1. Microbiome is essential.
   1. Useful
      1. indigestible parts 🡪digestable
   2. Protection
      1. Colonization is harmless
      2. Dual nature of pathogens.
      3. “the community of indigenous microbes forms an ecological barrier that prevents the ingress of pathogenic microorganisms.” (3)
      4. “Colonization resistance” (3)
      5. “top-down selection pressure, subdue microbial competition to promote microbes that benefit the host. the adaptive immune system has specifically evolved invertebrates to regulate and maintain beneficial microbial communities.” (5)
      6. Back up plans/diversity are important.
      7. “novel benefits by functioning as the third major genome in mammals along with the nuclear and mitochondrial genomes.” (4)
   3. Microbial genome > human genome (1)
      1. “an essential but largely ignored overlay” (2)
      2. “The inability of organisms to survive independently (GI microbiota) or to maintain normal health (mammalian hosts) is a strong indication of coevolved mutualism.” (4)
   4. Transition: “significant inter-individual variation in the indigenous microbiota This variation likely arises from the accumulated effects of genetic and environmental influences on the gut microbial community” (3)
2. Microbiome is individual.
   1. Not individual/Based on Community
      1. “Humans and their collective microbiota are segmented into many local communities. metacommunity. Another level of metacommunity organization exists because individual humans belong to social groups that tend to share a similar microbiota” (6)
   2. Individual
      1. Microbial signature: variable depending on environment, but also returning to a certain equilibrium state
      2. “Although some of this variation can be explained by litter and cohort effects, individual host genotype had a measurable contribution” (5)
      3. “at the species and strain levels the microbiota of an individual can be as unique as a fingerprint” (6)
      4. “intrapersonal variation is lower than interpersonal variation, as determined by 16S rRNA gene sequencing” (5)
   3. Individual also by chance:
      1. “Not only selection on community-level traits but also competition within the community and chance colonization events affect the structure of the microbiota” (6)
   4. Transition
      1. “gut microbiota converge toward an adultlike profile during first year of life” (2)
      2. “In humans, this period of succession persists until 18–24mo of age, when the gut microbiota attains its “adult-like” composition and begins to behave as a highly individualized climax community” (5)
3. Microbiome can develop and be changed by many factors, including antibiotics.
   1. Stable community, up to a point
      1. “an individual’s gut microbiota can have a relatively stable community composition over a period of months to years. These observations have led to the conclusion that the community of microbes in the gut is relatively resistant to perturbation by various ecological stressors. Subsequent environmental influences, including diet, host genetics, medication use, and exposure to infectious agents, can all influence the resultant microbial community” (3)
   2. Other Factors
      1. Sanitation and modernization increases risk
      2. Permanent changes caused by C-sections
   3. Antibiotics
      1. “the gut microbial community exhibited resilience as the community structure shifted back toward the base-line state following cessation of the treatment. However, the ability of this community to recover following antibiotic disturbance was not absolute. The administration of cefoperazone also caused dramatic shifts in community structure, but in this case, diversity did not recover even 6 weeks after the discontinuation of the drug. revealed a persistent, significant decrease in overall species richness in the gut community.” (3)
      2. “Antibiotics can markedly affect the composition of the microbiota in the short term, with most (but not all) families and genera of gut micro organisms returning to typical levels within weeks of exposure. However, pathogens can exploit the reduced competitiveness of a community disturbed by antibiotics, thereby establishing themselves in the host” (6)
      3. “The ability of the gut microbial community to recover to baseline following the cessation of antibiotic administration differed according to the antibiotic regimen administered. Severe antibiotic pressure resulted in reproducible, long-lasting alterations in the gut microbial community, including a decrease in overall diversity.” (3)
   4. Why is this so bad?
      1. Relate to back up plan/diversity
      2. Venezuela case study from book.
      3. “Anti-biotic disturbance of the normal community structure of the microbiota may allow the germination of environmentally acquired spores, with subsequent overgrowth of the pathogen and toxin production.” (3)
4. Therefore, antibiotics should be used more carefully
   1. Prevent resistance
   2. Protect original/individual microbiome
5. Case Study: France’s Program
   1. “France was also identified as the country with the highest antibiotic consumption in Europe [12] and one of the highest antimicrobial users worldwide. Thus, the French government initiated a long-term nationwide campaign to reduce antibiotic overuse and control the dissemination of resistant bacteria in the community. The national program, named ‘‘Keep Antibiotics Working,’’ was launched in 2001, targeting both the general public and health care professionals, to encourage surveillance of antibiotic use and resistance and to promote better-targeted antibiotic use”
6. Results/Success from France’s program
   1. “Our data show that the primary objective of the French national campaign was largely achieved, with a 30.1% decrease in antibiotic use in children.” (7)
   2. Evidence of assumption/claim that antibiotics 🡪 resistance
      1. “some evidence that decreasing antibiotic use can lower MRP rates [8]” (7)
      2. when antibiotic exposure is reduced, antibiotic-susceptible strains recover a survival advantage and tend to once again become more-dominant human colonizers.” (8)
   3. Drawbacks/Limitations/Why we need alternatives
      1. Multifaceted approach: cannot declare which factor was most effective and “give” that factor to other nations/programs
      2. “the effect on antimicrobial resistance is still unclear and difficult to separate from the effect of the conjugate pneumococcal vaccine. “ (9)
7. Alternative Solutions + technology
   1. Narrow Focus Medications (genome analysis)
      1. “treatment caused minimal effects on both the bacterial abundance and composition of the gut microbiome illustrating that pathogen-selective antibiotics can be developed to minimize disturbances to the microbiome.” (10)
   2. Vaccines that select for resistant strains.
      1. How vaccines work now
         1. “Vaccines can reduce the prevalence of resistance by reducing the need for antimicrobial use and can reduce its impact by reducing the total number of cases.” (12)
         2. “amplified by the indirect protection, or herd immunity, that results when vaccinated individuals do not themselves become infected or colonized, and hence do not transmit the pathogen to others. In this way, infections, resistant infections, and antimicrobial use can be reduced not only in vaccinated individuals but also in their contacts” (12)
      2. How vaccines should be specialized to be narrow focused and more effective
         1. “Because much selection for resistance is due to selection on bystander members of the normal flora, vaccination can reduce pressure for resistance even in pathogens not included in the vaccine” (12)
         2. “antiresistance vaccines should be more effective against drug-resistant strains than against drug-susceptible strains, either by specifically targeting resistant alleles of a conserved protein or by targeting proteins uniquely present in resistant isolates” (12)
   3. Probiotics
      1. “Probiotics are live microorganisms that when administered in adequate numbers confer a health benefit on the host. “ (4)
      2. What is normal/how to tailor to the individual/challenges
         1. “One difficulty with studying these mechanisms in human subjects is the inherent baseline variability of the microbiota in different individuals.” (3)
         2. “the gut microbiota can now be viewed as an environmental factor that itself is controlled in part by host genetic factors and potentially by interactions between host and microbial genomes.” (5)
      3. Potential solutions/use of technology
         1. “given the myriad permutations of genetics, life histories, behaviors, environments, and exposures, an individual’s microbiome is an emergent property whereby a potentially limitless number of microbial community structures can be distilled into a finite number of types. Knowledge of the factors that affect one’s community type profile will be critical as they continue to be associated with predisposition to diseases.” (11)
         2. “even with the considerable intra- and inter-personal variation in the human microbiome, this variation can be partitioned into community types that are predictive of each other and are likely the result of life history characteristics.” (11)

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