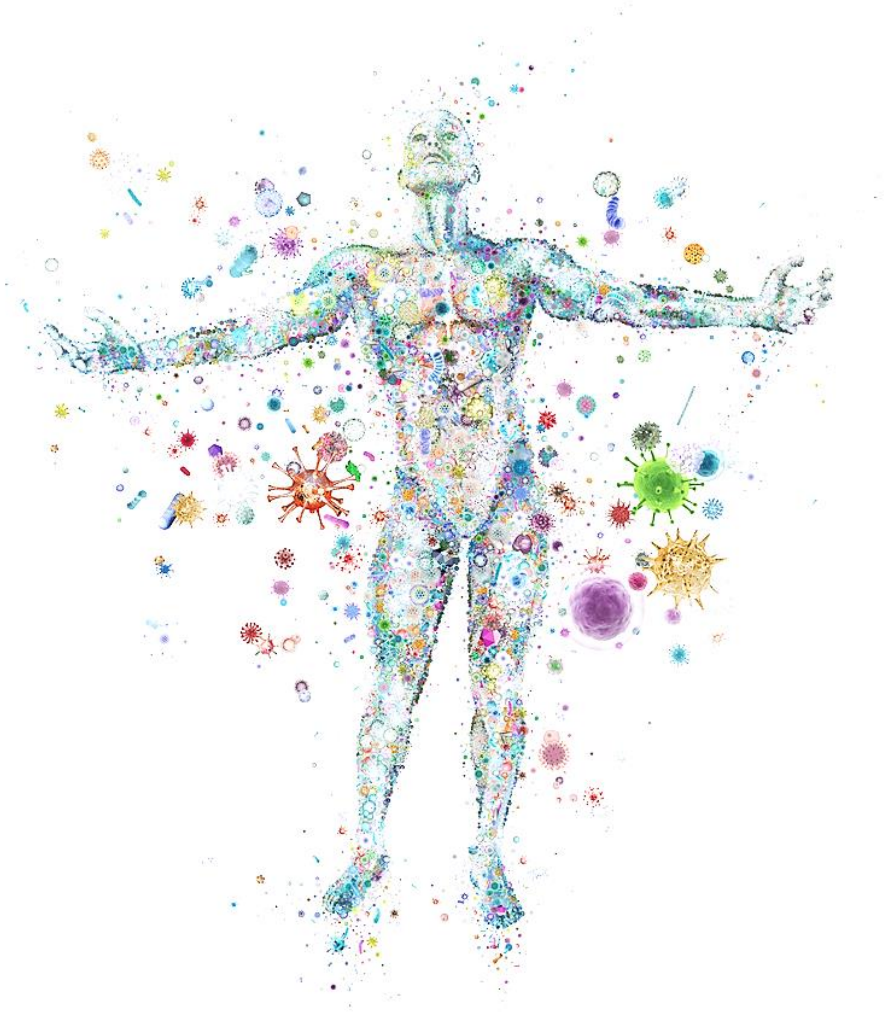
Mikrobiyota çok farklı ve önemli işlevlere sahip!

METABOLİK

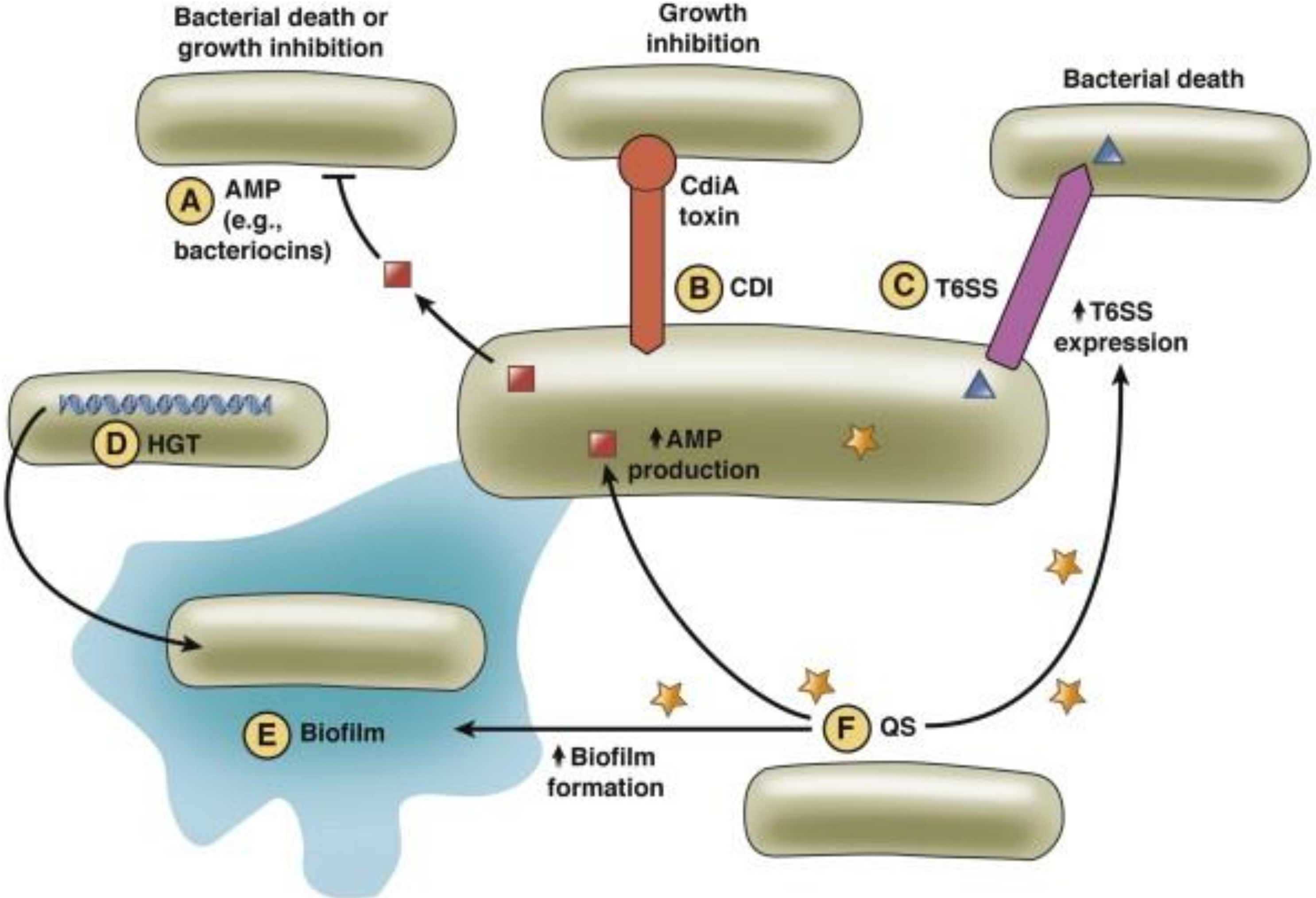
YAPISAL ve GELİŞİMSEL

İMMUNOLOJİK

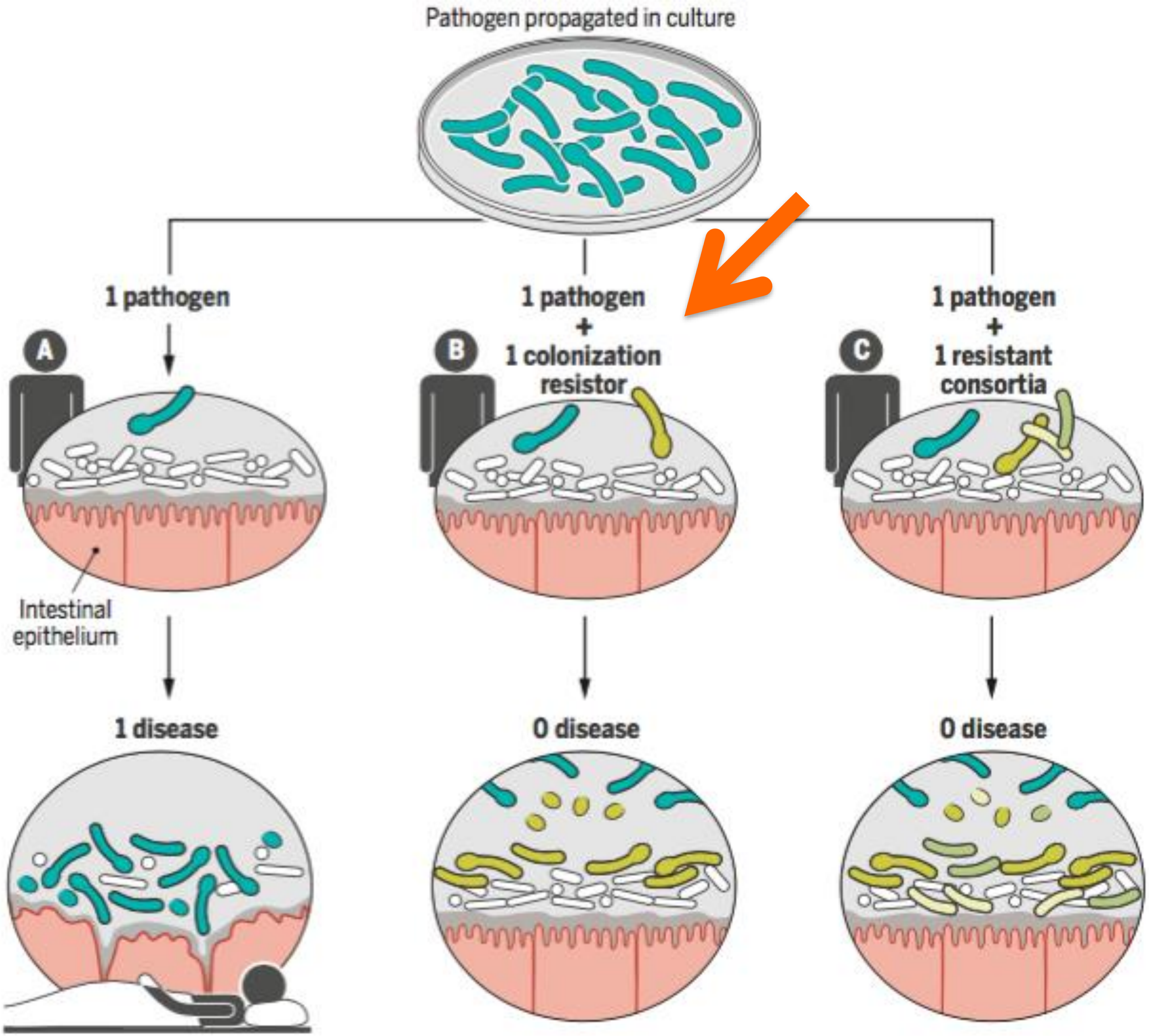
KOLONİZASYON DİRENCİ



Kolonizasyon direnci



Cell Mol Gastroenterol Hepatol 2015;1:28–40

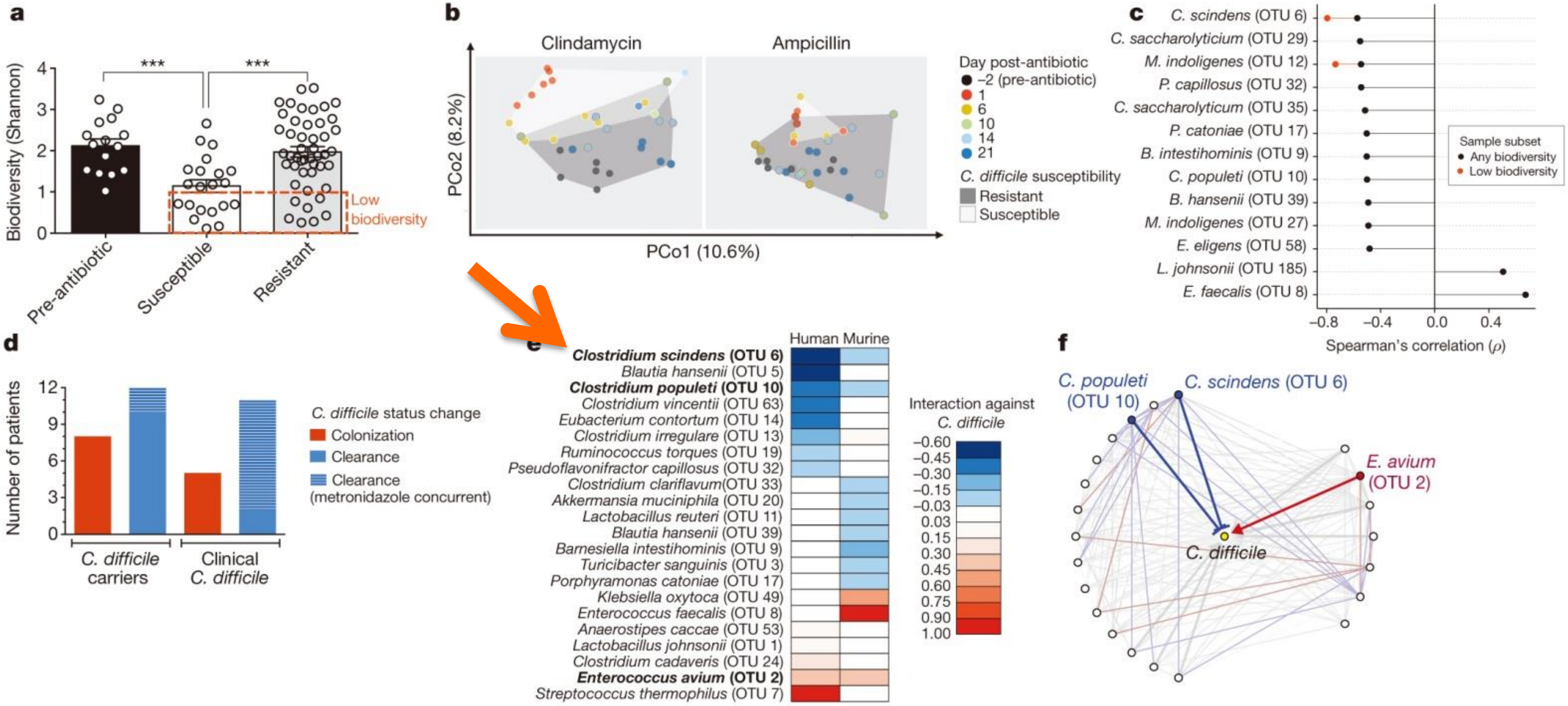


Science **351** (6270), 224-226. [doi: 10.1126/science.aad6753]

doi:10.1038/nature13828

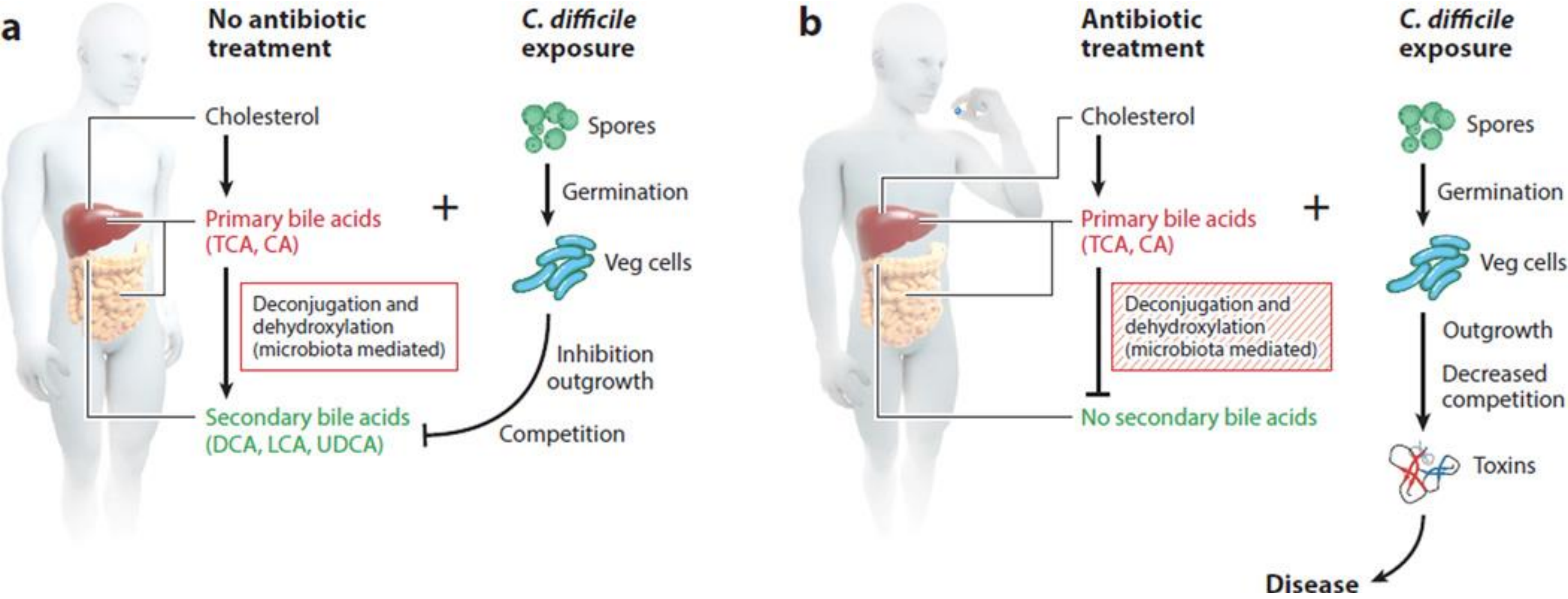
Precision microbiome reconstitution restores bile acid mediated resistance to *Clostridium difficile*

Charlie G. Buffie[1,2], Vanni Bucci[3,4], Richard R. Stein[3], Peter T. McKenney[1,2], Lilan Ling[2], Asia Gobourne[2], Daniel No[2], Hui Liu[5], Melissa Kinnebrew[1,2], Agnes Viale[6], Eric Littmann[2], Marcel R. M. van den Brink[7,8], Robert R. Jenq[7], Ying Taur[1,2], Chris Sander[3], Justin R. Cross[5], Nora C. Toussaint[2,3], Joao B. Xavier[2,3] & Eric G. Pamer[1,2,8]

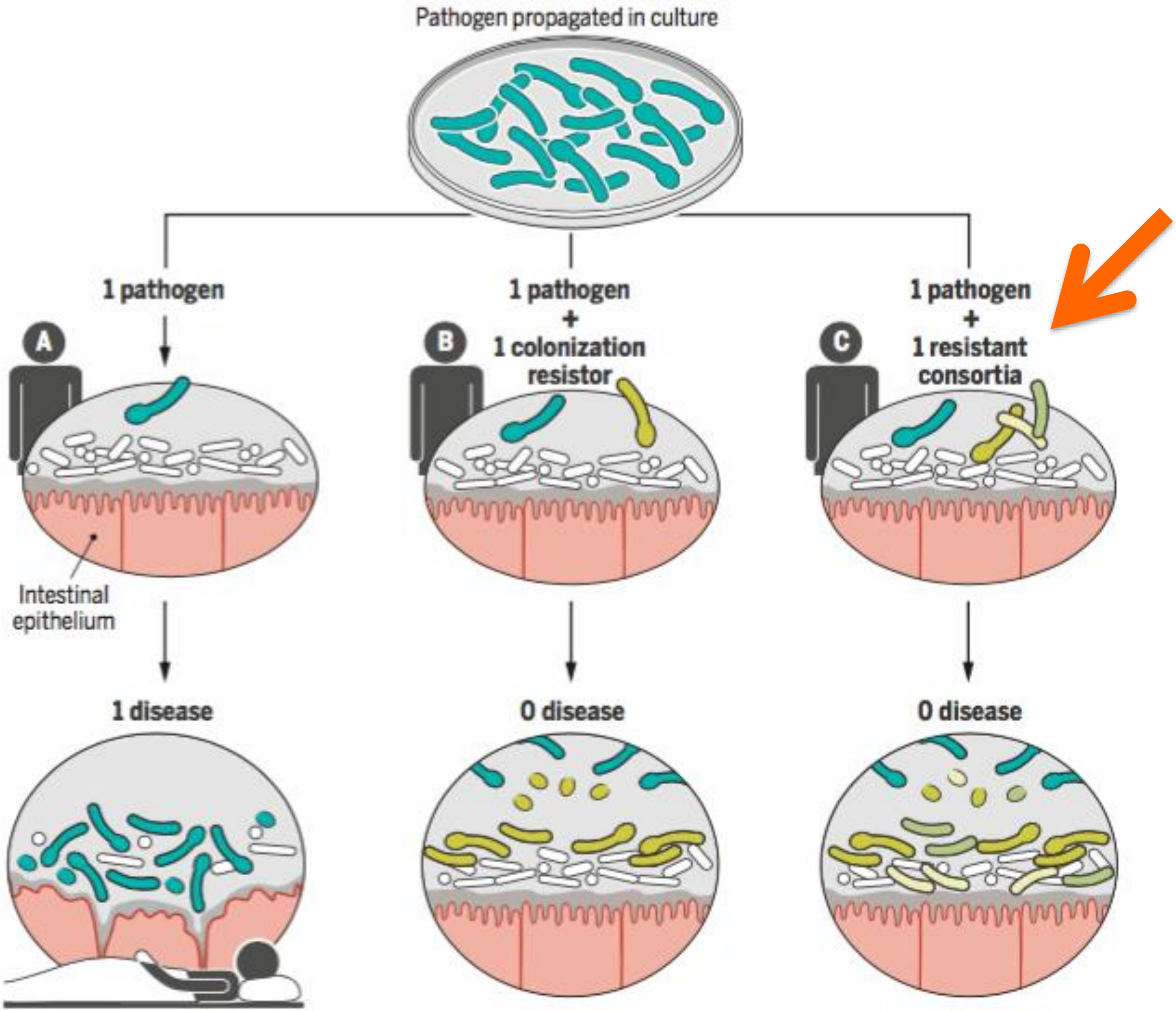


CG Buffie *et al. Nature* **517**, 205-208 (2015) doi:10.1038/nature13828

C diff ve sekonder safra asitleri



Annu. Rev. Microbiol. 2015. 69:445–61



Science **351** (6270), 224-226. [doi: 10.1126/science.aad6753]

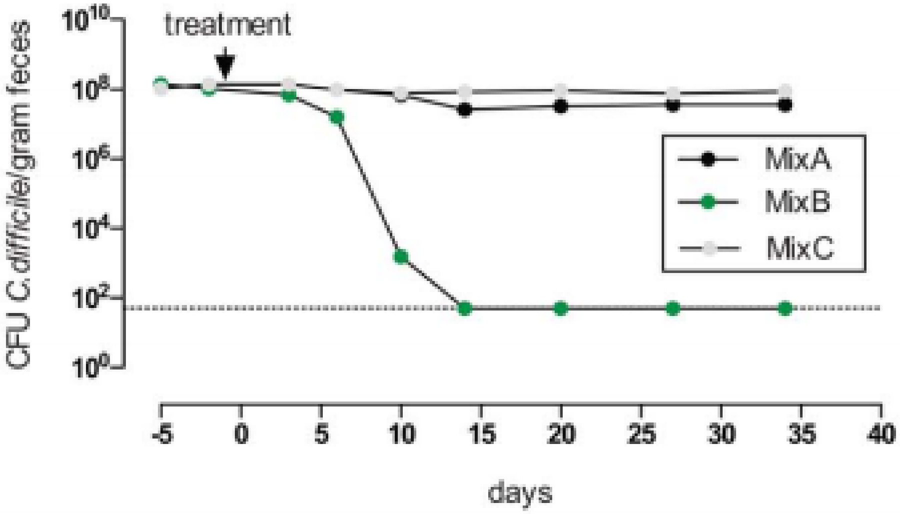
OPEN ACCESS Freely available online

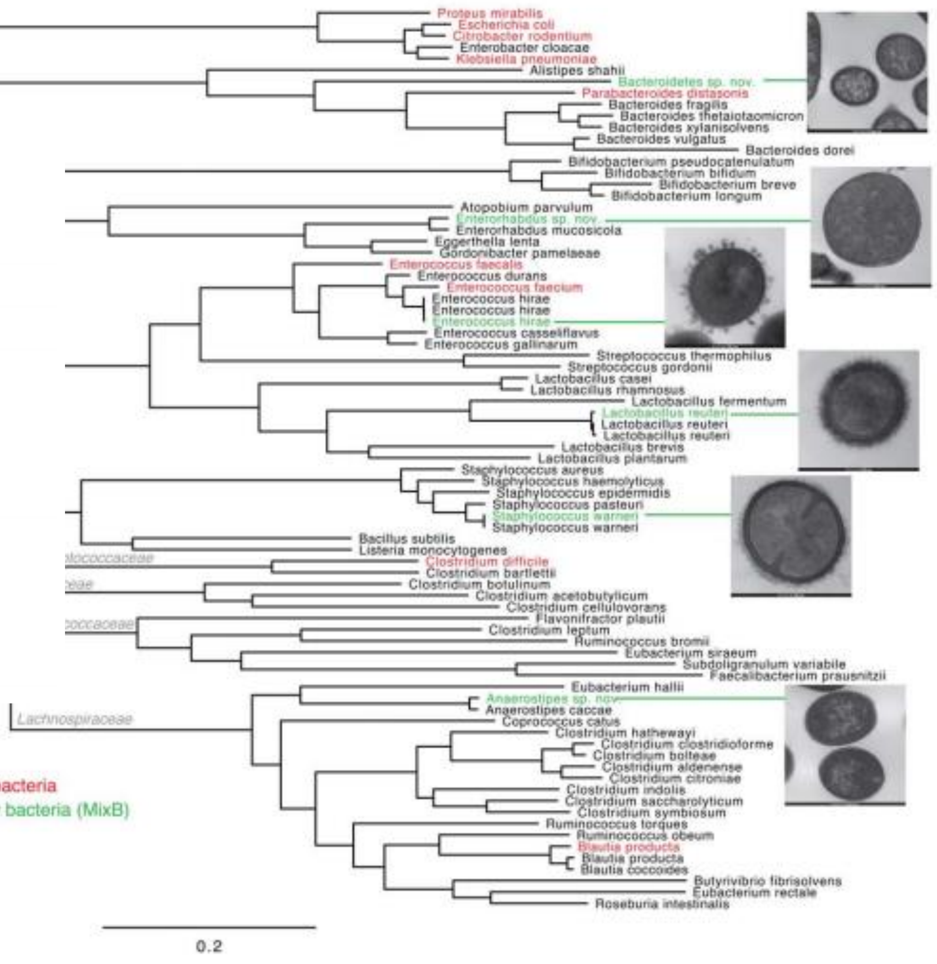
PLOS | PATHOGENS

Targeted Restoration of the Intestinal Microbiota with a Simple, Defined Bacteriotherapy Resolves Relapsing *Clostridium difficile* Disease in Mice

Trevor D. Lawley[1]*, Simon Clare[1☉], Alan W. Walker[1☉], Mark D. Stares[1], Thomas R. Connor[1], Claire Raisen[1], David Goulding[1], Roland Rad[1], Fernanda Schreiber[1], Cordelia Brandt[1], Laura J. Deakin[1], Derek J. Pickard[1], Sylvia H. Duncan[2], Harry J. Flint[2], Taane G. Clark[3], Julian Parkhill[1], Gordon Dougan[1]

1 Wellcome Trust Sanger Institute, Hinxton, United Kingdom, 2 Rowett Institute of Nutrition and Health, Aberdeen, United Kingdom, 3 London School of Hygiene and Tropical Medicine, London, United Kingdom





PLoS Pathog 8(10): e1002995. doi:10.1371/journal.ppat.1002995 doi:10.1038/nature13738

Members of the human gut microbiota involved in recovery from *Vibrio cholerae* infection

Ansel Hsiao[1], A. M. Shamsir Ahmed[2,3], Sathish Subramanian[1], Nicholas W. Griffin[1], Lisa L. Drewry[1], William A. Petri Jr[4,5,6], Rashidul Haque[3], Tahmeed Ahmed[3] & Jeffrey I. Gordon[1]

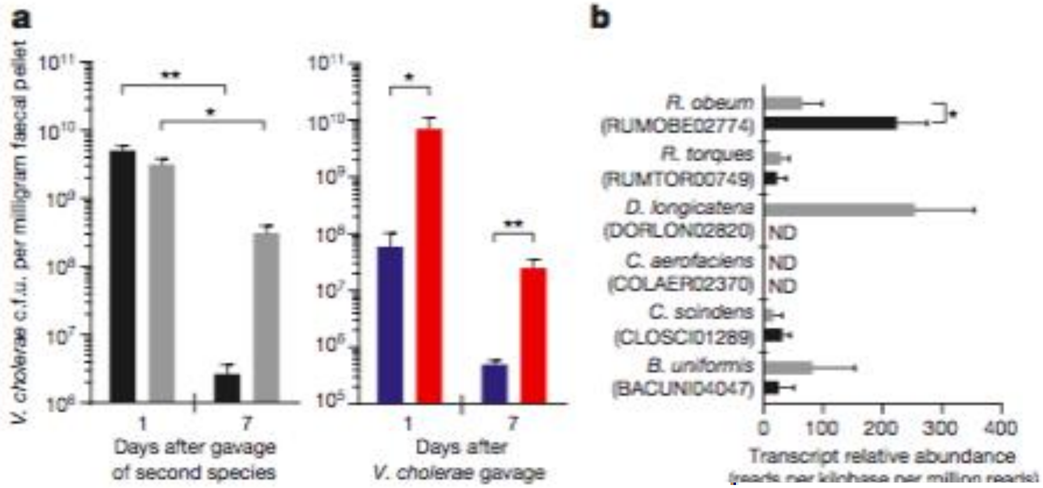


Figure 1 | *R. obeum* restricts *V. cholerae*
mice. a, *V. cholerae* levels in the faeces of
human gut bacterial species ($n = 4$–6 mice
R. obeum luxS AI-2 synthase in the 14-mem
introduction of 10^9 c.f.u. of *V. cholerae* or no
Note that *D. longicatena* levels fall precipito
(Supplementary Table 9). Mean values ± s.
$*P < 0.05$, $**P < 0.01$ (unpaired Mann–Whitney U-test).

biota maturation in healthy Bangladeshi children[3]. One of the species, *Ruminococcus obeum*, exhibits consistent increases in its relative abundance upon *V. cholerae* infection of the mice. Follow-up analyses, including mono- and co-colonization studies, establish that *R. obeum* restricts *V. cholerae* colonization, that *R. obeum luxS* (autoinducer-2 (AI-2) synthase) expression and AI-2 production increase significantly with *V. cholerae* invasion, and that *R. obeum* AI-2 causes quorum-sensing-mediated repression of several *V. cholerae* colonization factors. Co-colonization with *V. cholerae* mutants discloses that *R. obeum*

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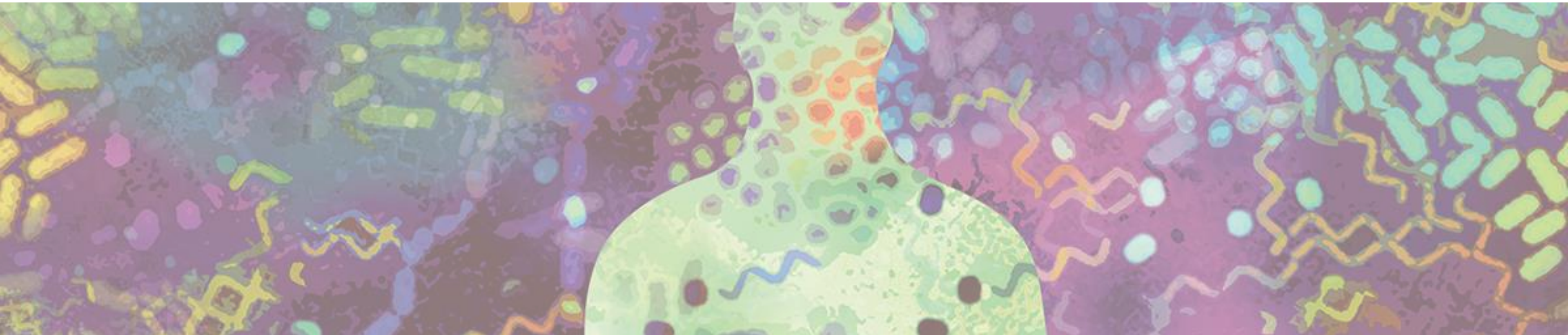
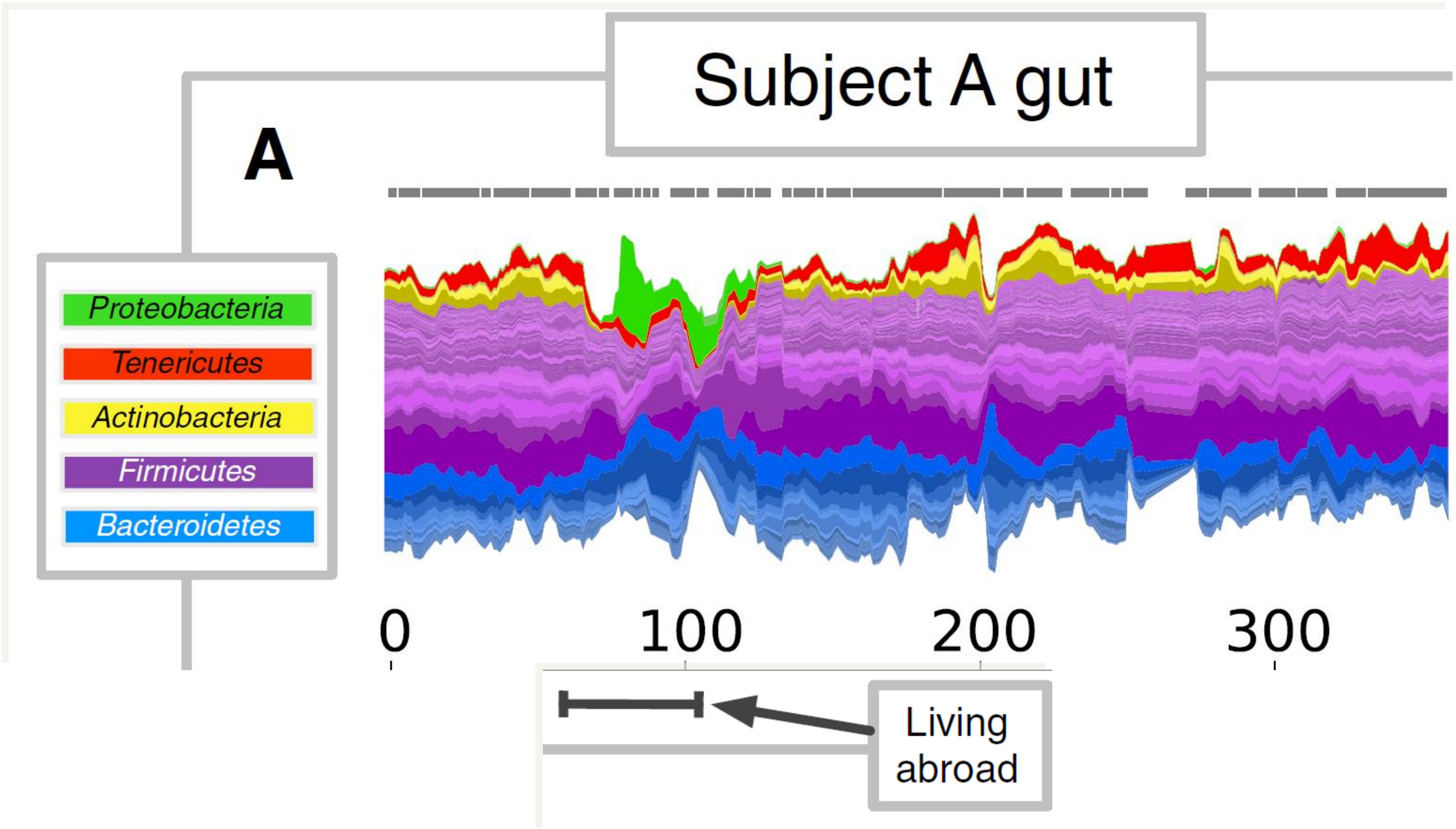
homeostaz bozulursa hastalıklar ortaya çıkabilir...

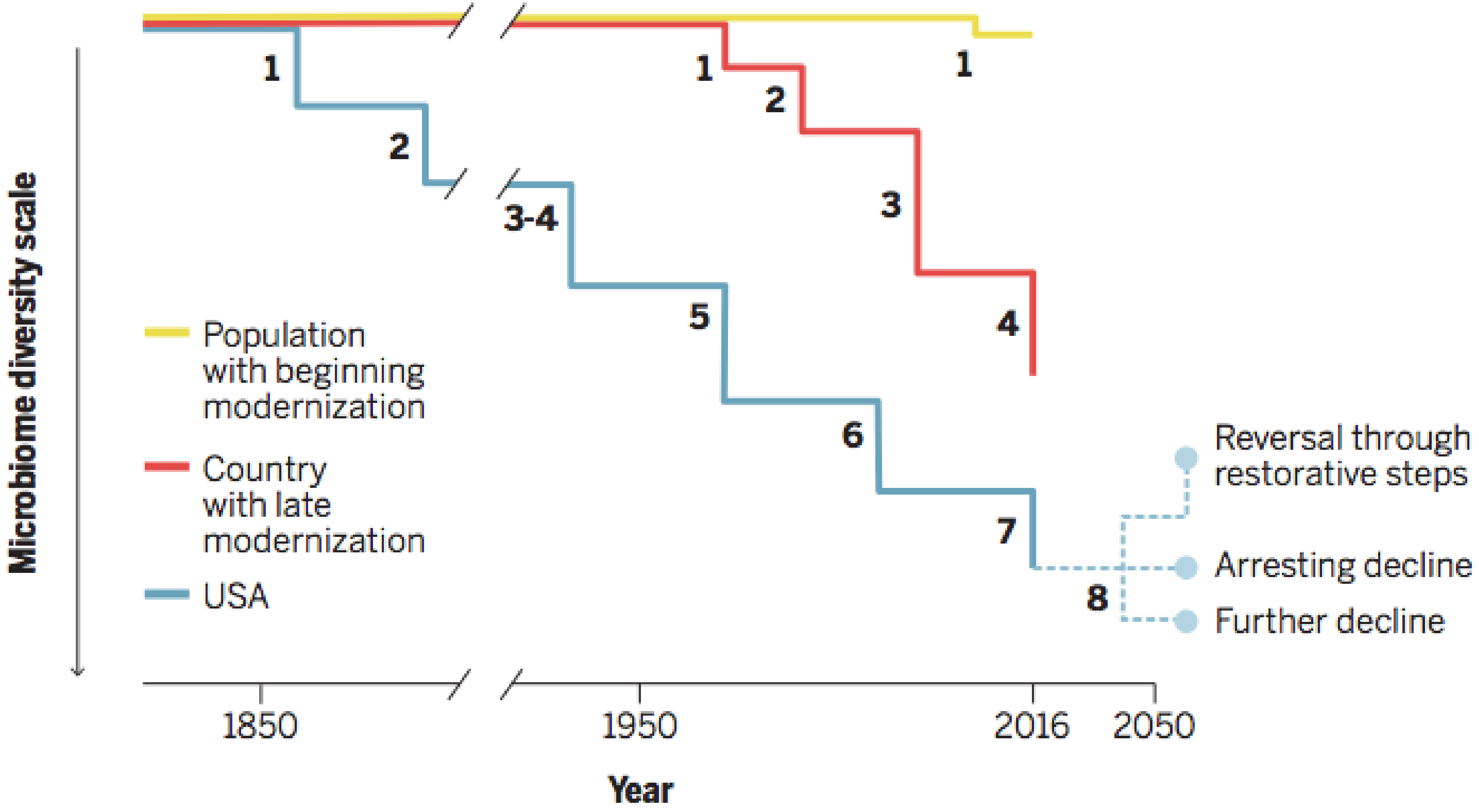


Mikrobiyom *dengesi* bozulabilir…



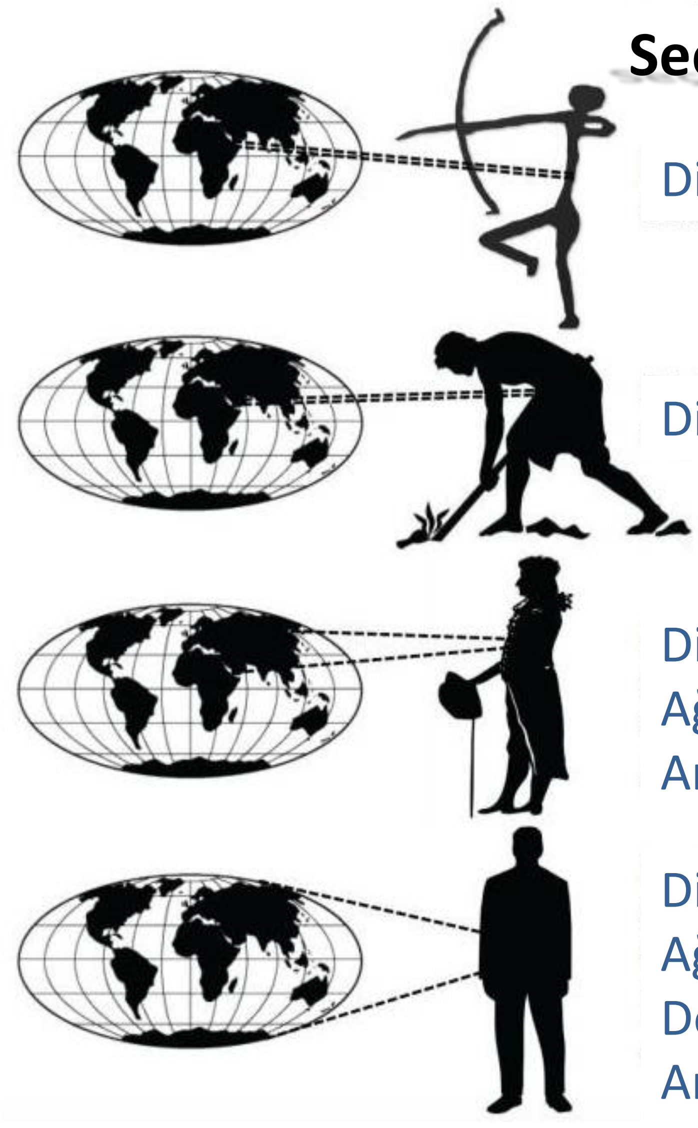
Genome Biology (2014)
David, et al.

Modernleşme çeşitlilikte azalmaya neden oluyor!



SCIENCE 29 APRIL 2016 • VOL 352 ISSUE 6285

Mikrobiyota üzerindeki seçici baskılar



Seçici baskı

Diyet

Diyet

Diyet
Ağır metaller
Arsenik

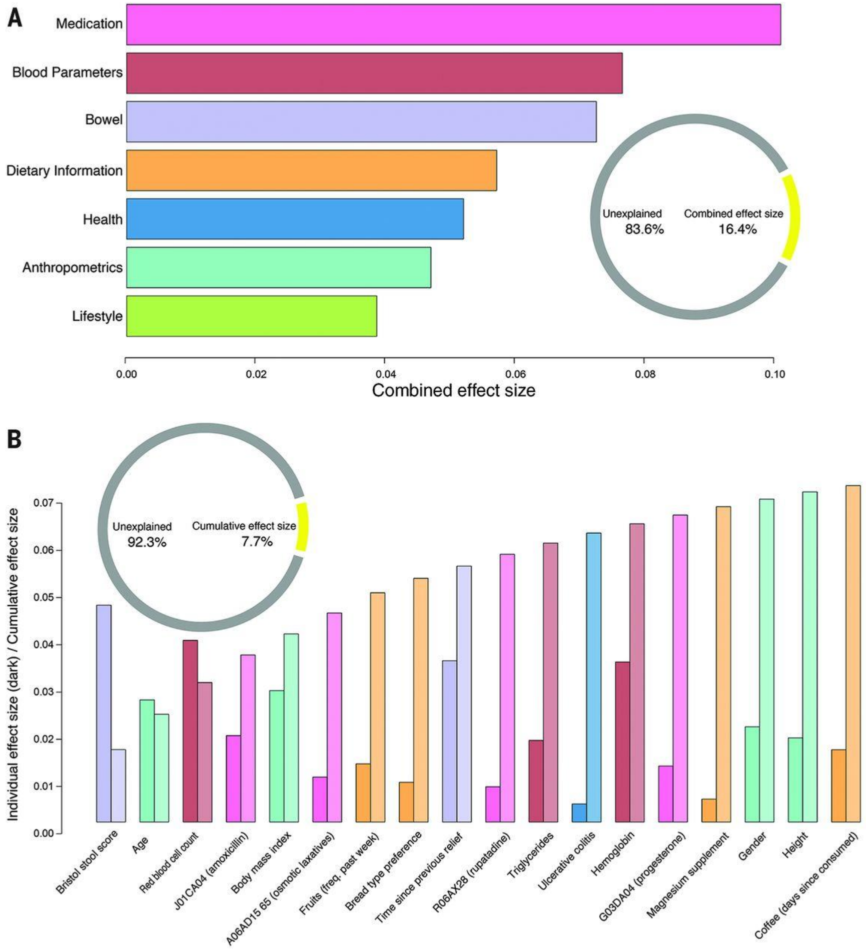
Diyet
Ağır metaller
Dezenfektanlar
Antibiyotikler

İnsanlar
54,083,964,813 standart birim (2010)
73,620,748,816 standart birim (2014)
Van Boeckel et al. Lancet Infect. Dis. 2014; 14: 742–750

Hayvanlar
63 milyon kg (2010)
Van Boeckel et al. PNAS. 2015; 112, 5649–5654.

Genes (Basel). 2015 Sep; 6(3): 841–857

İlaçlar mikrobiyom bileşimi üzerine en etkili faktör!



- Antibiyotikler
- Proton pompa inhibitörleri
- Ozmotik laksatifler
- IBH ilaçları
- Oral kontraseptifler
- Benzodiyazepinler
- Antidepresanlar
- Antihistaminik

Fig. 2 Microbiome covariates identified in the FGFP cohort (left) and their replication in the LLDeep study (right).

Gwen Falony et al. Science 2016;352:560-564

nature COMMUNICATIONS

ARTICLE

Received 23 Jun 2015 | Accepted 3 Dec 2015 | Published 26 Jan 2016

DOI: 10.1038/ncomms10410

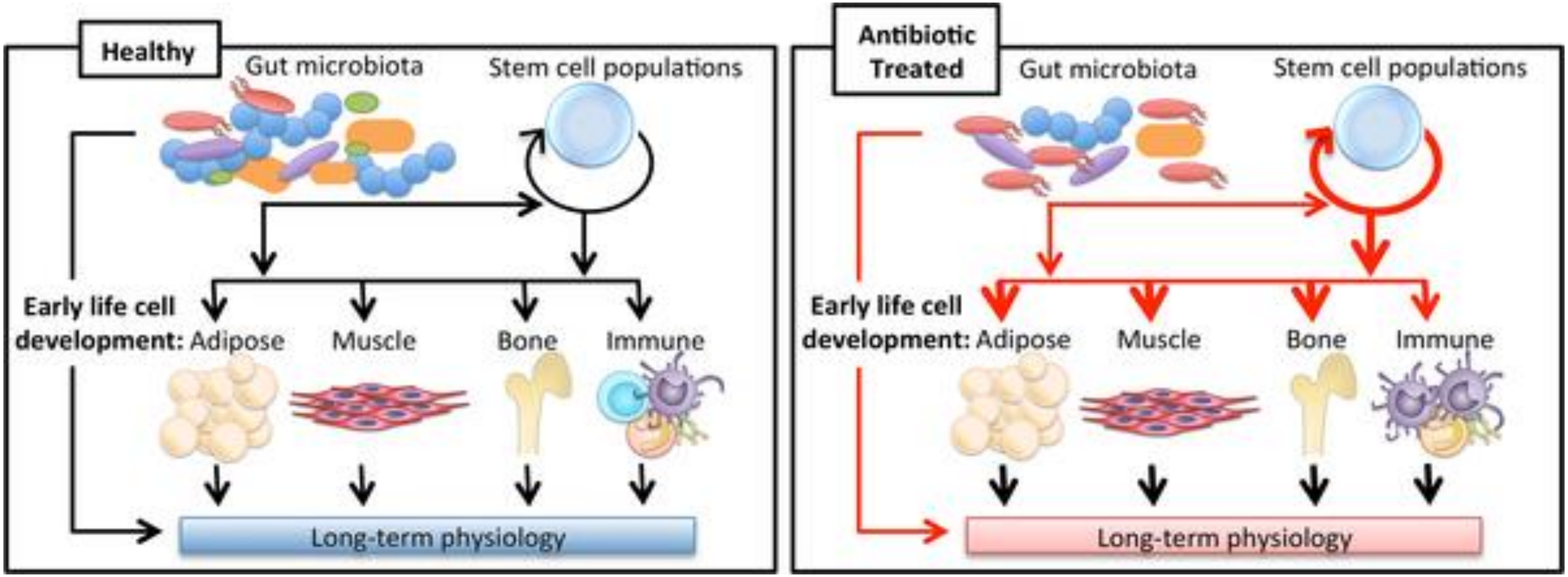
OPEN

Intestinal microbiome is related to lifetime antibiotic use in Finnish pre-school children

Katri Korpela[1], Anne Salonen[1], Lauri J. Virta[2], Riina A. Kekkonen[3], Kristoffer Forslund[4], Peer Bork[4] & Willem M. de Vos[1,5,6]

Early-life antibiotic use is associated with increased risk for metabolic and immunological diseases, and mouse studies indicate a causal role of the disrupted microbiome. However, little is known about the impacts of antibiotics on the developing microbiome of children. Here we use phylogenetics, metagenomics and individual antibiotic purchase records to show that macrolide use in 2-7 year-old Finnish children ($N = 142$; sampled at two time points) is associated with a long-lasting shift in microbiota composition and metabolism. The shift includes depletion of Actinobacteria, increase in Bacteroidetes and Proteobacteria, decrease in bile-salt hydrolase and increase in macrolide resistance. Furthermore, macrolide use in early life is associated with increased risk of asthma and predisposes to antibiotic-associated weight gain. Overweight and asthmatic children have distinct microbiota compositions. Penicillins leave a weaker mark on the microbiota than macrolides. Our results support the idea that, without compromising clinical practice, the impact on the intestinal microbiota should be considered when prescribing antibiotics.

Antibiyotik kullanımının uzun dönem etkileri olabilir!



Schulfer A, Blaser MJ (2015) Risks of Antibiotic Exposures Early in Life on the Developing Microbiome. PLoS Pathog 11(7): e1004903. doi:10.1371/journal.ppat.1004903
http://journals.plos.org/plospathogens/article?id=info:doi/10.1371/journal.ppat.1004903

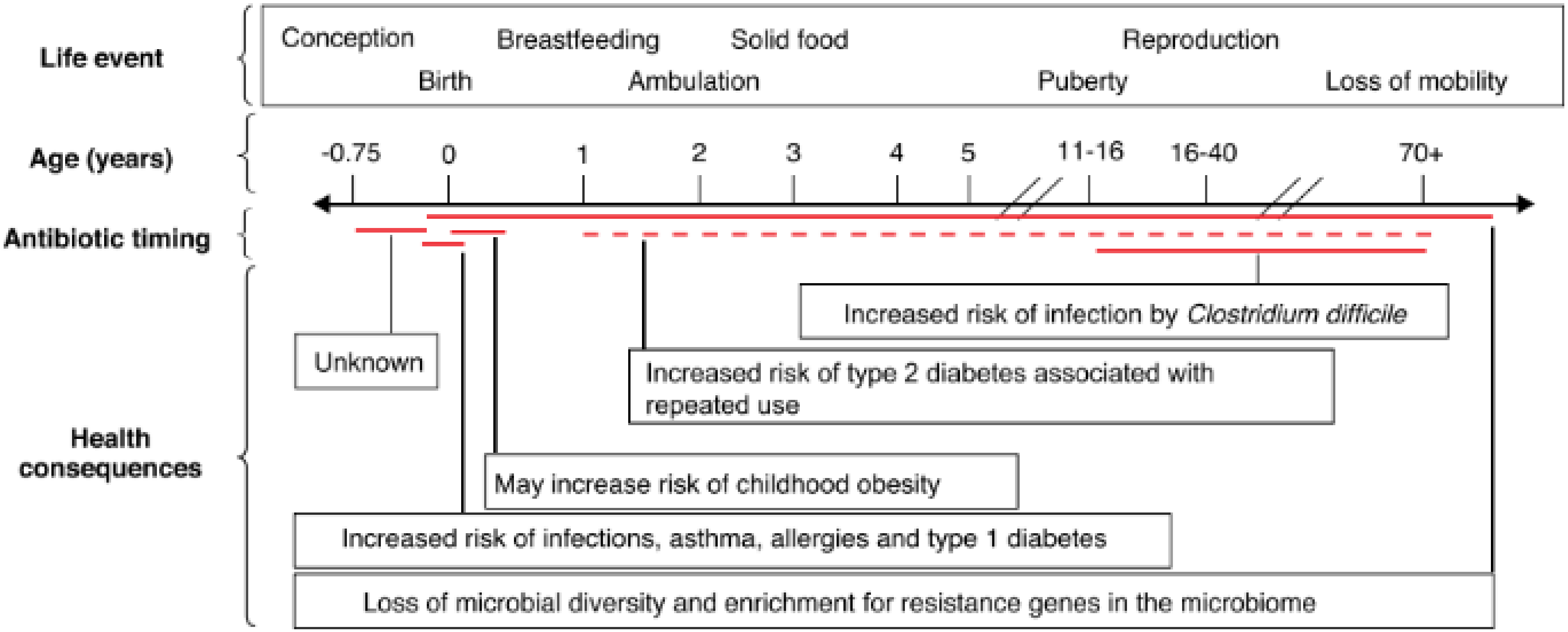
PLOS | PATHOGENS

Perinatal döneme dikkat!

TURDEP-II

Türkiye Diyabet, Hipertansiyon, Obezite ve Endokrinolojik Hastalıklar Prevalans Çalışması

- Türkiye'de erişkin toplumda diyabet prevalansı %13.7'dir.
- Obezite sıklığı %32'dir.



Langdon et al. Genome Medicine (2016) 8:39

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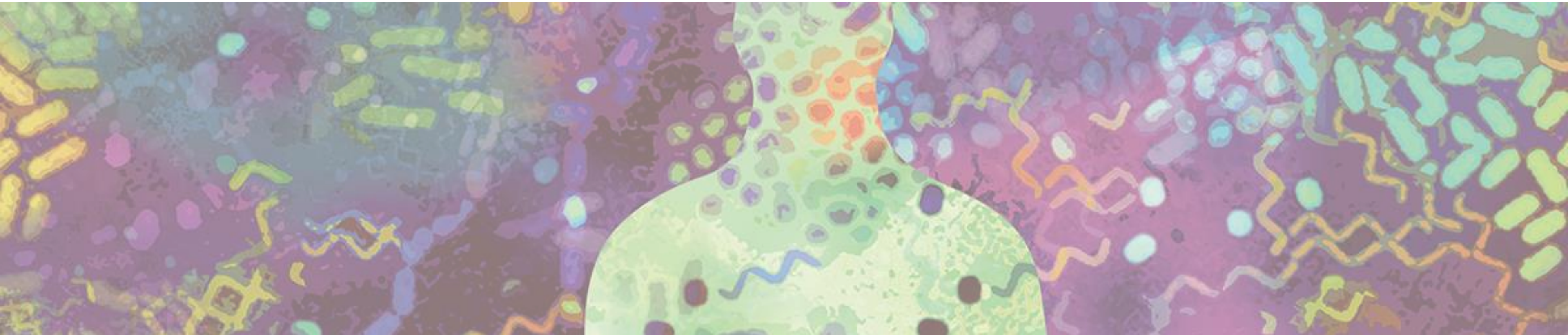
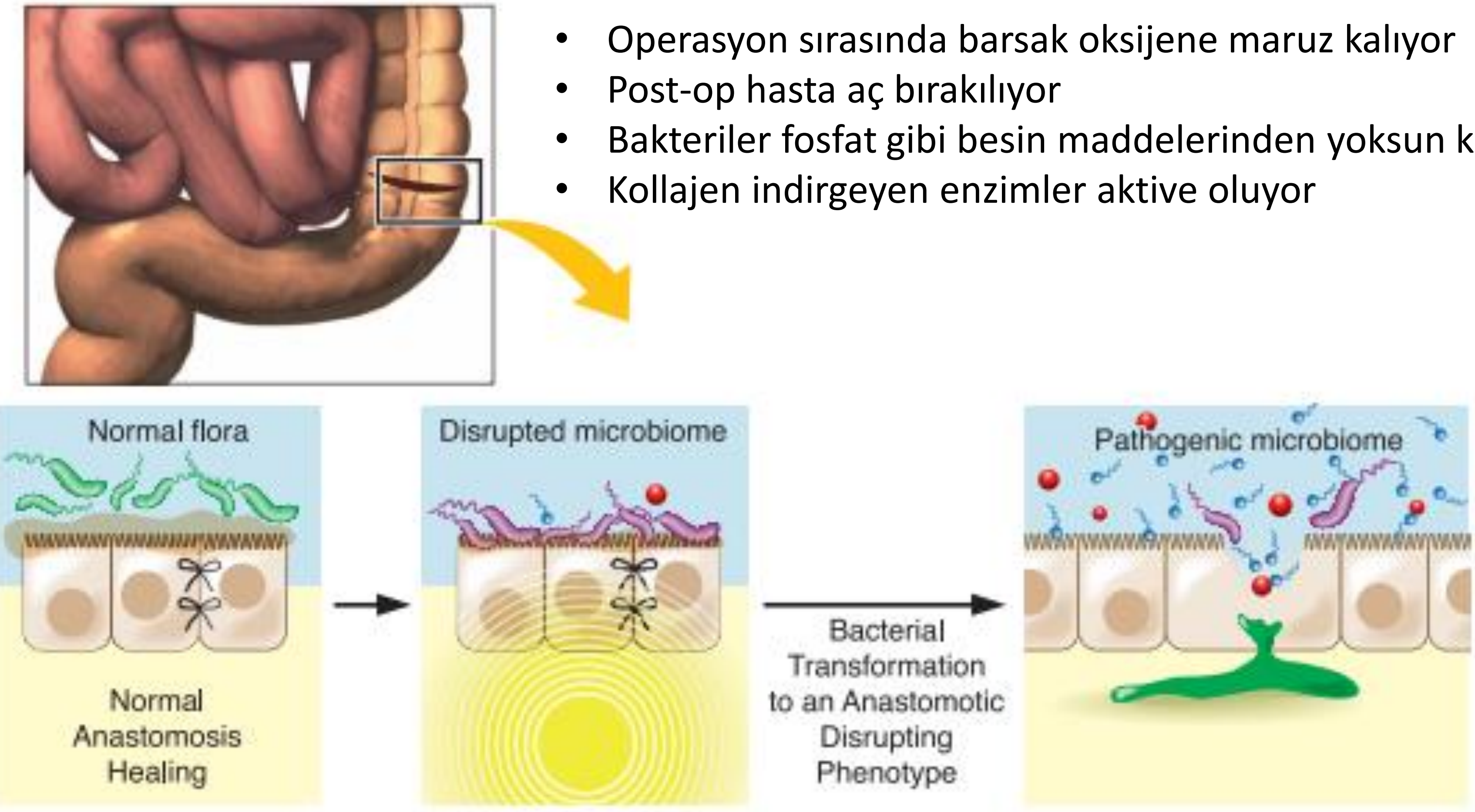
mikrobiyota *patojenin* davranışını (virülansını) değiştirebilir!



Homeostaz ve ötesi…

- Operasyon sırasında barsak oksijene maruz kalıyor
- Post-op hasta aç bırakılıyor
- Bakteriler fosfat gibi besin maddelerinden yoksun kalıyor
- Kollajen indirgeyen enzimler aktive oluyor



Curing an anastomotic leak.

Microbe—Volume 11, Number 1, 2016

Staphylococcus aureus Shifts toward Commensalism in Response to *Corynebacterium* Species

Matthew M. Ramsey[1,2], Marcelo O. Freire[2,3], Rebecca A. Gabrilska[4], Kendra P. Rumbaugh[4] and Katherine P. Lemon[1,5]*

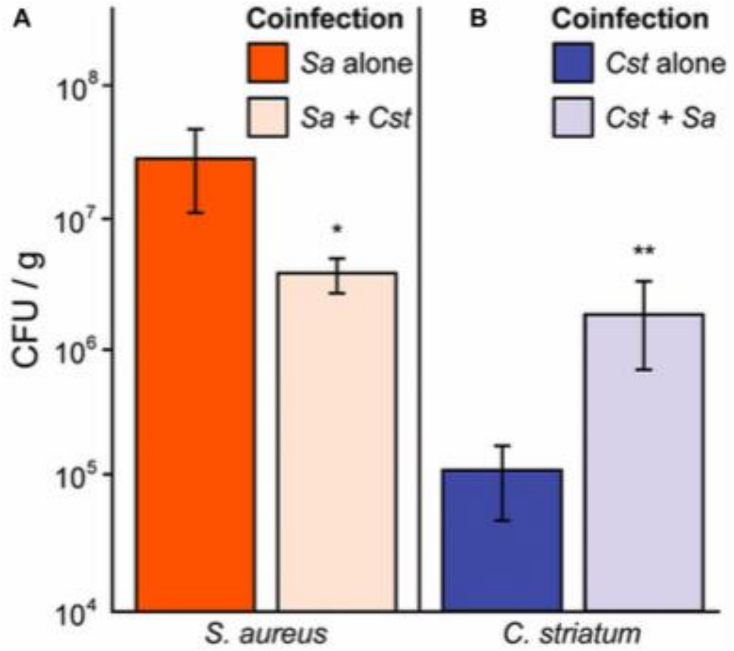
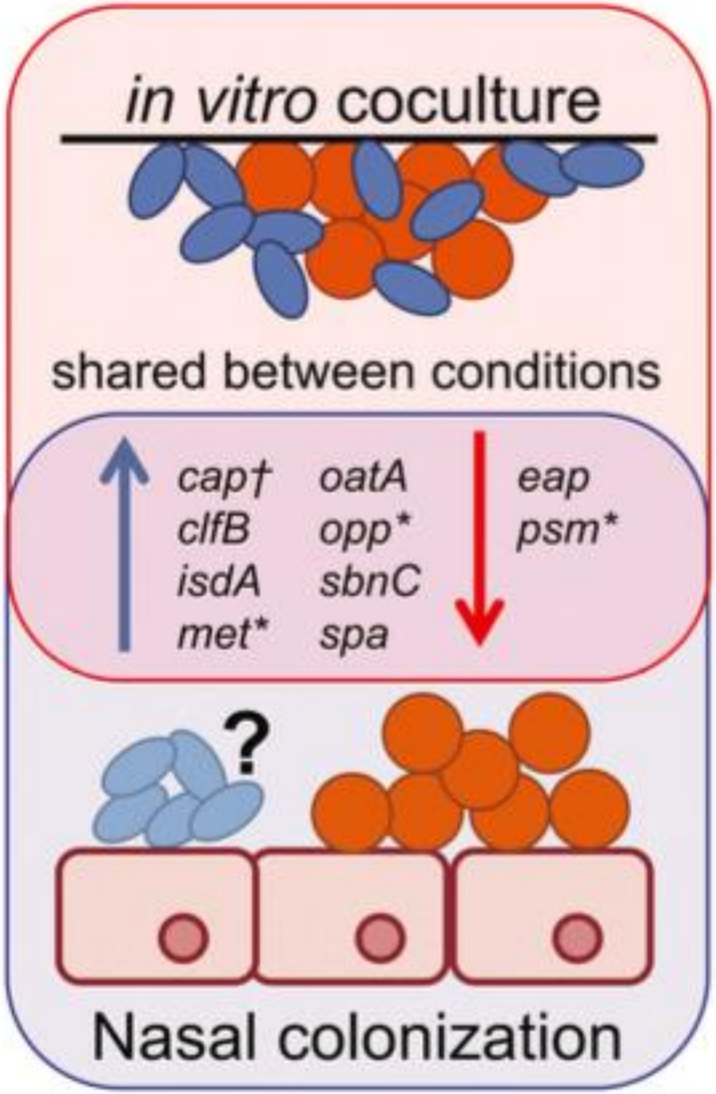
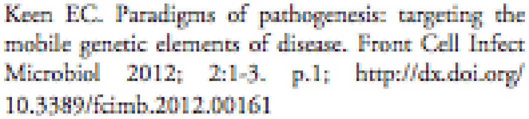


FIGURE 5 | *Staphylococcus aureus* abundance decreases *in vivo* when coinfected with *C. striatum* in a murine abscess model. (A) In a murine abscess infection model 4 days post-infection, wild-type *S. aureus* showed reduced numbers (CFU/g) during coinfection with *C. striatum* (light orange bar; *Sa* + *Cst*) compared to monoinfection (orange bar; *Sa* alone). **(B)** In the same model, *C. striatum* numbers increased significantly when coinfected with *S. aureus* (light blue bar; *Cst* + *Sa*) when compared to monoinfection (blue bar; *Cst* alone). For each bar, $n = 9$. Data were analyzed using the Mann Whitney *U*-test ($^{*}p < 0.03$, $^{**}p < 0.02$). Error bars represent SEM.



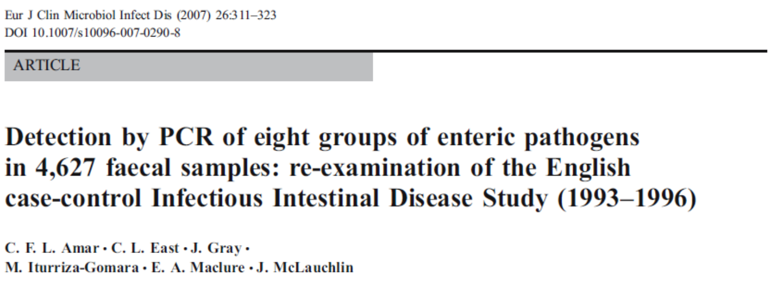
Front. Microbiol. 7:1230. doi: 10.3389/fmicb.2016.01230

- ..modern genomics is telling us that a pathogen is not a pathogen…



Keen EC. Paradigms of pathogenesis: targeting the mobile genetic elements of disease. Front Cell Infect Microbiol 2012; 2:1-3. p.1; http://dx.doi.org/10.3389/fcimb.2012.00161

Anomaliler?



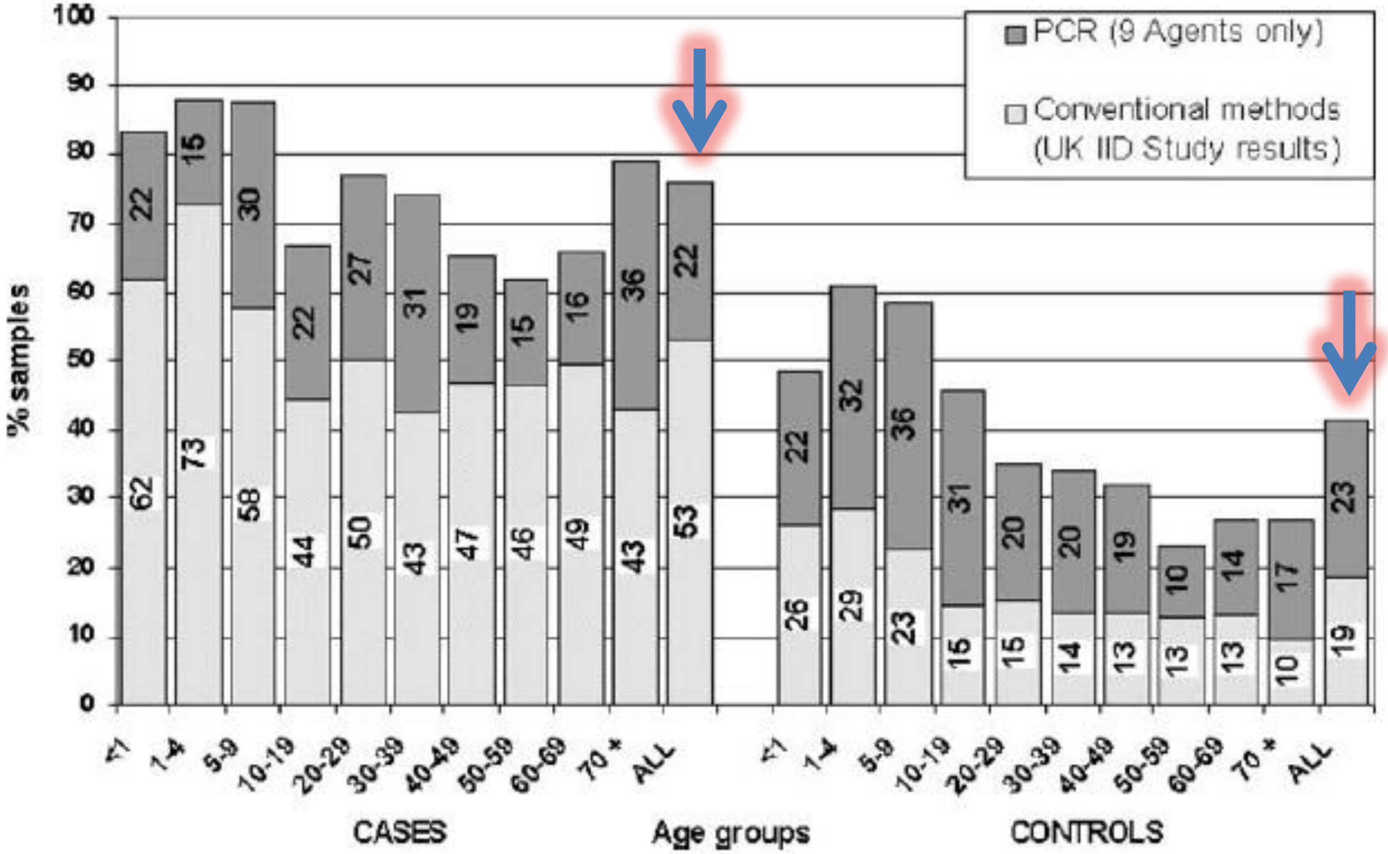
Eur J Clin Microbiol Infect Dis (2007) 26:311–323
DOI 10.1007/s10096-007-0290-8

ARTICLE

Detection by PCR of eight groups of enteric pathogens in 4,627 faecal samples: re-examination of the English case-control Infectious Intestinal Disease Study (1993–1996)

C. F. L. Amar · C. L. East · J. Gray ·
M. Iturriza-Gomara · E. A. Maclure · J. McLauchlin

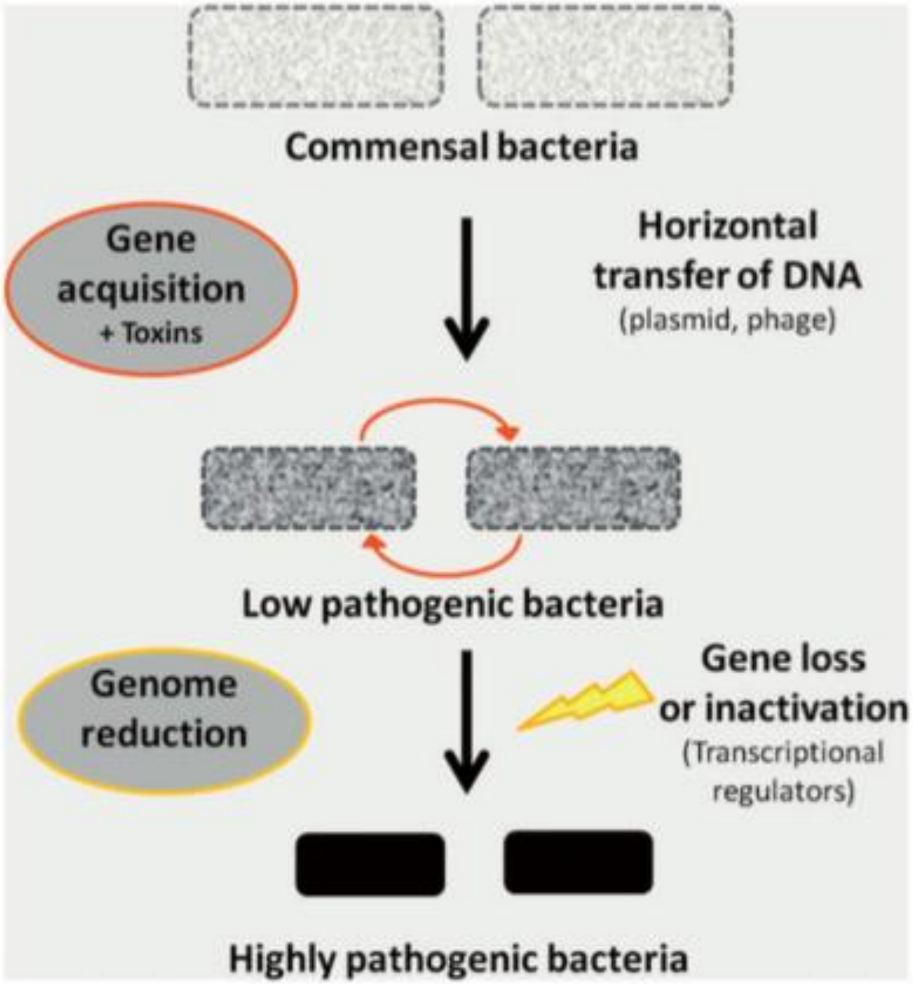
PCR ile hem olgu hem de *kontrol grubunda* enterik patojen saptama oranı artmıştır.



BRIEFINGS IN FUNCTIONAL GENOMICS. VOL 12. NO 4. 291–304 doi:10.1093/bfgp/elt015

Postgenomic analysis of bacterial pathogens repertoire reveals genome reduction rather than virulence factors

Vicky Merhej, Kalliopi Georgiades and Didier Raoult

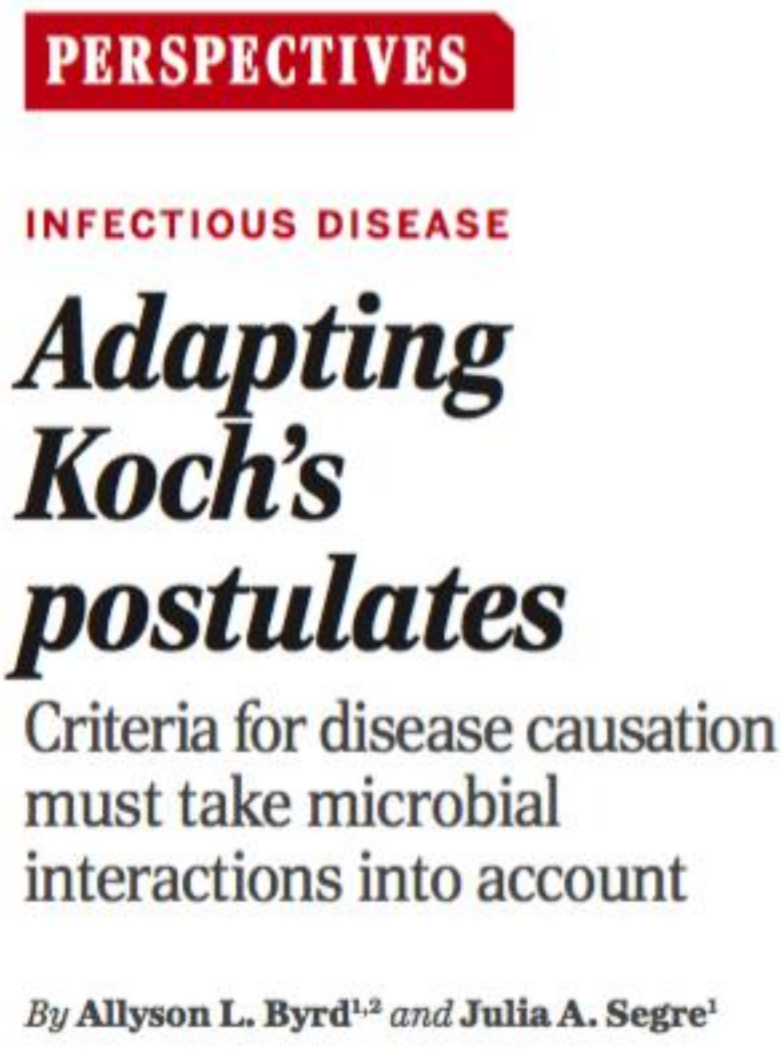


Patojen nedir?

Koch önermelerinin *evrimi*

2000’ler 2016

Byrd & Segre
(2016)



PERSPECTIVES

INFECTIOUS DISEASE

Adapting Koch’s postulates

Criteria for disease causation must take microbial interactions into account

By **Allyson L. Byrd**[1,2] *and* **Julia A. Segre**[1]

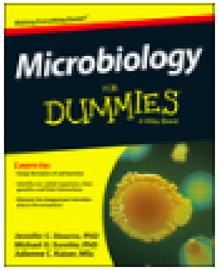
Allyson L. Byrd and Julia A. Segre (January 14, 2016) *Science* **351** (6270), 224-226. [doi: 10.1126/science.aad6753]

Byrd-Serge ölçütleri

- Örnekteki mikrop topluluğunu dizileme yoluyla tanımla
- Biyoinformatik modelleri kullanarak olası patojen(ler)i belirle
- Belirlenen patojenleri (kültürde) soyutla
- Soyutlanan köken(ler)i türün bilinen diğer üyeleri ile birlikte hastalık modelinde test et.

Allyson L. Byrd and Julia A. Segre (January 14, 2016) *Science* **351** (6270), 224-226. [doi: 10.1126/science.aad6753]

THE FUTURE OF MICROBIOLOGY



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Microbiology For Dummies

By **Jennifer Stearns, Michael Surette**

Today is perhaps the best time in history to be a microbiologist! The development of new experimental techniques and ability to sequence organisms without actually culturing them in the laboratory first has revealed diversity and complexity in the microbial world not previously known.

REMEMBER

Most microorganisms can't be grown in the lab, so they were previously unknown before the development of DNA sequencing techniques. Exploiting this microbial biodiversity for drug discovery and biotechnology applications is an exciting area of research.