

Infectieziekten en het microbioom

Joost Wiersinga, MD, PhD, MBA

12de Nationale Symposium Zoönosen

RIVM, Bilthoven, 11 December 2018



Rijksinstituut voor Volksgezondheid
en Milieu
*Ministerie van Volksgezondheid,
Welzijn en Sport*



Microbiota Center Amsterdam



Disclosures

Received funding from:

- Netherlands Organisation for Scientific Research (NWO)
- Netherlands Organisation for Health Research and Development (ZonMW)
- Academic Medical Center, Amsterdam
- European Union H2020 programme

COMMENTAAR

Het microbioom: hype of écht belangrijk?

Vanessa C. Harris en W.J. (Joost) Wiersinga

ntv^g

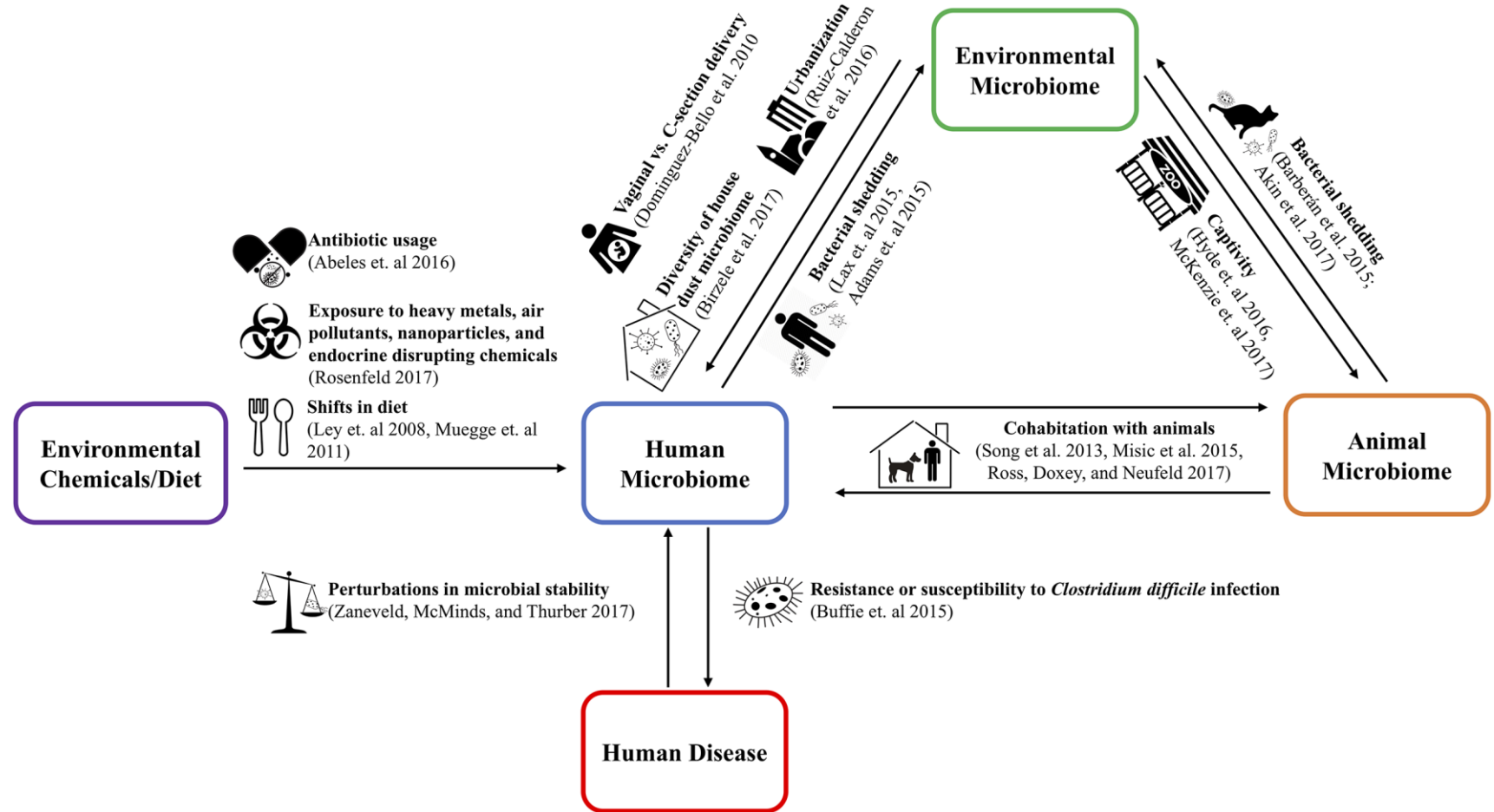
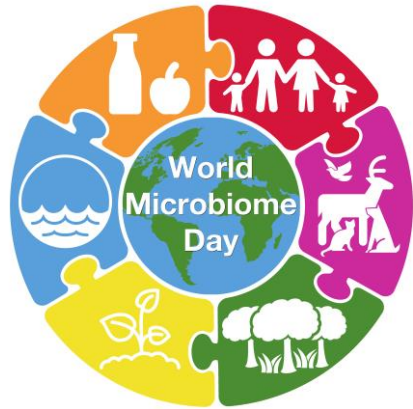
Nederlands
Tijdschrift
voor
Geneeskunde



Infectieziekten en het microbioom

- Intro: samenstelling en verandering van het darm microbioom
- Voorbeelden:
 - Invloed van antibiotica
 - Rol microbioom bij vaccinaties
 - Communicatie tussen darm en long bij pneumonie en sepsis
- Therapeutische manipulatie van de darmflora

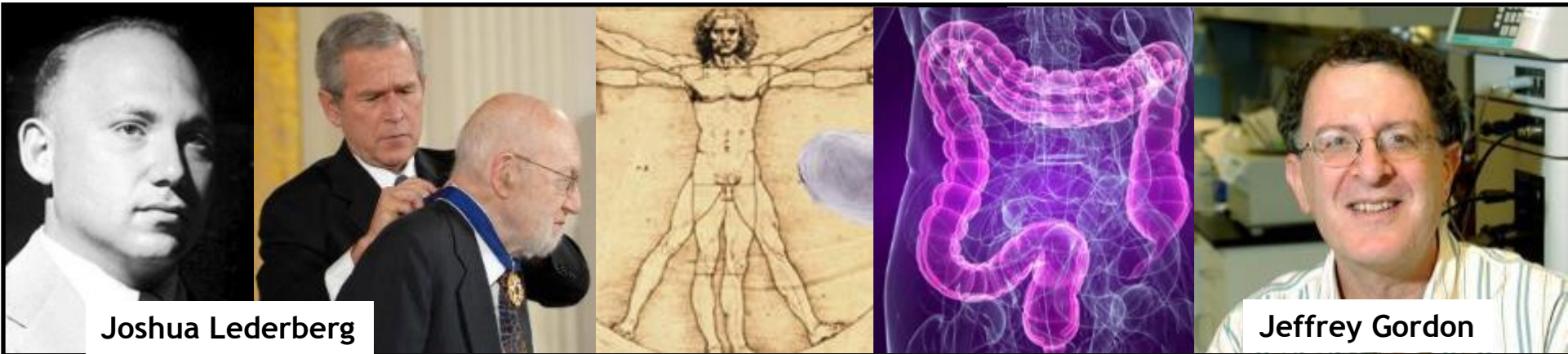
One Health Relationships Between Human, Animal, and Environmental Microbiomes





De mens als een ‘supra-organisme’

- Joshua Lederberg, nobelprijs geneeskunde 1958, introduceert de term “microbioom” en ziet de mens als de samenstelling van meerdere species
- Microbiota = een gemeenschap van micro-organismen in het lichaam, bv. de darmflora
- Microbioom = het gemeenschappelijke genetische materiaal (genoom) van een microbiota, is 100 maal groter dan menselijk genoom!



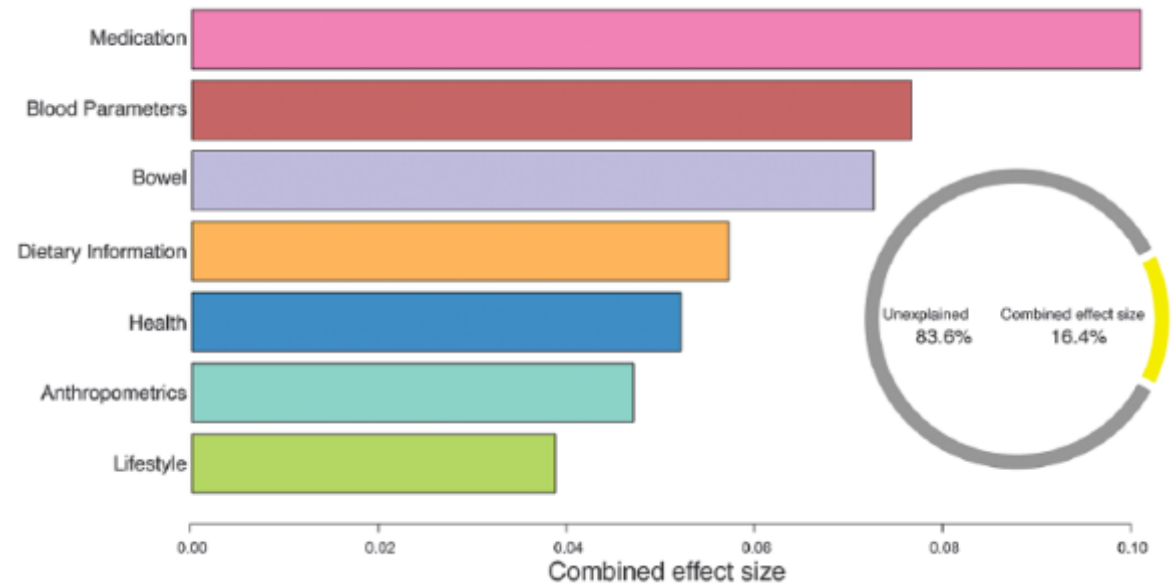
Hoe ziet het normale microbioom eruit? Als het bestaat.. En hoe wordt de samenstelling ervan beïnvloedt?

MICROBIOME

Population-level analysis of gut microbiome variation

Gwen Falony,^{1,2*} Marie Joossens,^{1,2,3*} Sara Vieira-Silva,^{1,2*} Jun Wang,^{1,2*} Youssef Darzi,^{1,2,3} Karoline Faust,^{1,2,3} Alexander Kurilshikov,^{4,5} Marc Jan Bonder,⁶ Mireia Valles-Colomer,^{1,2} Doris Vandeputte,^{1,2,3} Raul Y. Tito,^{1,2,3} Samuel Chaffron,^{1,2,3} Leen Rymenans,^{1,2,3} Chloë Verspecht,^{1,2} Lise De Sutter,^{1,2,3} Gipsi Lima-Mendez,^{1,2} Kevin D'hoë,^{1,2,3} Karl Jonckheere,^{2,3} Daniel Homola,^{2,3} Roberto Garcia,^{2,3} Ettje F. Tigchelaar,^{6,7} Linda Eeckhaudt,^{2,3} Jingyuan Fu,^{6,8} Liesbet Henckaerts,^{1,9} Alexandra Zhernakova,^{6,7} Cisca Wijmenga,⁶ Jeroen Raes^{1,2,3} †

Fecal microbiome variation in the average, healthy population has remained under-investigated. Here, we analyzed two independent, extensively phenotyped cohorts: the Belgian Flemish Gut Flora Project (FGFP; discovery cohort; $N = 1106$) and the Dutch LifeLines-DEEP study (LLDeep; replication; $N = 1135$). Integration with global data sets (N combined = 3948) revealed a 14-genera core microbiota, but the 664 identified genera still underexplores total gut diversity. Sixty-nine clinical and questionnaire-based covariates were found associated to microbiota compositional variation with a 92% replication rate. Stool consistency showed the largest effect size, whereas medication explained largest total variance and interacted with other covariate-microbiota associations. Early-life events such as birth mode were not reflected in adult microbiota composition. Finally, we found that proposed disease marker genera associated to host covariates, urging inclusion of the latter in study design.



Samenstelling van de darmmicrobiota

- Foetuses *in utero* zijn steriel, ontwikkeling fingerprint in eerste 2 jaar (40-50% via ouders, rest lifestyle).
- Volwassen darmmicrobiota: $\sim 10^{14}$ microorganismen (95% bacteriën)
- Compositie van darmmicrobiota ook afhankelijk van anatomie en leeftijd
- ~ 1000 verschillende bacterie soorten, dominerende phyla:

Phylum	Characteristics	Examples
<u>Firmicutes</u>	Gram-positive; diverse in their morphology (rod, coccoid, spiral), physiology (anaerobic, aerobic); include commensal and beneficial bacteria	<i>Lactobacillus</i> , <i>Ruminococcus</i> , <i>Clostridium</i> , <i>Staphylococcus</i> , <i>Enterococcus</i> , <i>Faecalibacterium</i>
<u>Bacteroidetes</u>	Gram-negative; composed of 3 large classes widely distributed in the environment, including soil, seawater, and guts of animals	<i>Bacteroides</i> , <i>Prevotella</i>
Proteobacteria	Gram-negative; include a wide variety of pathogens	<i>Escherichia</i> ; <i>Pseudomonas</i>
<u>Actinobacteria</u>	Gram-positive; diverse morphology; major antibiotic producers in the pharmaceutical industry	<i>Bifidobacterium</i> ; <i>Streptomyces</i> , <i>Nocardia</i>



De darmmicrobiota als orgaan: functies

- **Metabolisme**
 - Omzetting onverteerbare voedingsstoffen
 - Synthese van vitamines en co-factoren
- **Ontwikkeling van het immuunsysteem**
- **Afweer tegen pathogenen**
 - Competitie om ruimte en voedingsstoffen
 - Productie van bacteriocines
 - Stimuleren productie van antimicrobiële peptides
 - ‘Priming’ van systemische afweercellen

Invloed van antibiotica?





“Each generation could be beginning life with a smaller endowment of ancient microbes than the last.”



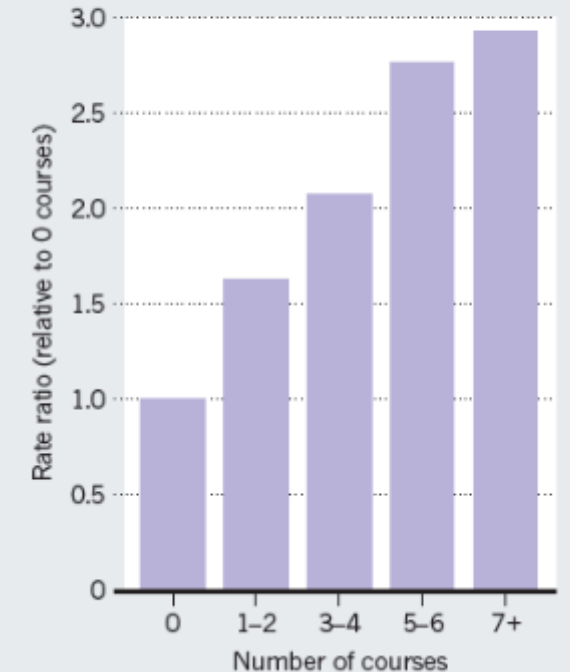
Dosed up: could excessive prescription of antibiotics be hampering children's ability to fight disease?

Stop the killing of beneficial bacteria

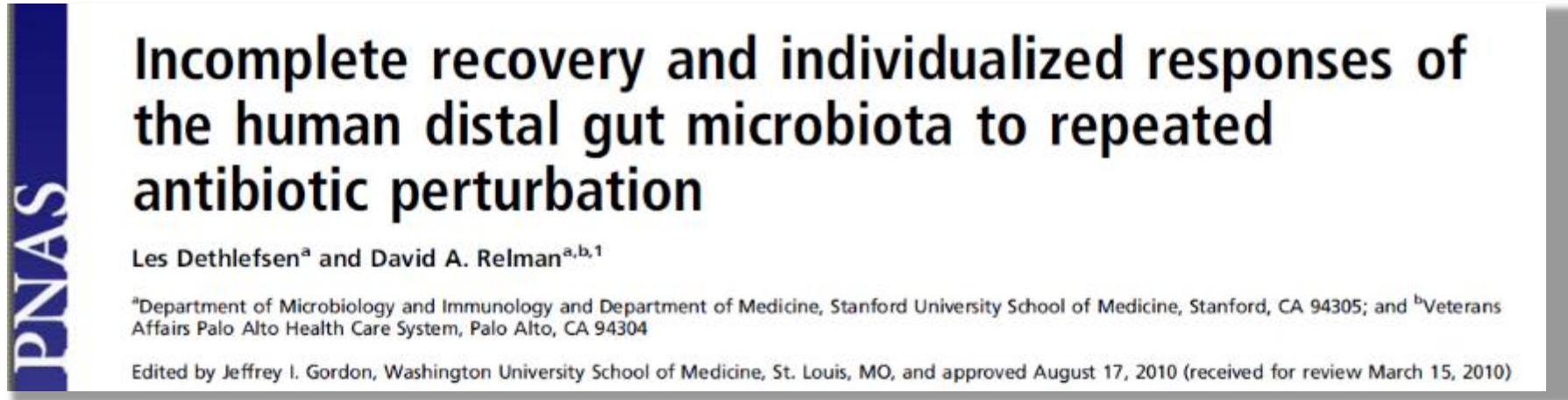
Concerns about antibiotics focus on bacterial resistance — but permanent changes to our protective flora could have more serious consequences, says **Martin Blaser**.

TROUBLING CORRELATION

The risk of inflammatory bowel diseases in children rises with the number of courses of antibiotics taken.



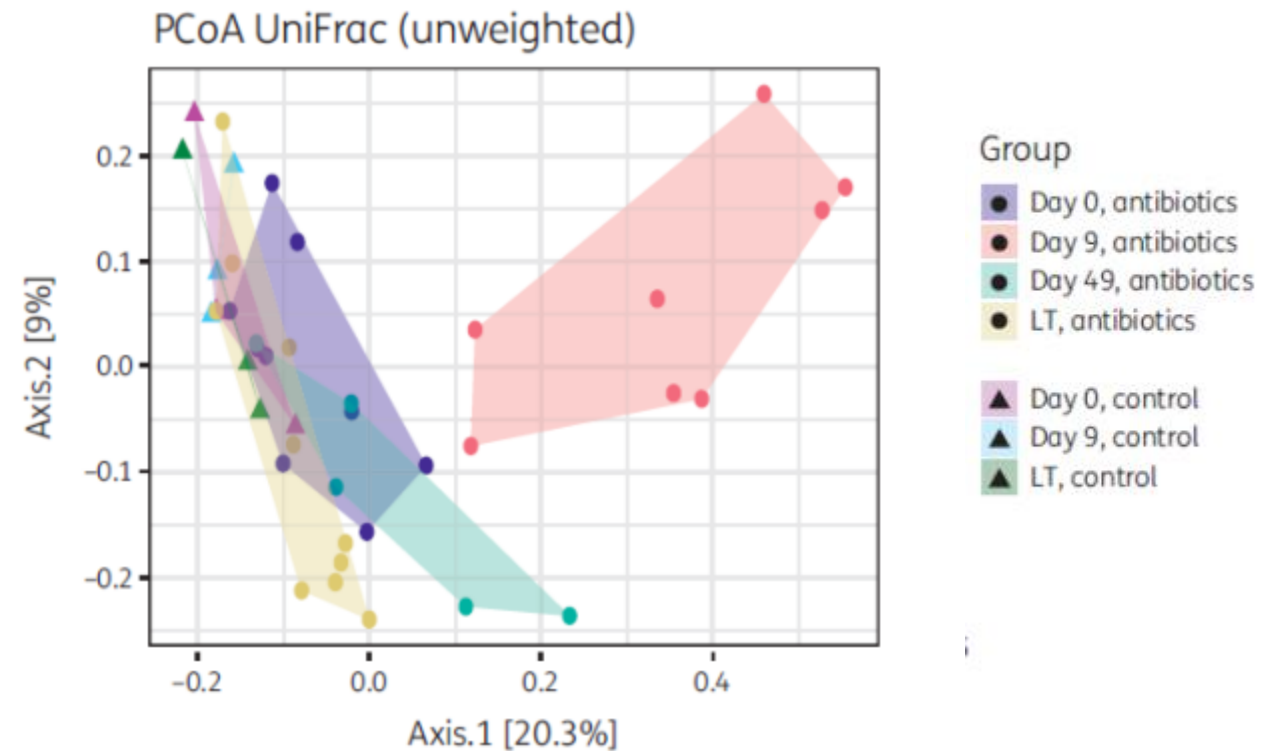
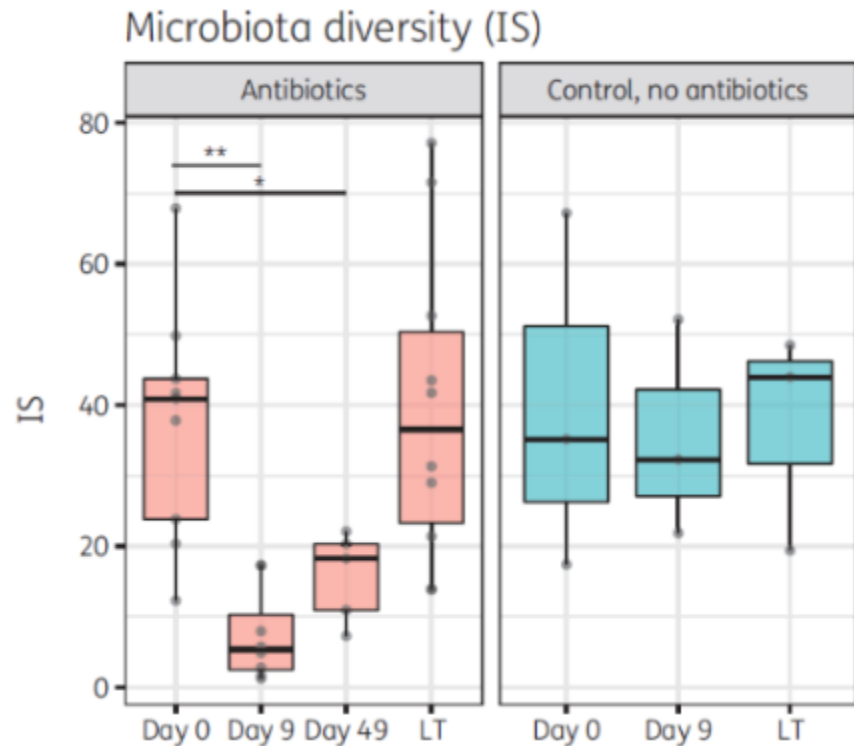
De invloed van antibiotica



- Een eenvoudige antibioticumkuur verandert de menselijke darmmicrobiota snel en drastisch. Duurt maanden voordat darmmicrobiota zich herstelt.
- Ook bacteriesoorten die niet intrinsiek gevoelig zijn voor het voorgeschreven antibioticum kunnen door onderlinge afhankelijkheid worden weggevaagd. Vancomycine bijvoorbeeld doet ook Gram-negatieve stammen verdwijnen.

Long-term impact of oral vancomycin, ciprofloxacin and metronidazole on the gut microbiota in healthy humans

Bastiaan W. Haak ^{1*}, Jacqueline M. Lankelma¹, Floor Hugenholtz¹, Clara Belzer²,
Willem M. de Vos³ and W. Joost Wiersinga^{1,4}



Rol microbioom bij vaccinaties?



Microbiota: een 'natuurlijk' vaccin adjuvans?

Immunity

Article

CellPress

TLR5-Mediated Sensing of Gut Microbiota Is Necessary for Antibody Responses to Seasonal Influenza Vaccination

Jason Z. Oh,^{1,2} Rajesh Ravindran,^{1,2} Benoit Chassaing,⁴ Frederic A. Carvalho,^{4,5} Mohan S. Maddur,^{1,2} Maureen Bower,⁶

Significant Correlation Between the Infant Gut Microbiome and Rotavirus Vaccine Response in Rural Ghana



Vanessa C. Harris,^{1,2} George Armah,⁵ Susana Fuentes,³ Katri E. Korpela,⁶ Umesh Parashar,⁷ John C. Victor,⁸ Jacqueline Tate,⁷ Carolina de Weerth,⁴ Carlo Giaquinto,⁹ Willem Joost Wiersinga,² Kristen D. C. Lewis,^{2,a} and Willem M. de Vos^{3,6}

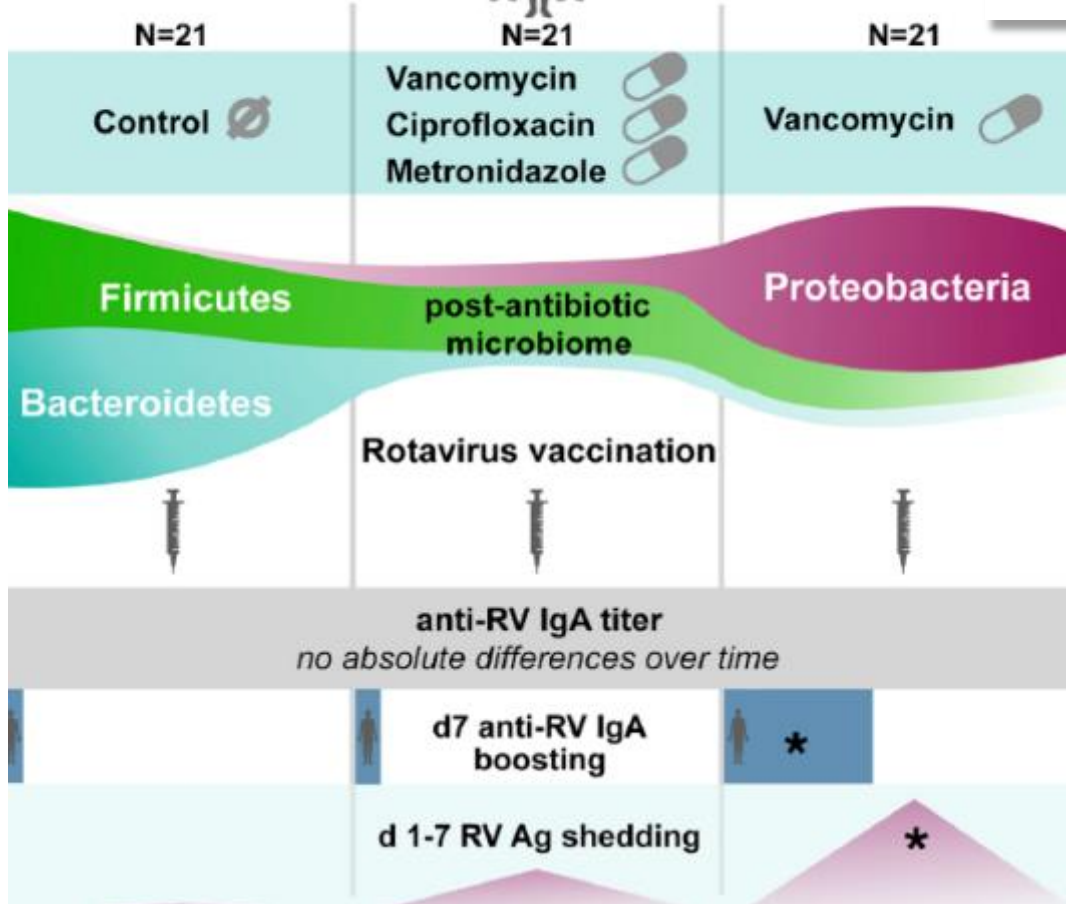
BRIEF REPORT

OPEN ACCESS

Check for updates

Rotavirus vaccine response correlates with the infant gut microbiota composition in Pakistan

Vanessa Harris ^{a,b}, Asad Ali^c, Susana Fuentes^c, Katri Korpela^{d,e}, Momin Kazi^c, Jacqueline Tate^f, Umesh Parashar^f, W. Joost Wiersinga^b, Carlo Giaquinto^g, Carolina de Weerth^h, and Willem M. de Vos ^{d,e}

Adult randomized
control trial

Effect of Antibiotic-Mediated Microbiome Modulation on Rotavirus Vaccine Immunogenicity: A Human, Randomized-Control Proof-of-Concept Trial

Vanessa C. Harris, Bastiaan W. Haak,
Scott A. Handley, ...,
Ester M.M. van Leeuwen,
Michael Boele van Hensbroek,
Willem Joost Wiersinga

In Brief

Rotavirus vaccines (RVV) are less effective in poor-resourced settings. This randomized-controlled trial in adults tested the effect of microbiome modulation via broad-spectrum, narrow-spectrum, or no antibiotics on RVV performance. Absolute anti-RV IgA titer did not change. However, antibiotics resulted in higher day-7 boosting and increased RV-antigen shedding.

Rol voor microbioom bij pneumonie en sepsis?



Samenstelling van het microbioom tijdens sepsis

Membership and Behavior of Ultra-Low-Diversity Pathogen Communities Present in the Gut of Humans during Prolonged Critical Illness

Alexander Zaborin,^a Daniel Smith,^{b*} Kevin Garfield,^c John Quensen,^c Baddr Shakhsheer,^a Matthew Kade,^a Matthew Tirrell,^a James Tiedje,^c Jack A. Gilbert,^{a,b} Olga Zaborina,^a John C. Alverdy^a

ORIGINAL

Critically ill patients demonstrate large interpersonal variation in intestinal microbiota dysregulation: a pilot study

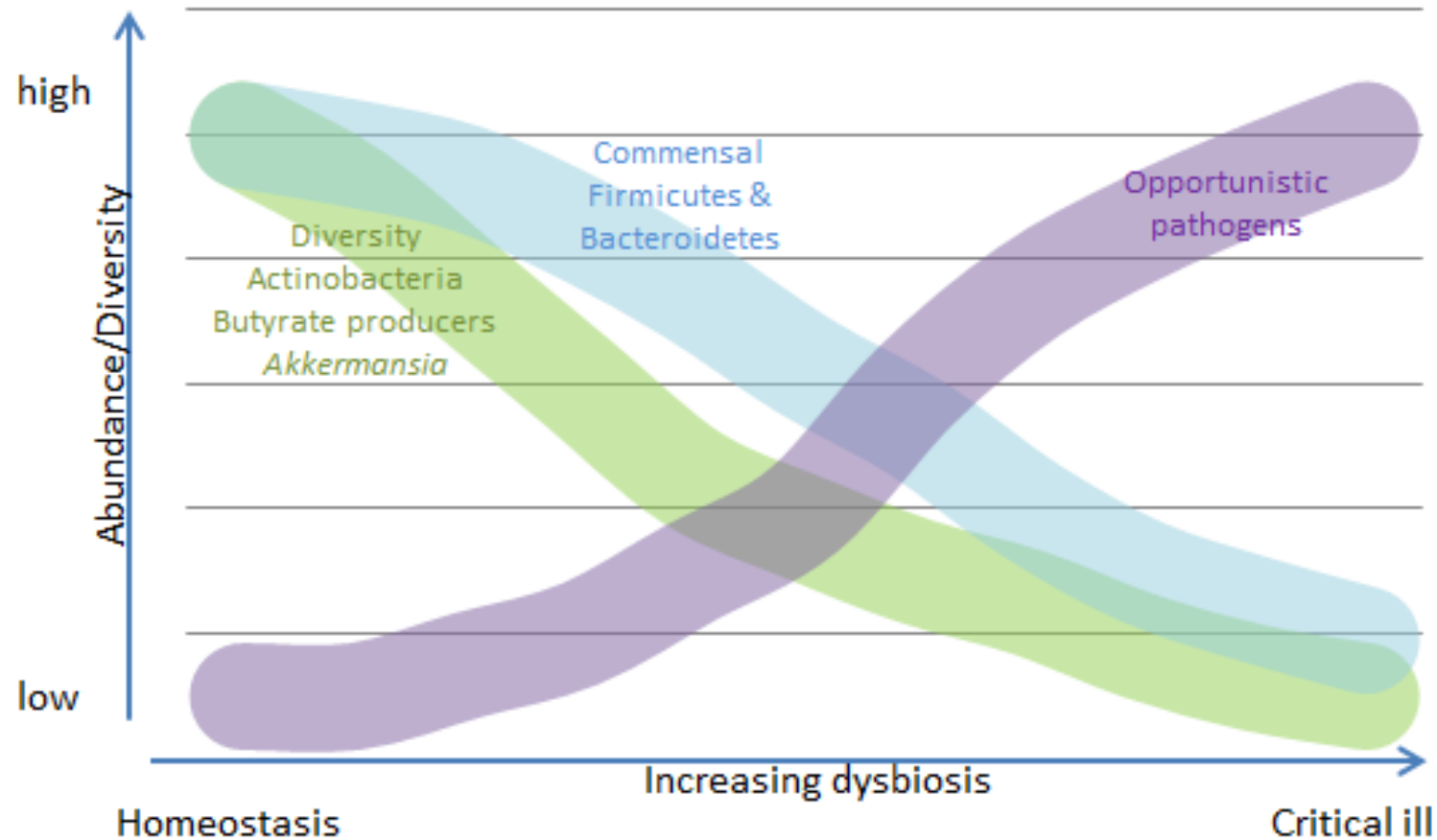


Jacqueline M. Lankelma^{1*}, Lonneke A. van Vught¹, Clara Belzer², Marcus J. Schultz³, Tom van der Poll^{1,4}, Willem M. de Vos^{2,5} and W. Joost Wiersinga^{1,4}

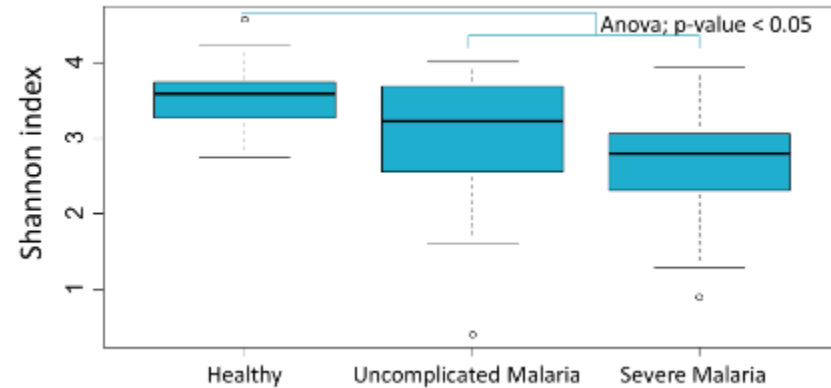
Extreme Dysbiosis of the Microbiome in Critical Illness

Daniel McDonald,^a Gail Ackermann,^a Ludmila Khailova,^b Christine Baird,^b Daren Heyland,^c Rosemary Kozar,^d Margot Lemieux,^c Karrie Derenski,^e Judy King,^f Christine Vis-Kampen,^f Rob Knight,^a Paul E. Wischmeyer^b

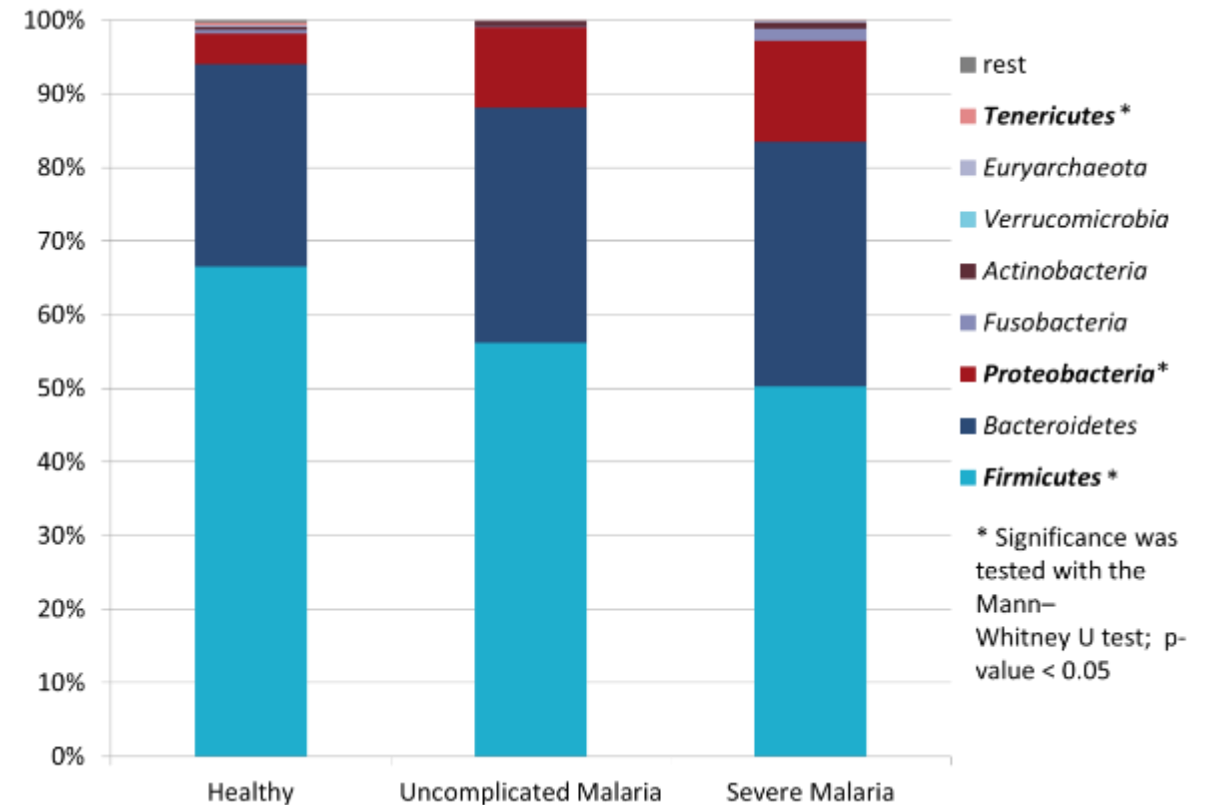
Het microbioom tijdens sepsis: verlies van diversiteit en overgroei van opportunistische pathogenen



Compositie van het darm microbioom en ernst van ziekte in patiënten met malaria



- Relative abundance of Firmicutes decreases and Proteobacteria increases in patients with malaria (n=86)



Wat zijn de oorzaken van deze totale ontregeling van het microbioom bij sepsis?



Causes and consequences of microbiota disruption in sepsis

Dysbiosis in sepsis linked to AKI, ARDS, encephalopathy and muscle weakness

Endogenous modulators of the gut microbiota during sepsis

Increased production of opioids

Decreased bile-salt concentration

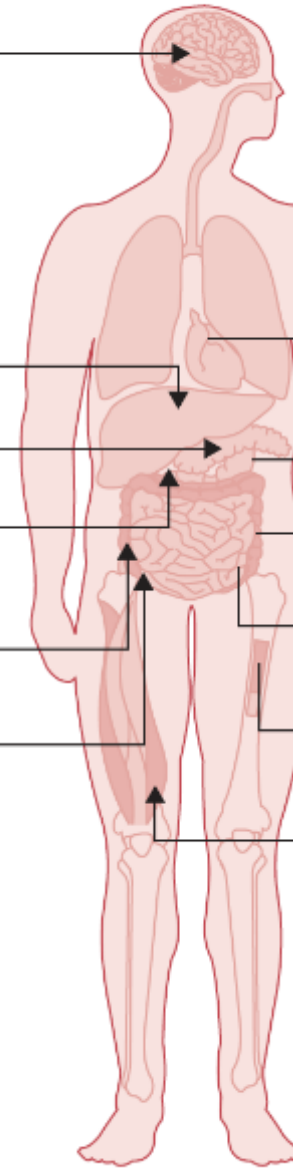
Gastrointestinal dysmotility

Increased production of catecholamines

Loss of epithelial integrity in the intestine

External modulators of the gut microbiota during clinical sepsis care

Antibiotics
SOD/SDD
Gastric-acid inhibition
Enteral/parenteral feeding
Sedatives
Opioids
Catecholamines



Potential consequences of dysbiosis during sepsis

Decreased systemic SCFA levels

Potentially increased risk of acute kidney injury

Increased microbial virulence

Bacterial translocation in systemic and lymphatic circulation

Reduced modulation of systemic immune responses

Potentially increased risk of sepsis-induced muscle wasting

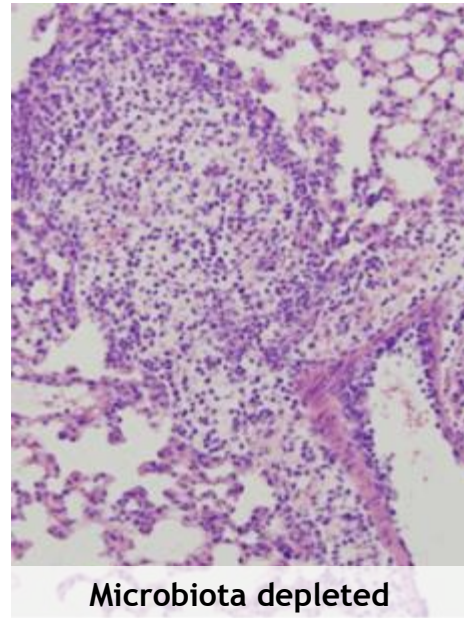
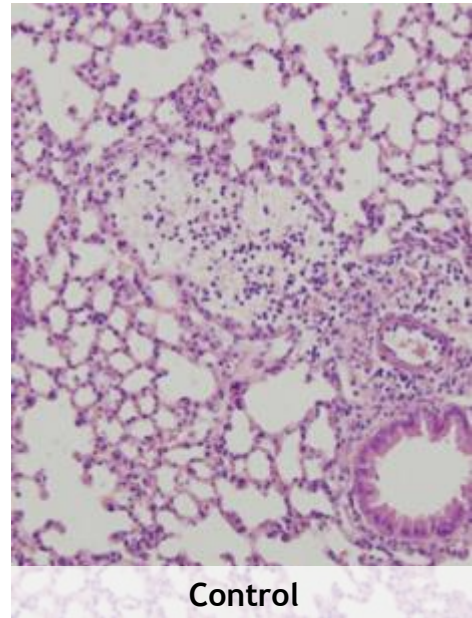
Wat is de functie van het darm microbioom tijdens sepsis? Bijvoorbeeld bij pneumosepsis?



The gut microbiota plays a protective role in the host defence against pneumococcal pneumonia

Tim J Schuijt,^{1,2,3} Jacqueline M Lankelma,¹ Brendon P Scicluna,¹
Felipe de Sousa e Melo,¹ Joris J T H Roelofs,⁴ J Daan de Boer,¹ Arjan J Hoogendijk,¹
Regina de Beer,¹ Alex de Vos,¹ Clara Belzer,⁵ Willem M de Vos,^{5,6}
Tom van der Poll,^{1,2} W Joost Wiersinga^{1,2}

LUNG PATHOLOGY



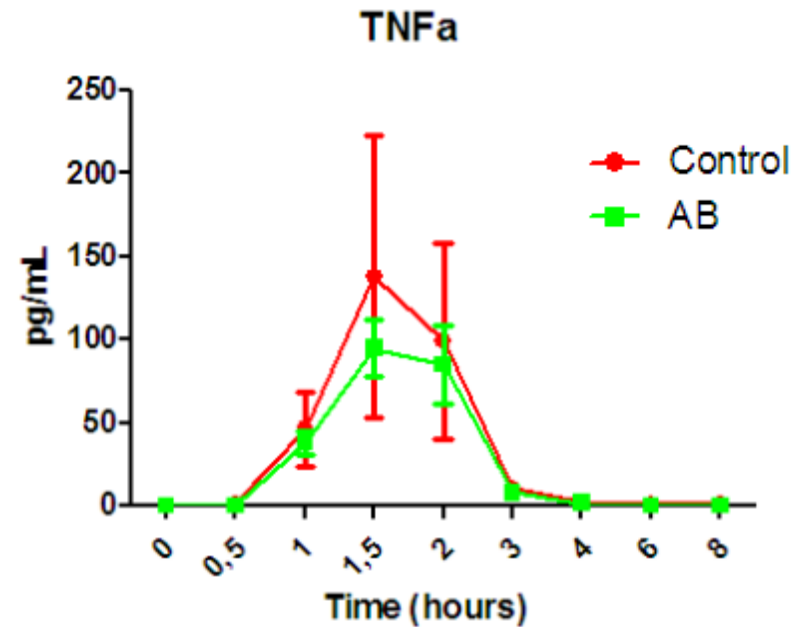
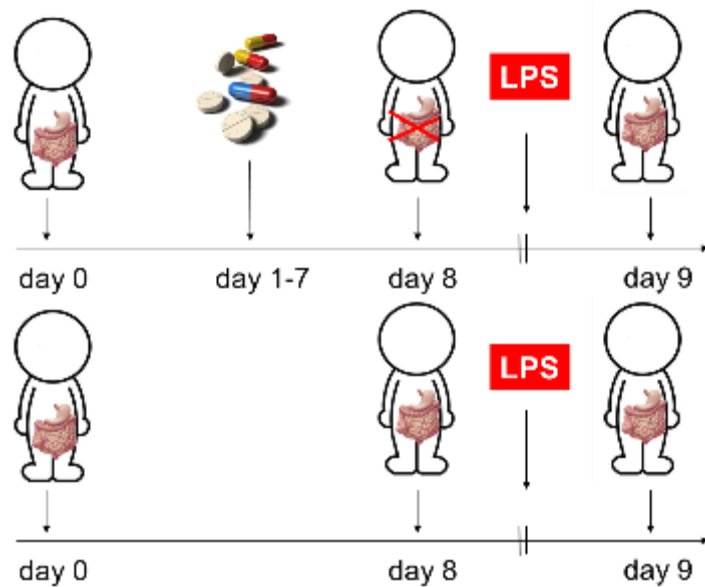
Maar is dit ook belangrijk bij mensen?



Antibiotic-induced gut microbiota disruption during human endotoxemia: a randomised controlled study

Jacqueline M Lankelma,¹ Duncan R Cranendonk,¹ Clara Belzer,² Alex F de Vos,¹ Willem M de Vos,^{2,3} Tom van der Poll,^{1,4} W Joost Wiersinga^{1,4}

ciprofloxacin, vancomycin
and metronidazole

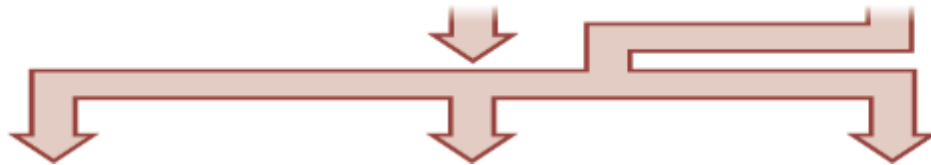


Therapeutische manipulatie van de microbiom



Therapeutische manipulatie

Gezonde darmflora Na antibiotica Woestijn met onkruid



Probiotica



Prebiotica



Bacteriotherapy/FMT



Wat zouden slimme microbiom geassocieerde interventies bij sepsis kunnen zijn?
Als preventie, tijdens sepsis en/of na sepsis?

Herstelde darmflora



A randomized synbiotic trial to prevent sepsis among infants in rural India

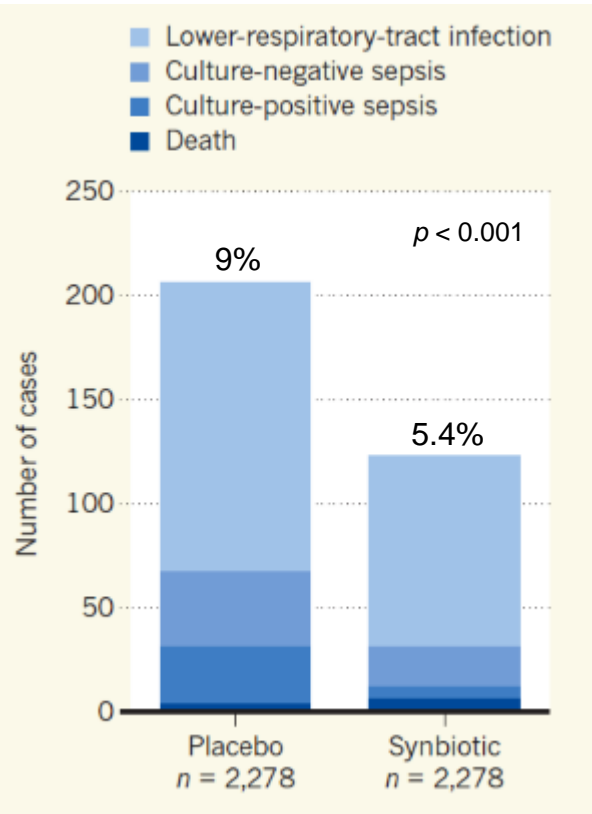
Pinaki Panigrahi^{1,2}, Sailajanandan Parida³, Nimai C. Nanda⁴, Radhanath Satpathy⁵, Lingaraj Pradhan⁶, Dinesh S. Chandel⁷, Lorena Baccaglini¹, Arjit Mohapatra⁵, Subhranshu S. Mohapatra⁵, Pravas R. Misra⁵, Rama Chaudhry⁸, Hegang H. Chen⁹, Judith A. Johnson¹⁰, J. Glenn Morris Jr¹⁰, Nigel Paneth¹¹ & Ira H. Gewolb¹²



- Double-blind, placebo-controlled RCT trial among 4556 infants: >2,000g at birth, >35 wks of gestation, no sepsis/comorbidity
- Intervention: oral *Lactobacillus plantarum* + fructooligosaccharide or placebo in first week of life
- Primary outcome: combination of sepsis + death in first 60 days of life
- Study terminated halfway to target enrolment size: interim results convincingly in favour of synbiotic preparation

A randomized synbiotic trial to prevent sepsis among infants in rural India

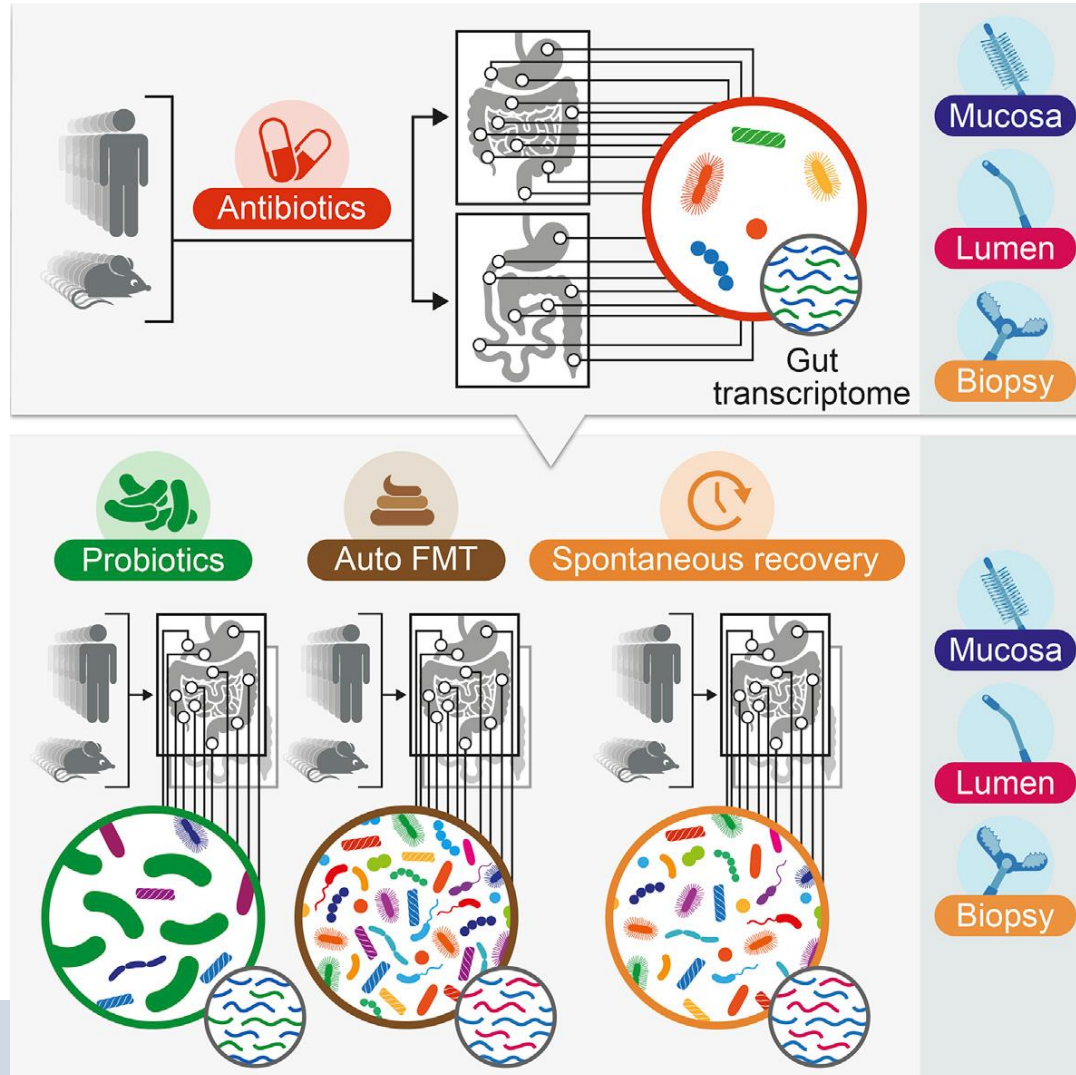
Pinaki Panigrahi^{1,2}, Sailajanandan Parida³, Nimai C. Nanda⁴, Radhanath Satpathy⁵, Lingaraj Pradhan⁶, Dinesh S. Chandel⁷, Lorena Baccaglioni¹, Arjit Mohapatra⁵, Subhranshu S. Mohapatra⁵, Pravas R. Misra⁵, Rama Chaudhry⁸, Hegang H. Chen⁹, Judith A. Johnson¹⁰, J. Glenn Morris Jr¹⁰, Nigel Paneth¹¹ & Ira H. Gewolb¹²



- Double-blind, placebo-controlled RCT trial among 4556 infants: >2,000g at birth, >35 wks of gestation, no sepsis/comorbidity
- Intervention: oral *Lactobacillus plantarum* + fructooligosaccharide or placebo in first week of life
- Primary outcome: combination of sepsis + death in first 60 days of life
- Study terminated halfway to target enrolment size: interim results convincingly in favour of synbiotic preparation
- The week-long treatment costs US\$1 with a NNT of 27: the investment needed to prevent one sepsis case is about \$27

Post-Antibiotic Gut Mucosal Microbiome Reconstitution Is Impaired by Probiotics and Improved by Autologous FMT

Cell



Authors

Jotham Suez, Niv Zmora,
Gili Zilberman-Schapira, ...,
Zamir Halpern, Eran Segal, Eran Elinav

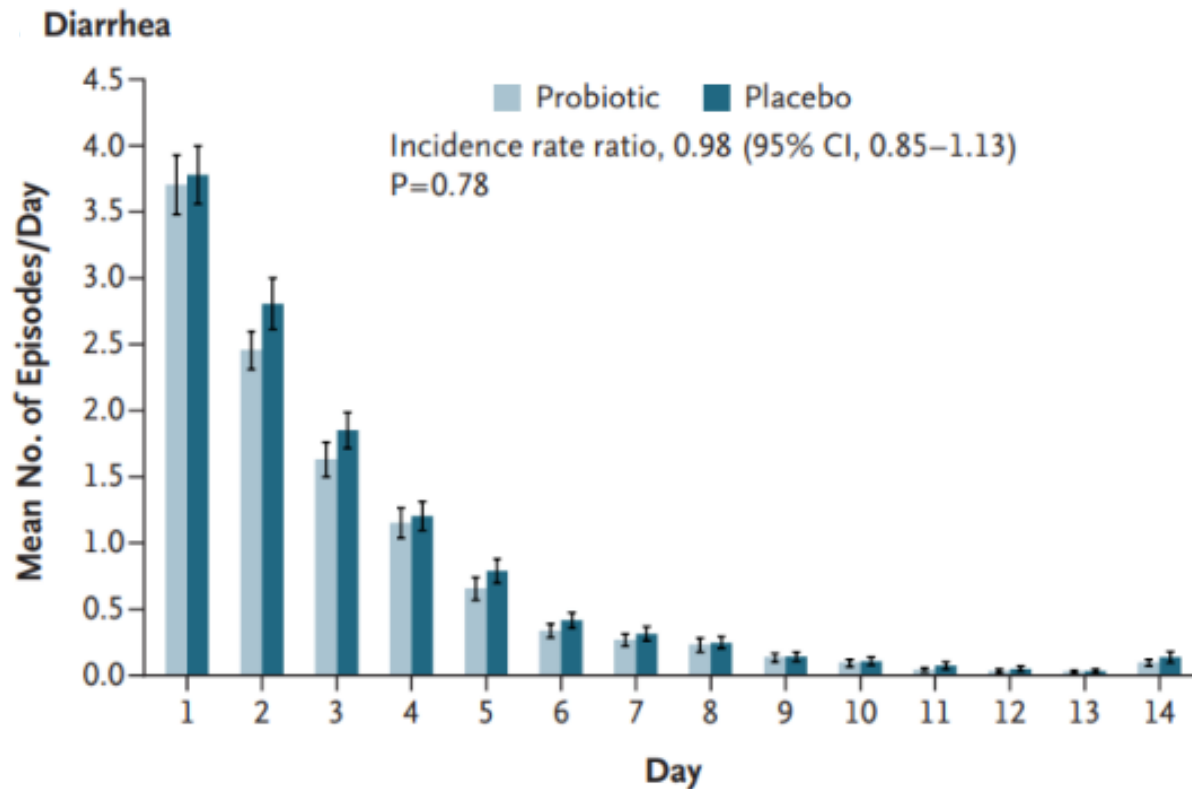
Probiotics perturb rather than aid in microbiota recovery back to baseline after antibiotic treatment in humans.

NEW

ORIGINAL ARTICLE

Multicenter Trial of a Combination Probiotic for Children with Gastroenteritis

Stephen B. Freedman, M.D.C.M., Sarah Williamson-Urquhart, B.Sc.Kin.,



- ✓ N = 886 children 3 to 48 months of age with gastroenteritis in Canada
- ✓ Intervention: 5-day course of probiotics (*Lactobacillus rhamnosus* R0011 and *L. helveticus* R0052, 4.0×10^9 CFU twice daily) or placebo

Fecal Microbiota Transplantation for sepsis?

Harnessing the microbiome in sepsis: during sepsis



Therapeutic Modulation and Reestablishment of the Intestinal Microbiota With Fecal Microbiota Transplantation Resolves Sepsis and Diarrhea in a Patient

Qirong Li, MD, PhD¹, Chenyang Wang, MA¹, Chun Tang, BA¹, Qin He, MA¹, Xiaofan Zhao, BA¹, Ning Li, MD¹ and Jieshou Li, MD¹

RESEARCH

Open Access

Successful treatment of severe sepsis and diarrhea after vagotomy utilizing fecal microbiota transplantation: a case report

Qirong Li^{*}, Chenyang Wang, Chun Tang, Qin He, Xiaofan Zhao, Ning Li and Jieshou Li^{*}

Critical Care

RESEARCH

Open Access

Successful treatment with fecal microbiota transplantation in patients with multiple organ dysfunction syndrome and diarrhea following severe sepsis



Yanling Wei, Jun Yang, Jun Wang, Yang Yang, Juan Huang, Hao Gong, Hongli Cui^{*} and Dongfeng Chen^{*}

FMT for *Clostridium difficile*: future perspective

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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.

LETTER

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. Stein³, Peter T. McKenney^{1,2}, Lilan Ling², Asia Gobourne², Daniel No², Hui Liu⁵,
Melissa Kinnebrew^{1,2}, Agnes Viale⁶, Eric Littmann², Marcel R. M. van den Brink^{7,8}, Robert R. Jenq⁷, Ying Taur^{1,2}, Chris Sander³,
Justin R. Cross⁵, Nora C. Toussaint^{2,3}, Joao B. Xavier^{2,3} & Eric G. Pamer^{1,2,8}

Preliminary Communication

Oral, Capsulized, Frozen Fecal Microbiota Transplantation for Relapsing *Clostridium difficile* Infection

Ilan Youngster, MD, MMSc; George H. Russell, MD, MSc; Christina Pindar, BA; Tomer Ziv-Baran, PhD;
Jenny Sauk, MD; Elizabeth L. Hohmann, MD

Infection Control in the Multidrug-Resistant Era: Tending the Human Microbiome

Pritish K. Tosh^{1,2} and L. Clifford McDonald²

¹Epidemic Intelligence Service, and ²Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia

- Idea: intact communities of commensals prevent colonisation with MDROs
- Limitations of current MDRO control strategies
 - Vicious circle: antibiotics exert tremendous collateral damage to the microbiome, MDROs are treated with ever-more broad spectrum antibiotics
- Strategies to harness the human microbiome to reduced colonisation by MDRO
 - Refocus stewardship efforts on reducing impact on microbiome
 - Develop more microbiome-sparing antimicrobial therapy
 - **Restore the microbiome, e.g. use “microbiome auto-banking and transplantation”**



Take home: Infectieziekten en het microbioom

Het microbioom is integraal onderdeel van menselijke lichaam met zowel lokale als systemisch effecten

Voorbeelden: Potentiële lange termijn bijwerkingen van antibiotica
 Mogelijke invloed van het microbioom op de effectiviteit van vaccins
 Beschermende rol van het microbioom in pneumonie en sepsis

Beperkingen:

Bij ongeveer elke ziekte wordt het microbioom onderzocht, maar associatie \neq causaliteit

Muis \neq mens..

Naast darm microbioom, ook long, huid etc. microbioom...

Niet alleen bacteriën, maar ook virussen, schimmels...

Thank you!



People always ask me about the microbiome, It's fantastic. Let me tell you about the microbiome. I do very well with microbes. I love the microbiome. No one loves the microbiome more than me, BELIEVE ME. The microbiome loves me. We're going to have so many microbiomes you are going to get sick of microbiomes. The microbiome just got 10 feet higher. I have the best microbiome!

