Microbiota and Vaccines

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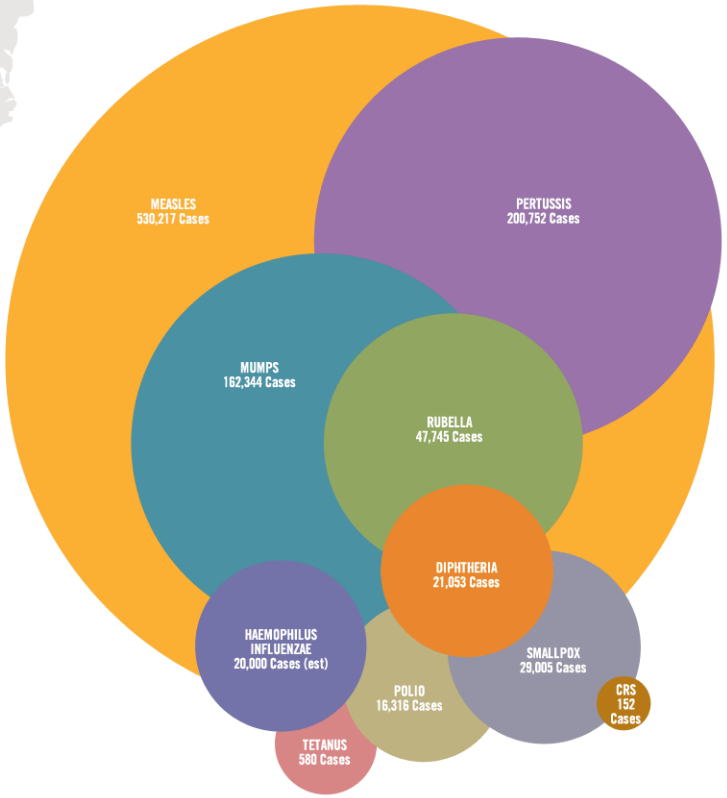
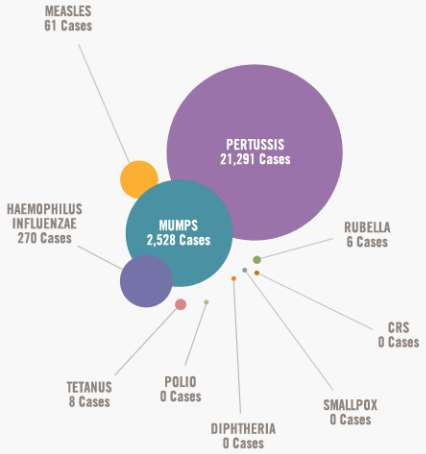
VACCINES WORK

These bubbles are sized according to the annual number of disease cases in the US during the 1900s versus 2010. We've come so far. It's a reminder that while disease rates are low, most diseases haven't disappeared. This is why we continue to vaccinate.

	THEN	NOW
SMALLPOX	29,005	0
DIPHTHERIA	21,053	0
PERTUSSIS	200,752	21,291
TETANUS	580	8
POLIO	16,316	0
MEASLES	530,217	61
MUMPS	162,344	2,528
RUBELLA	47,745	6
CRS	152	0
HAEMOPHILUS INFLUENZAE	20,000	270





[9] Centers for Disease Control and Prevention (CDC). Parents Guide to Childhood Immunizations. http://www.cdc.gov/vaccines/pubs/parents-guide/default.htm. Accessed August 15, 2011.
[10] CDC. Impact of Vaccines in the 20th & 21st Centuries. http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/G/impact-of-vaccines.pdf. Updated January 2011. Accessed August 15, 2011.

However there is a relative lack of licensed, effective oral vaccines which are able to give life-long protective immunity

Developing Oral Vaccines

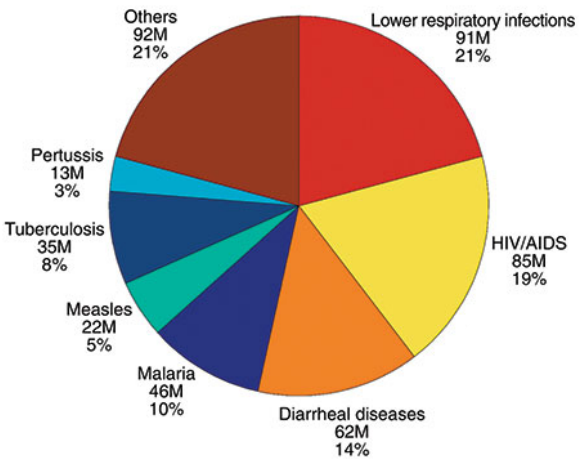
Diarrheal diseases caused by *Salmonella, E. coli, Shigella* etc. remain a significant worldwide health issue

Gold standard = development of a vaccine

Development of vaccines for mucosal pathogens has been a major challenge:

-> Poor understanding of the determinants of gut immunity

-> Vaccines have reduced efficacy and immunogenicity in developing countries (areas of poor sanitation)

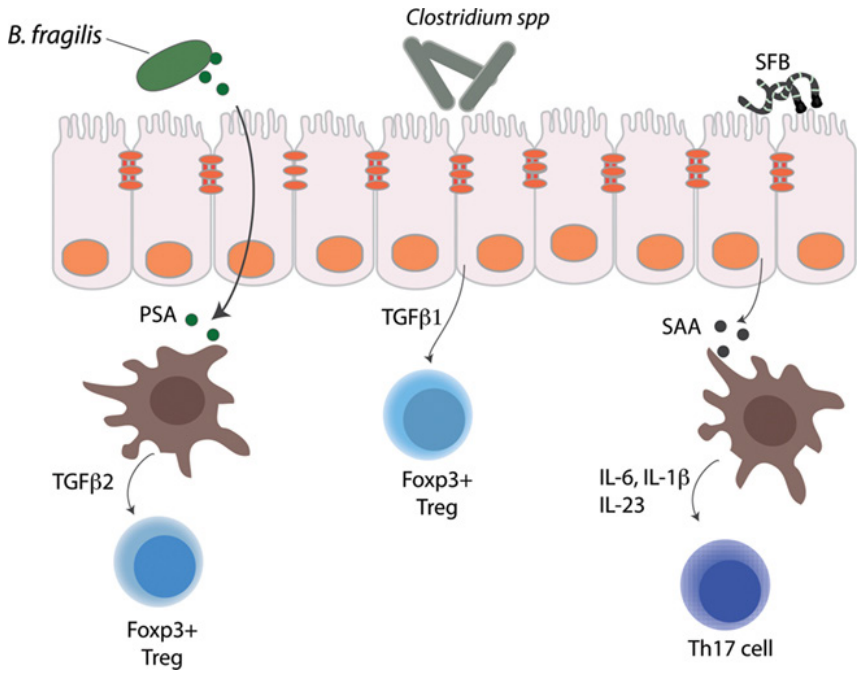


Disability Life Years

Microbial Links to the Immune System

Specific gut microbial species affect the immune system

A shift in the intestinal microbiota composition could alter the functioning and development of the immune system

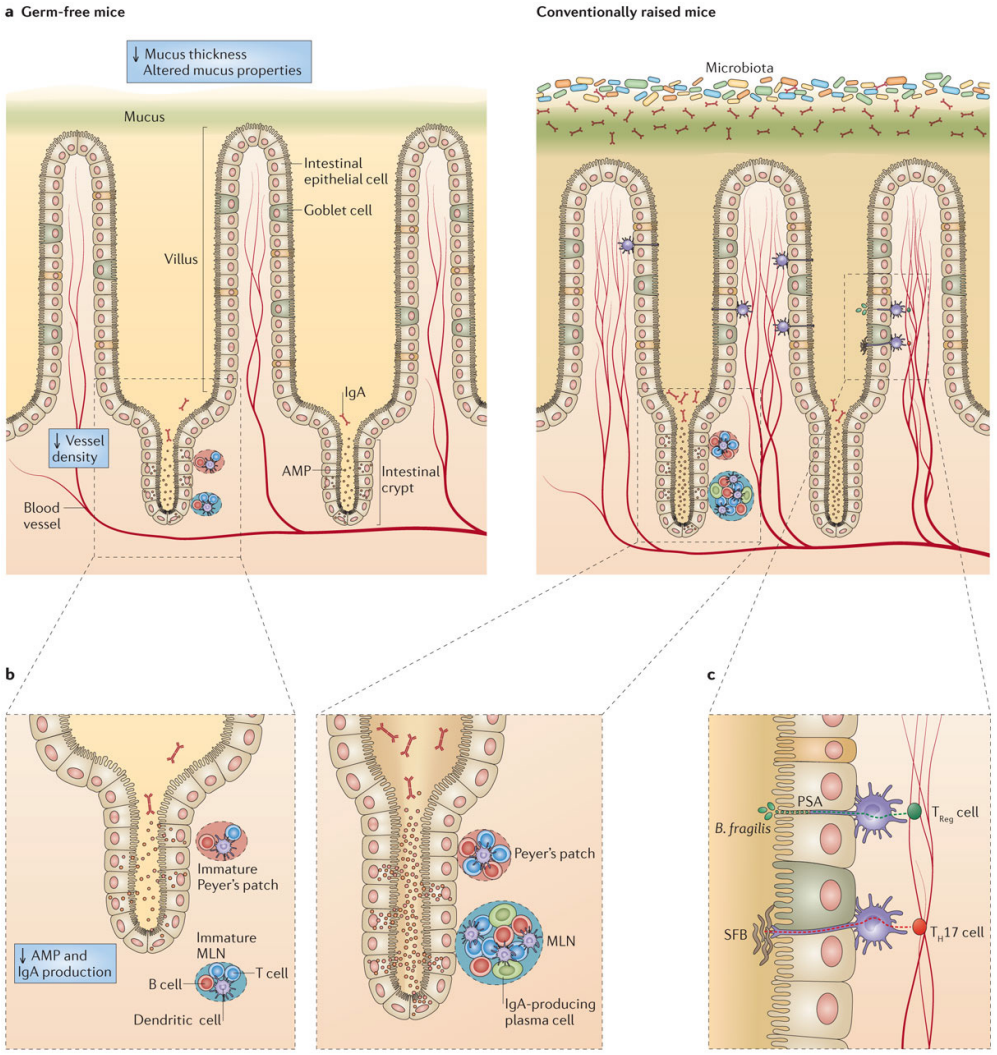


Smith and Garrett 2011 Front Microbiol 2: 1-6.

Presence of a complex, host-adapted microbiota, promotes development of the intestinal immune system

Germ-free mice immune system

- Reduced numbers and size of Peyer's patches
- Decreased lamina propria CD4+ T-cell numbers
- Reduced levels of the class-switched antibodies IgA and IgG
- Lack of a developed Gut-associated lymphoid tissue
- Don't develop tolerance



Sommer F. & Backhed F. 2013. Nat Rev Micro doi 10.1038/nrmicro2974

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PLoS PATHOGENS

Opinion

Should the Human Microbiome Be Considered When Developing Vaccines?

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Early days- not much data..

Could our newfound knowledge of the impacts of the gut microbiota be a missing link to improve oral vaccine efficacy and develop more effective oral vaccines?

Developing country vaccine responses less than in developed countries

- Many studies showing responses to polio, rotavirus (less than 50% efficacy vs 80-95%), cholera, dysentery, ETEC (worked in Americans, no protection in Egypt), and typhoid are less in developing countries
- Nicaraguan children have blunted antibody responses to oral cholera vaccine when compared to developed country (Sweden) (Hallander et al. 2002 Vaccine)
- Small intestinal bacterial overgrowth contributes to lower antibodies to cholera vaccine (MM Levine)

Blunted Vaccine Responses in Areas of Poor Sanitation

Many possible reasons, including:

- Increased antigen exposure
- Malnutrition
- Nutrient deficiency (eg. vitamin A, zinc)
- Antibiotics
- Breast milk antibodies
- Parasites

However, all these changes can feed into microbiota composition

Levine, MM 2010 BMC Biology

Microbiota is different in children from developed and developing countries

Could the microbiota be implicated in why vaccines show reduced efficacy in developing countries?

Diet and malnutrition can shift microbial assemblages

Filippo et al., 2010 PNAS 107: 14691-14696

Modulating the flora to enhance the adaptive immune response: the case for probiotic or prebiotic vaccine adjuvants

Study	Vaccine-used	Microbiota link
Fang, H et al., 2000	Oral Salmonella typhi vaccine	*Lactobacillus* intake modulated the humoral immune response and antibody titer
Isolauri, E et al.,1995	Oral Rotavirus	*Lactobacillus casei* intake correlated with improved immunogenicity of the rotavirus vaccine
Paineau, D et al.,2008	Oral Cholera vaccine	Seven probiotic strains of *Bifidobacterium* and *Lactobacillus* affect specific antibody response to vaccination, double blind study
Benyacoub J et al., 2008	Oral Salmonella vaccine	Fructooligosaccharide mix (FOS) enhances the *Salmonella* vaccine efficacy in mice
Vos et al., 2006	Influenza vaccine	FOS mix stimulates Delayed type hypersensitivity in murine vaccination model

Can we manipulate the microbiota to improve vaccine responses?

- Similarly, probiotics have been shown to increase responses to parenteral vaccines diphtheria, tetanus, hepatitis B
- Particularly important early in life (c-section/formula feeding can decrease probiotic microbiota constituents)
- No long term follow up studies
- Studies show variable effectiveness
- Mechanisms unclear

Needs

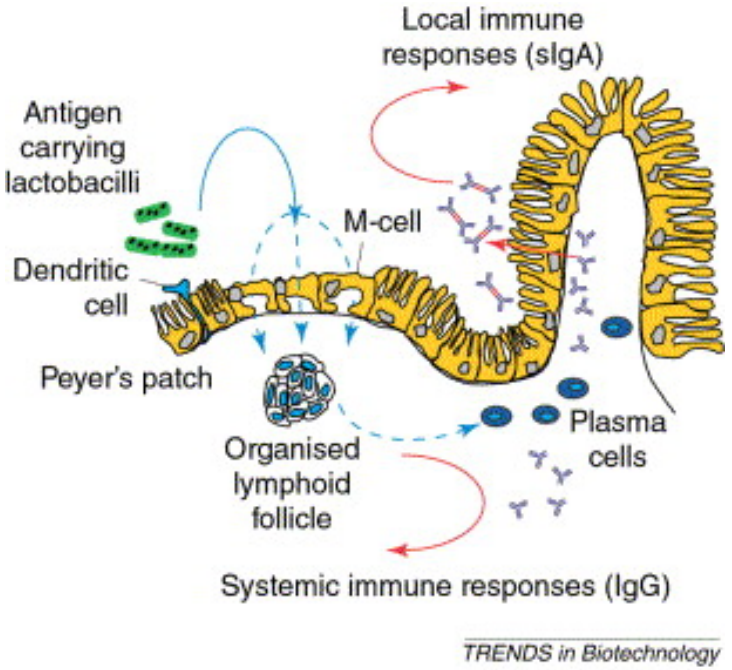
- Synbiotics? Could help with colonization efficiency, no studies as of yet

Probiotics to deliver vaccine antigens

- Showing some potential
- Probiotics themselves can affect immune responses to some extent
  - Antibody responses, epithelial barrier, cellular immune responses
- Use probiotics to deliver antigens?
- Proof of concept:
  - *Lactobacillus lactis* expressing *Listeria* internalin
  - Internilizes and delivers gene to small intestine

(Innocentin *et al.* 2009 App. Environ. Microbiol.)

No data on efficacy in animals or humans as of yet



Seegers *et al.* Trends Biotech.

Relevant with what we now know about IgA responses (Andrew Macpherson)

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PLOS ONE

Differential Response of the Cynomolgus Macaque Gut Microbiota to *Shigella* Infection

Anna M. Seekatz[1], Aruna Panda[2], David A. Rasko[1,4], Franklin R. Toapanta[3], Emiley A. Eloe-Fadrosh[1], Abdul Q. Khan[8], Zhenqiu Liu[1,7], Steven T. Shipley[2], Louis J. DeTolla[2,6,7], Marcelo B. Sztein[3,5], Claire M. Fraser[1,4,6]*

- Effect of oral *Shigella dysenteriae* 1 vaccine on microbiota in macaques from geographically different places, then challenged
- Different MHC, and microbiota (16s) based on geography
- No real change in microbiota due to vaccine
  - Obvious when challenged and dysentery
- Responded differently to vaccine
  - But both made antibodies (differing amounts)
  - Shigellosis only in non-Mauritian animals

Impact on microbiota and genetic background in vaccine trials -not all Macaques are the same

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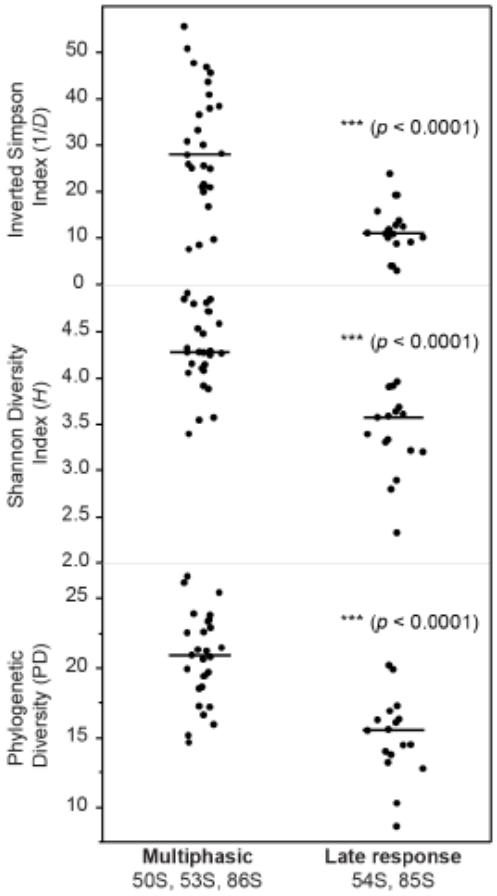
PLOS ONE

Impact of Oral Typhoid Vaccination on the Human Gut Microbiota and Correlations with *S.* Typhi-Specific Immunological Responses

Emiley A. Eloe-Fadrosh[1], Monica A. McArthur[2], Anna M. Seekatz[1], Elliott F. Drabek[1], David A. Rasko[1,3], Marcelo B. Sztein[2]*, Claire M. Fraser[1,4]*

- Effect of oral *S.* Typhi Ty21A vaccine on human microbiota
- No real change in microbiota due to vaccine
- Another study showed RotaTeq rotavirus vaccine did not change children's microbiota
- Individuals displaying multiphasic cell-mediated immune responses had more diverse, complex communities (more Clostridiales)



Experimental Design: Antibiotic Treatment from Birth or Adult Mice

Treat C57BL/6 mice with antibiotic

90ug of vaccine with CpG
1ug orally

21 days

25ug of vaccine with CpG
1ug orally

14 days

Take spleen, serum, intestines, caecum, fecal sample

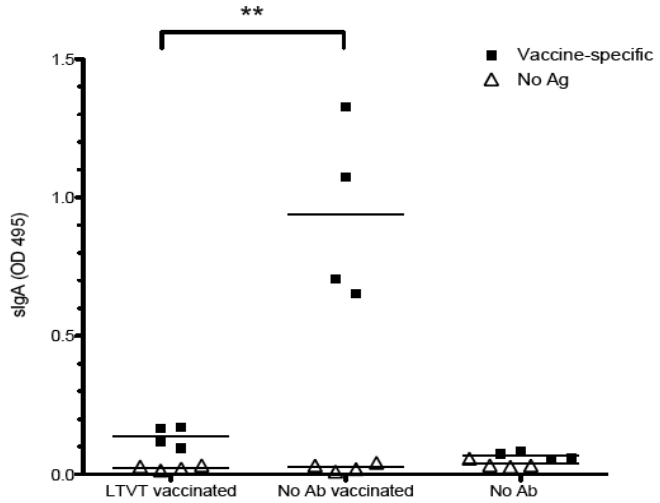
Controls:

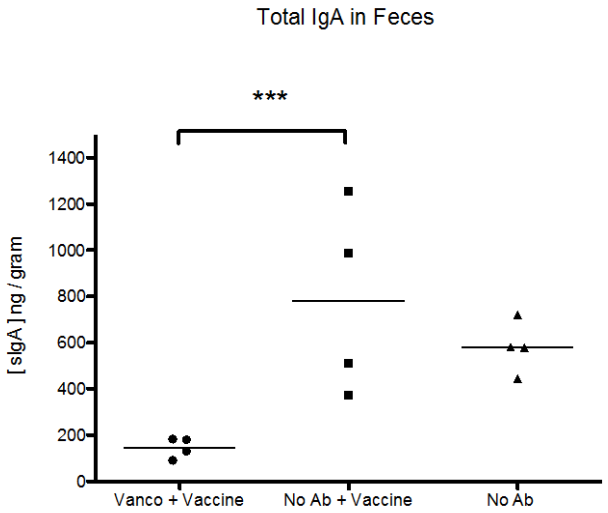
No antibiotic + vaccine

No antibiotic + saline

Antibiotic + saline

Long-term Vancomycin Treatment Alters the Vaccine-specific IgA Response to non-typhoidal subunit vaccine





Mice treated with vancomycin from birth have an abrogated vaccine-specific sIgA response

These mice have lower colonic Tregs, helper function for IgA

Adult mice with vancomycin showed increased antibody responses to oral vaccination

The Road Ahead: Gaps, Needs and Challenges

Challenges

- Human microbiome studies (more relevant but correlative) vs animal models (poor translation to vaccines but more mechanistic) – need a balance of both
- Fecal microbiota composition not always reflective of function at mucosal sites
- Difficult to study small intestinal and mucosal-associated microbiota in humans

Significant gap between animal and human studies in microbiome and vaccine research

Needs

- Mice with humanized immune systems, more translatable to vaccine research

Can vaccines be used to target specific species from the microbiota?

Definite need as we begin identify keystone species and pathobionts

We only have blunt tools at our disposal to alter specific species/pathobionts in our microbial community

(eg Antibiotics, diet, prebiotics, phage therapy, etc)

Keystone Pathobionts in Periodonitis

Cell Host & Microbe
Article

Low-Abundance Biofilm Species Orchestrates Inflammatory Periodontal Disease through the Commensal Microbiota and Complement

George Hajishengallis,[1,2,7,*] Shuang Liang,[2] Mark A. Payne,[3] Ahmed Hashim,[3] Ravi Jotwani,[2] Mehmet A. Eskan,[1,2] Megan L. McIntosh,[1,2] Asil Alsam,[3] Keith L. Kirkwood,[4] John D. Lambris,[5] Richard P. Darveau,[6,7,*] and Michael A. Curtis[3,7,*]

Presence of *Porphyromonas gingivalis* alone alters function and state of the microbial community

Periodontal vaccine

- Liu et al, 2010, Vaccine 28:3496
- Targeted an outer membrane porin (FomA) from oral microbiota species *Fusobacterium nucleatum* for vaccine
- FomA and bacterium form a bridge for *Porphyromonas gingivalis*, enabling it to adhere and form biofilm, ultimately causes gingivitis
- Worked nicely in mouse model of gingivitis

Targeting Pathobionts with Vaccines

- Mutualists or commensals that can occasionally be pathogenic
- *Haemophilus influenzae* type B (Hib) vaccine has virtually eliminated Hib from phyrngeal microbiota
  - before vaccine, 3-5% healthy kids carried it
  - Replaced by less virulent *Haemophilus* strains
- *Streptococcal pneumoniae* 7 valent vaccine
  - 77% decrease in disease
  - Replaced by other (non-vaccine) strains of Strep that appear less virulent

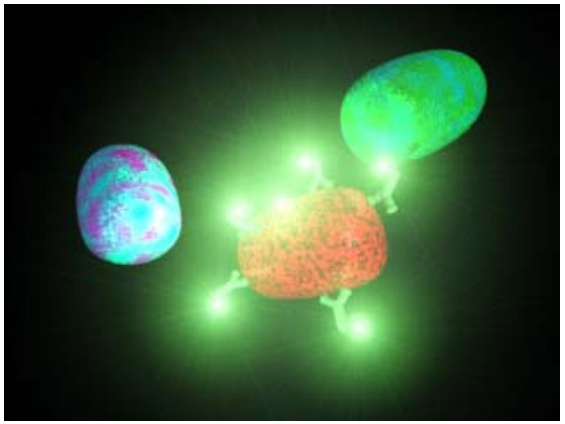
1. Can target specific microbiota with vaccines
2. Appear to be replaced by other closely related species

Example: Microbiota-Targeted Vaccine for Autism?

- 90% of autistic kids have GI irritation (constipation, diarrhea)
- *Clostridium bolteae* overabundant in intestine of kids with autism
  - makes toxins, SCFA that could go systemic into bloodstream to have toxic neurological affects
- Vancomycin (oral) adminstered to kids with severe autism with chronic persistant diarrhea
  - Short term improvement in 8/10 kids (Sandler et al. 2000 J Child Neurol.)
  - No long term effects, prolonged use of vanc. didn't work
- Pequegnat et al Guelph (Vaccine, 2013) making vaccine to specific cell wall polysaccharide-immunogen

What Could be the Consequences of Targeting Microbiota with Vaccines?

- Virtually unexplored
- May cause community “ripple-down” effects
- Very difficult to predict, need for more basic science on community interactions (D. Relman)
  - Would need to know contribution of species to community, etc.



Microbial ecosystem a complex adaptive system= non-linear

Small changes can have profound effects

Future challenges and Questions

1) Can the microbiota be altered to improve vaccine responses?

2) Can microbiota be used to deliver vaccine antigens?

3) Can specific vaccines be designed to target particular microbiota strains?