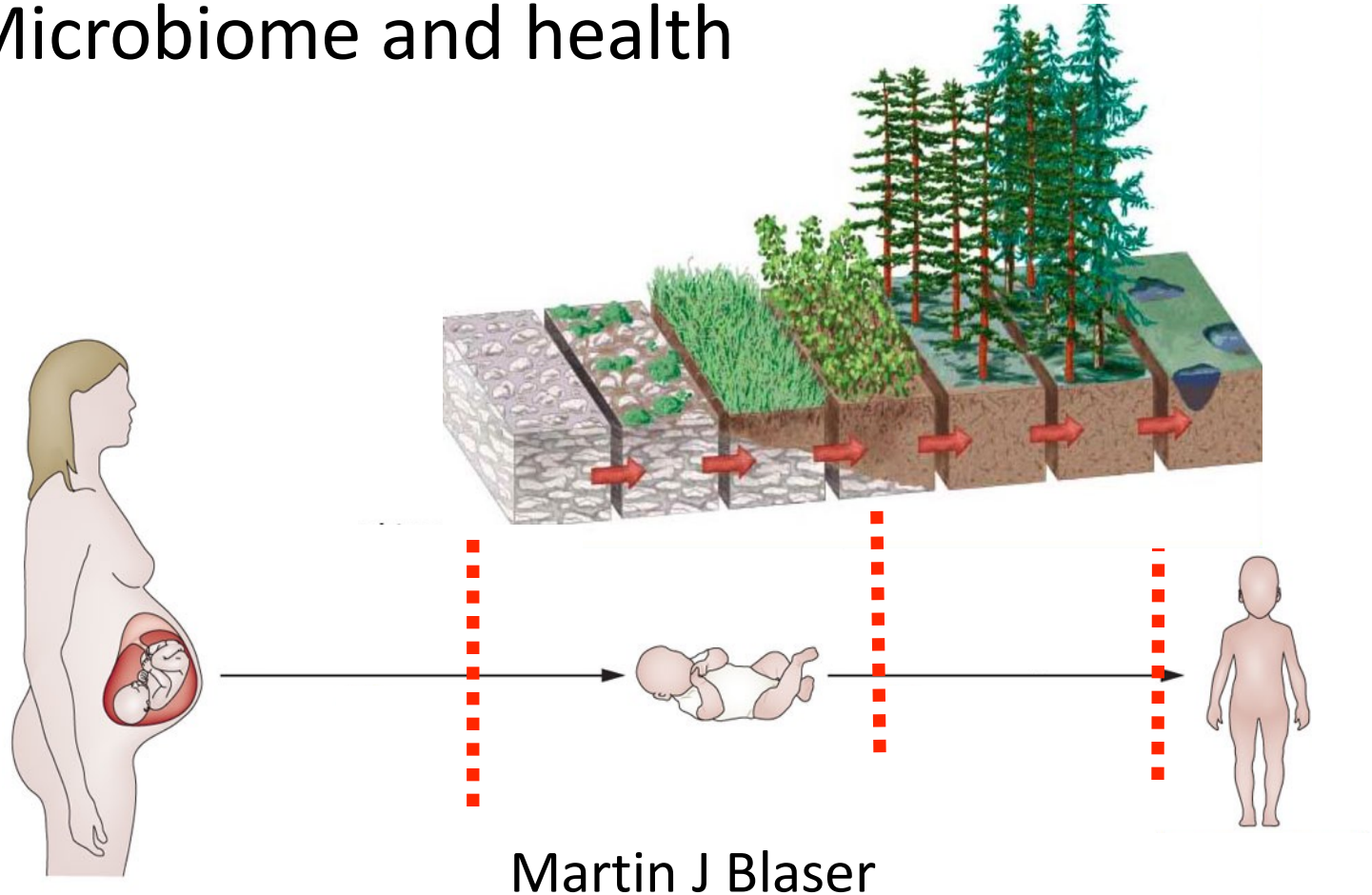
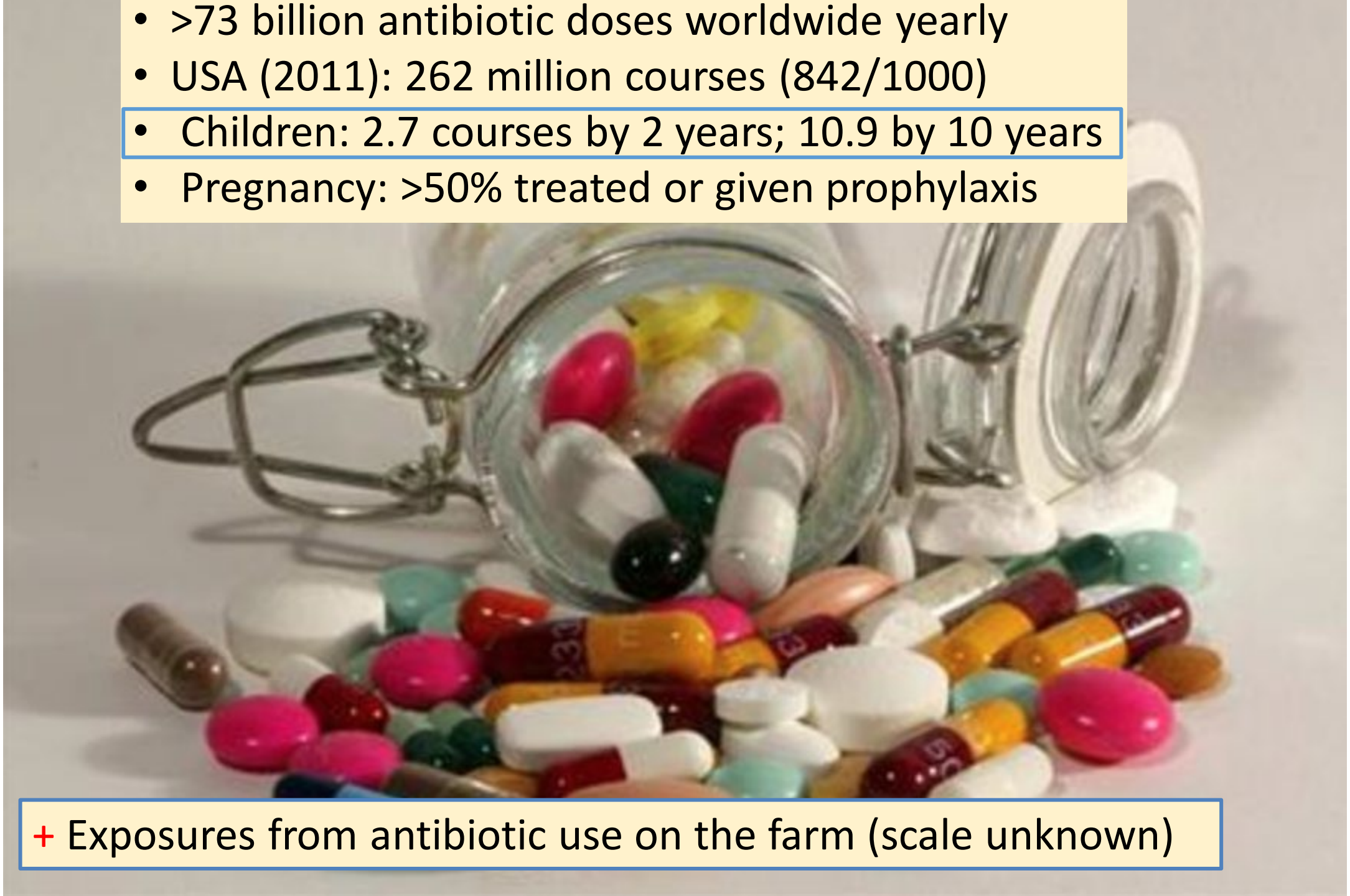
# Microbiome and health



Martin J Blaser
Center for Advanced Biotechnology and Medicine
Rutgers University, New Brunswick NJ

RUTGERS
Robert Wood Johnson
Medical School

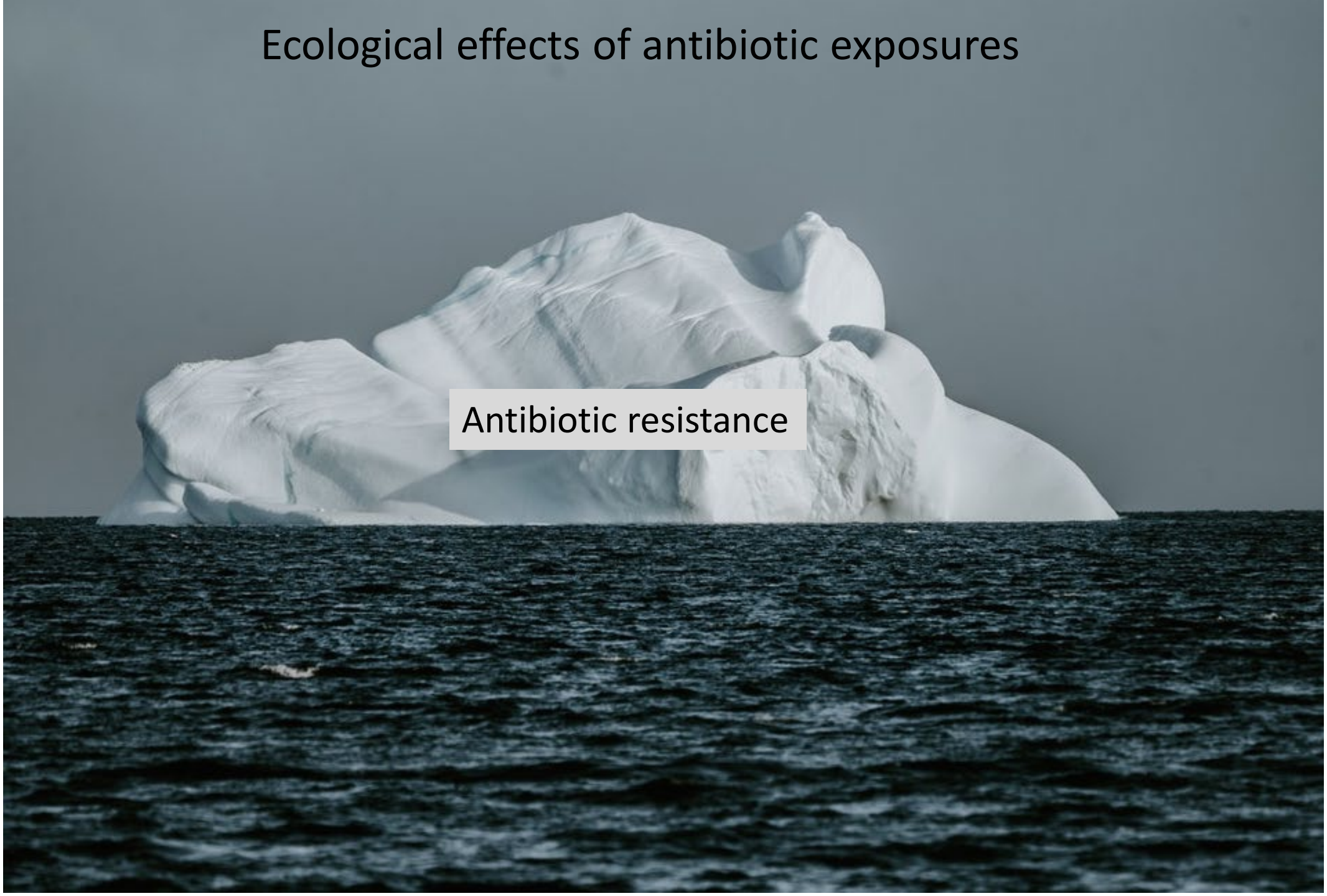
- >73 billion antibiotic doses worldwide yearly
- USA (2011): 262 million courses (842/1000)
- Children: 2.7 courses by 2 years; 10.9 by 10 years
- Pregnancy: >50% treated or given prophylaxis

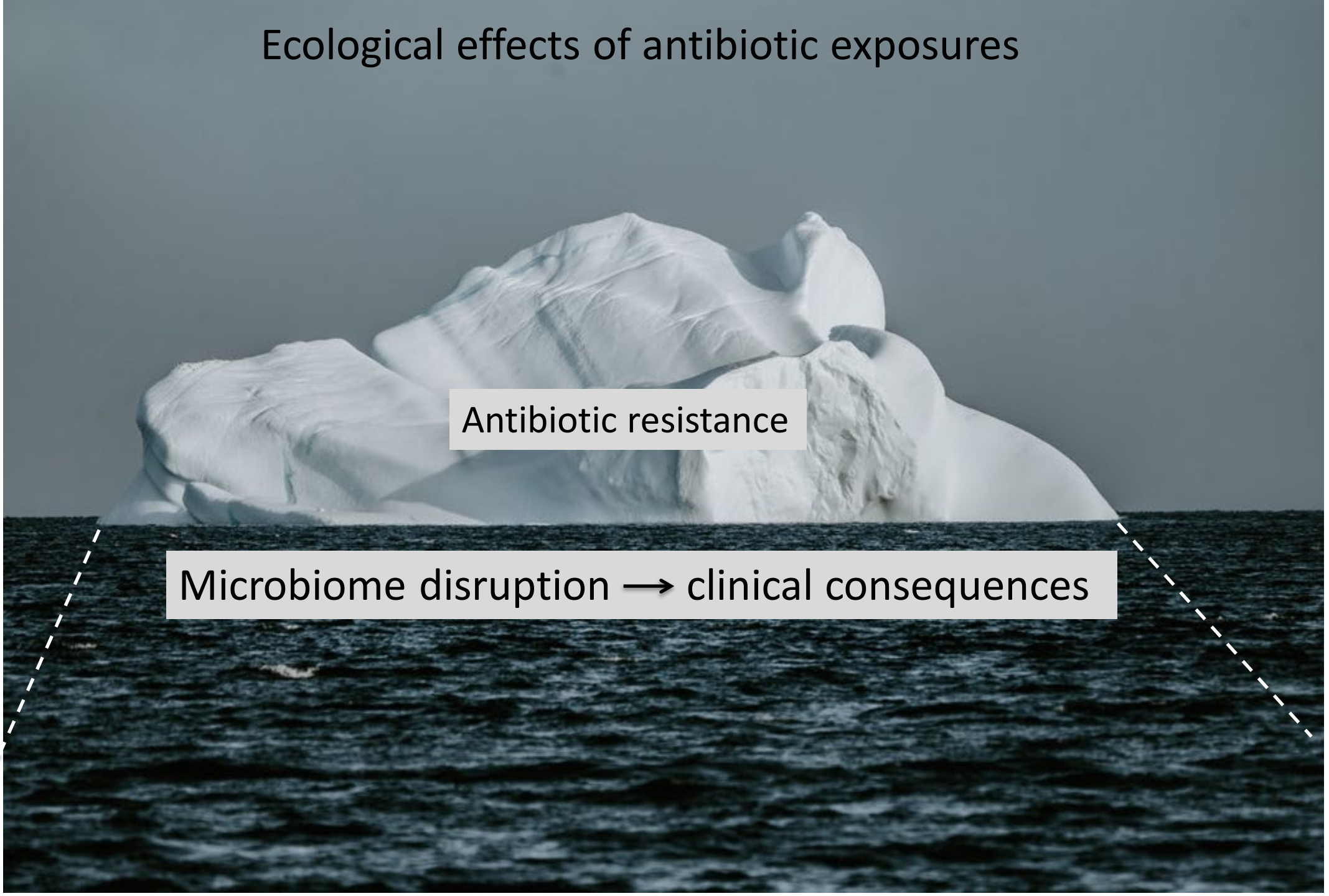


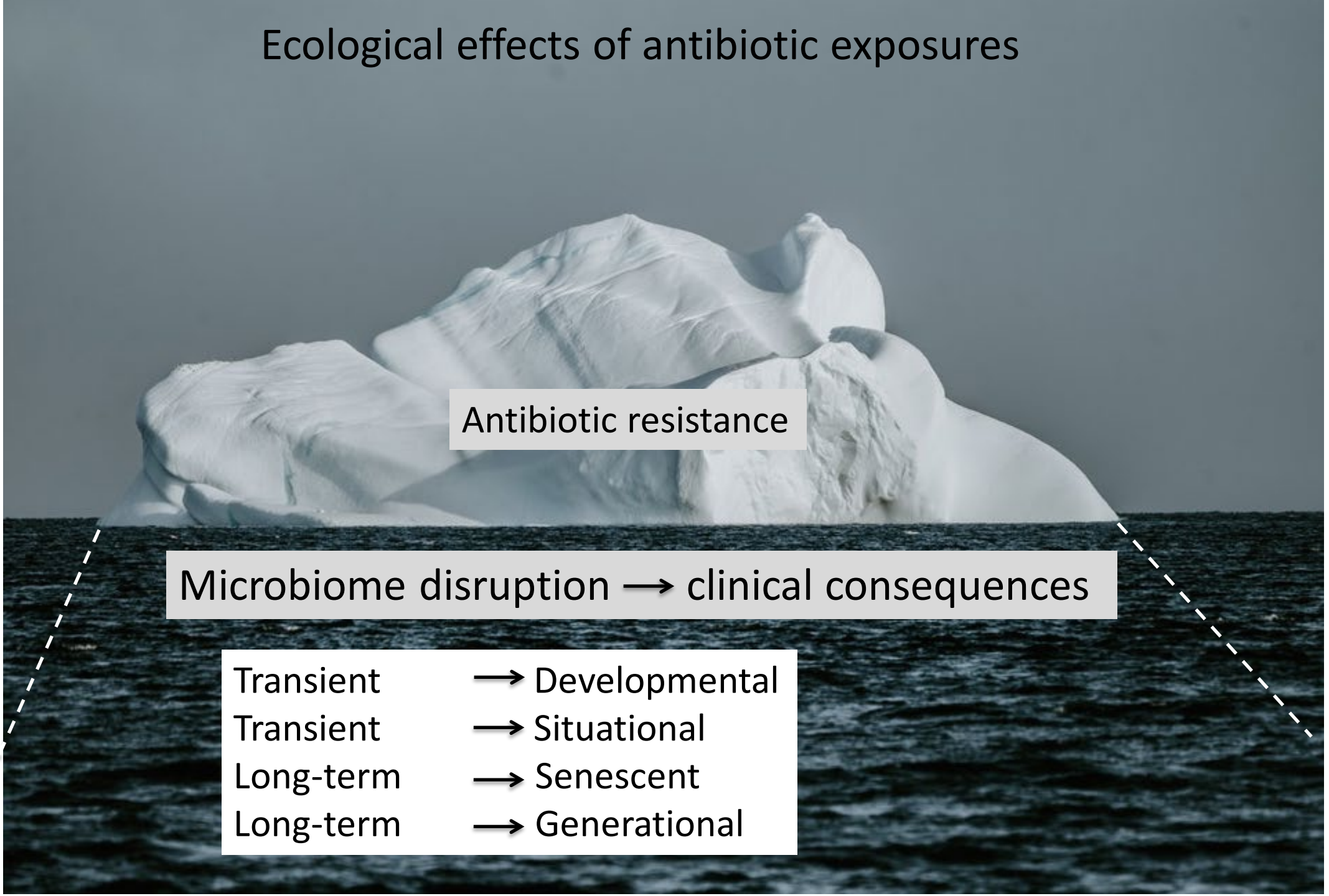
+ Exposures from antibiotic use on the farm (scale unknown)

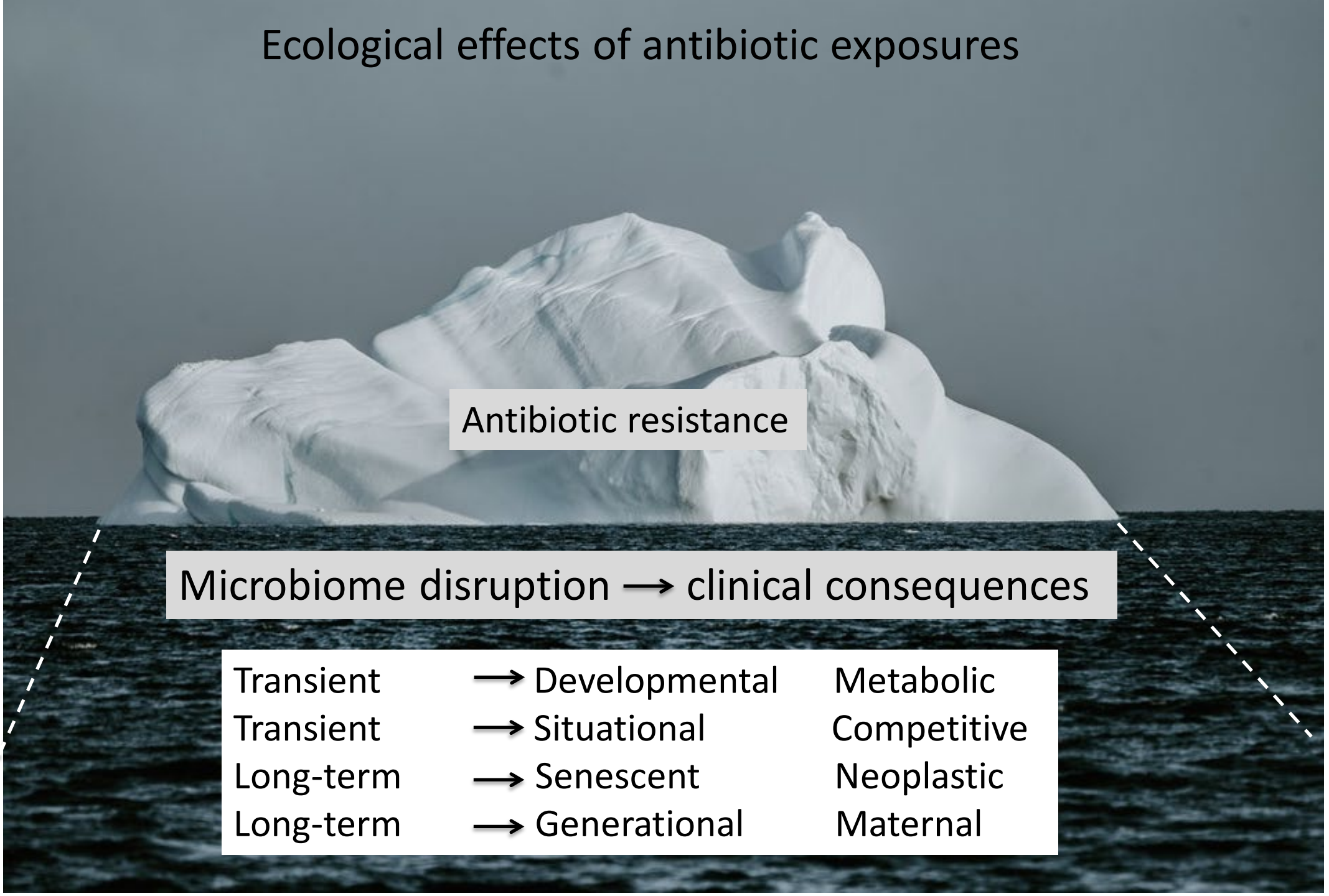
# Ecological effects of antibiotic exposures

# Ecological effects of antibiotic exposures

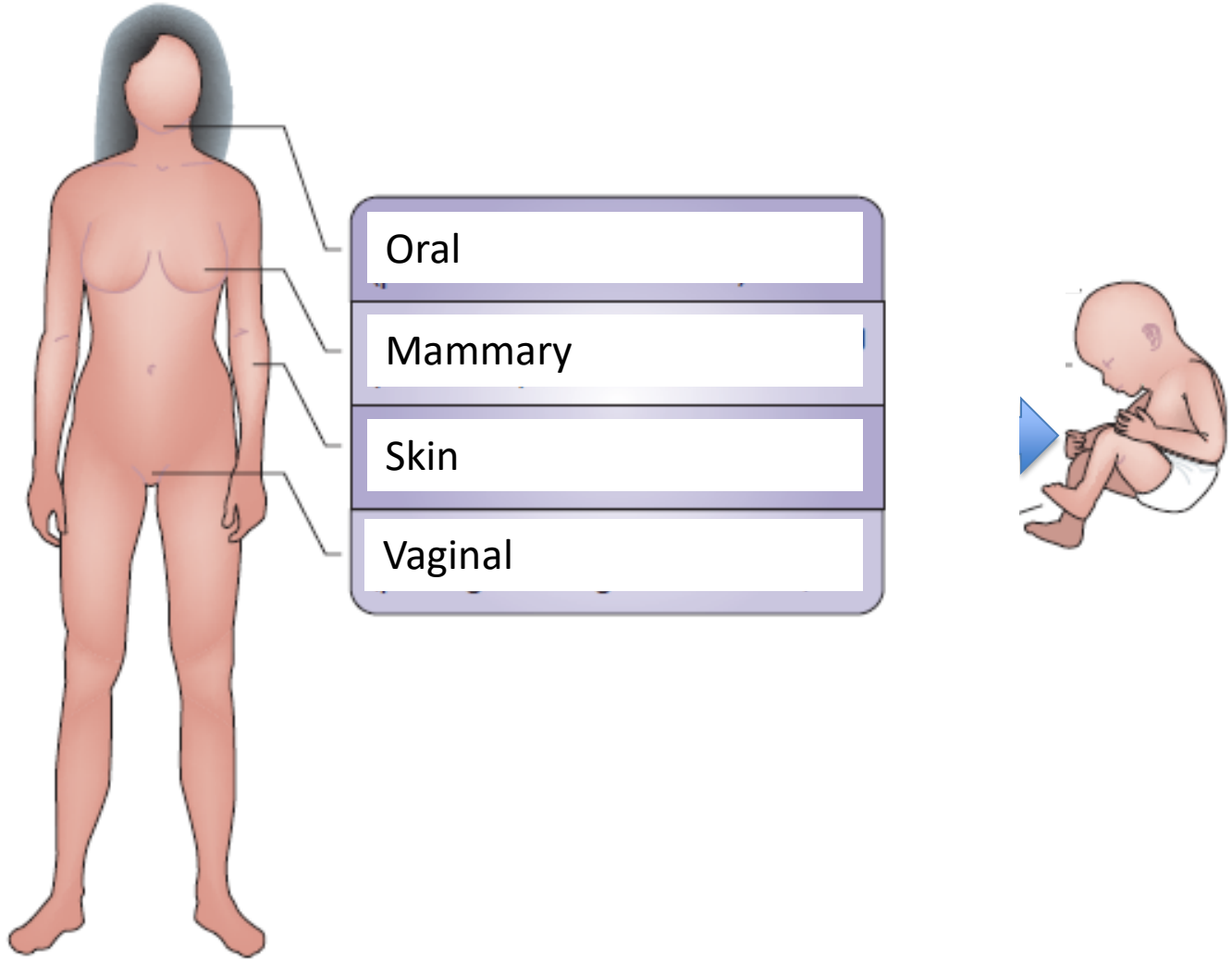



Ecological effects of antibiotic exposures
Antibiotic resistance
Microbiome disruption ⟶ clinical consequences


Ecological effects of antibiotic exposures
Antibiotic resistance
Microbiome disruption ⟶ clinical consequences
Transient ⟶ Developmental
Transient ⟶ Situational
Long-term ⟶ Senescent
Long-term ⟶ Generational


Ecological effects of antibiotic exposures
Antibiotic resistance
Microbiome disruption ⟶ clinical consequences
Transient ⟶ Developmental Metabolic
Transient ⟶ Situational Competitive
Long-term ⟶ Senescent Neoplastic
Long-term ⟶ Generational Maternal

# Mother→ Child Transfer of Microbes (Ancient)

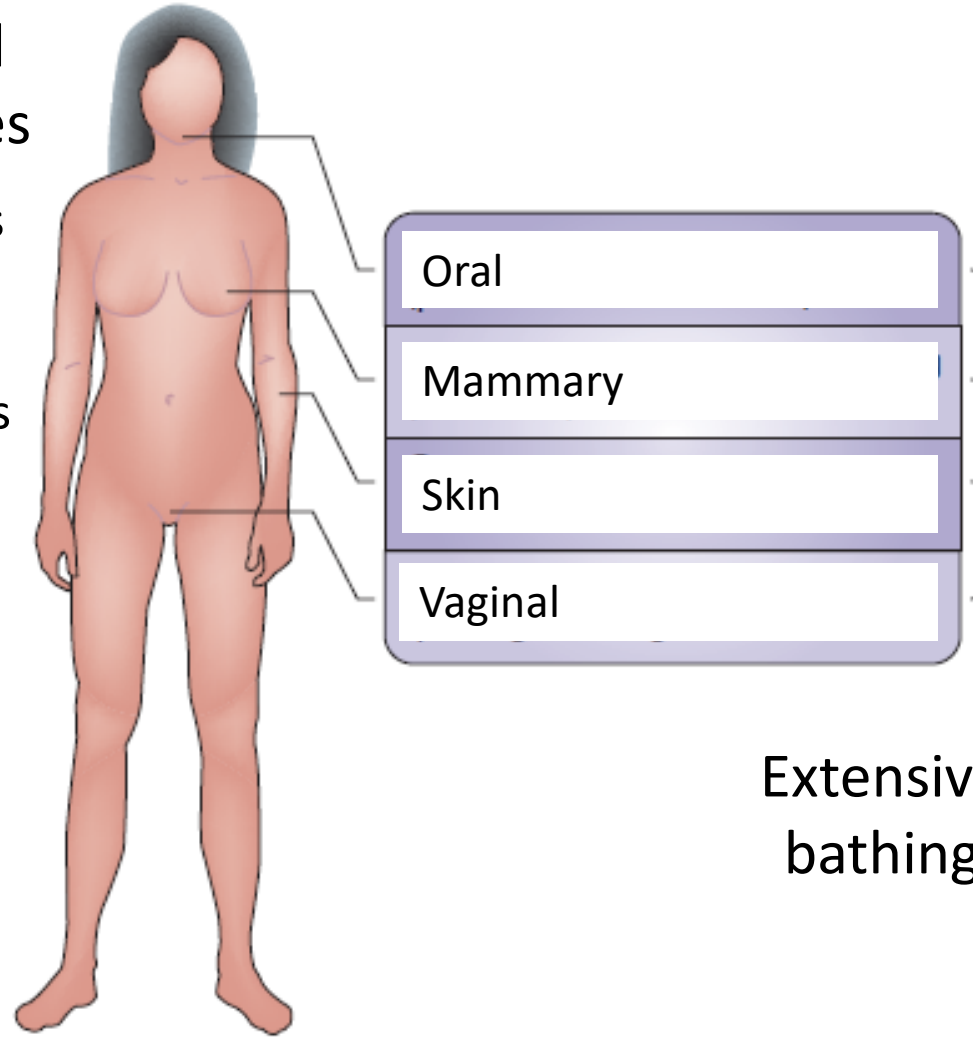



*Nature Reviews Genetics* 2012;13:260-70

# Mother→ Child Transfer of Microbes (Modern)

Maternal exposures

- Antiseptics
- Antibiotics
- Dietary antibacterials




Bottle feeding

Antibiotics

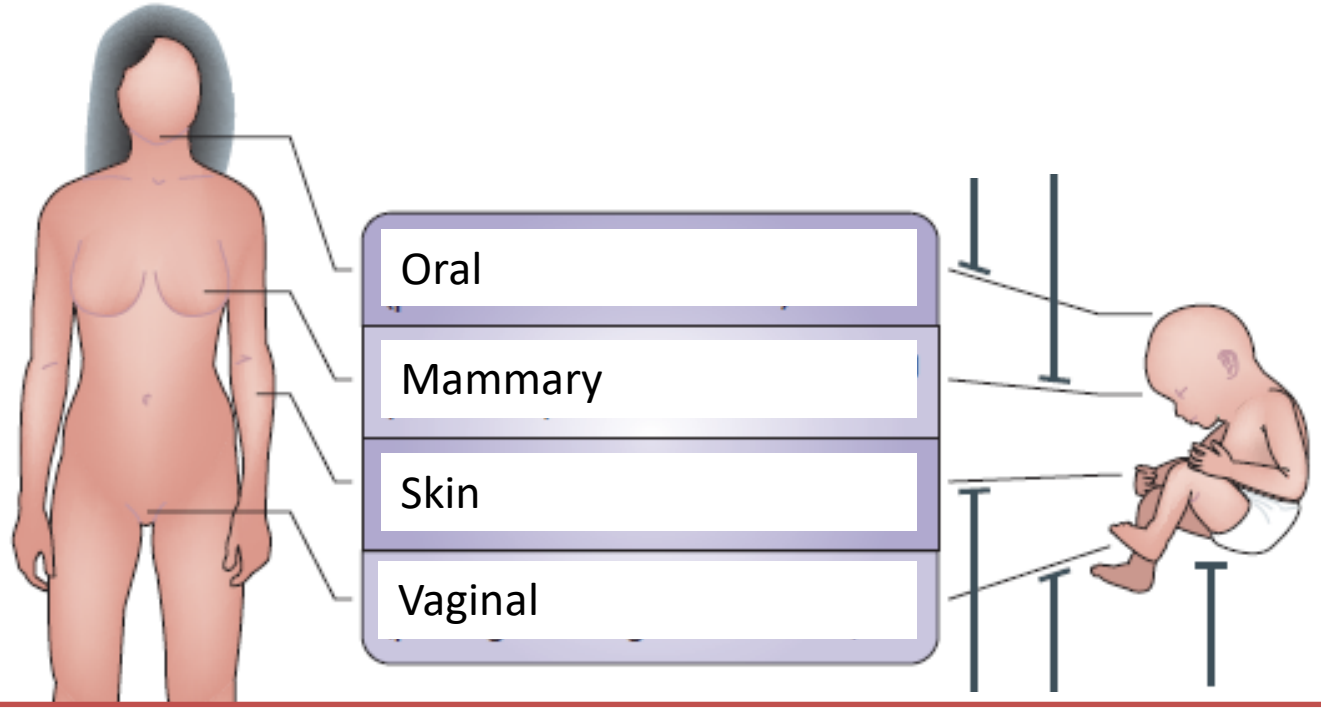
Extensive bathing

Caesarean section

Other medications
Other exposures

*Nature Reviews Genetics* 2012;13:260-70

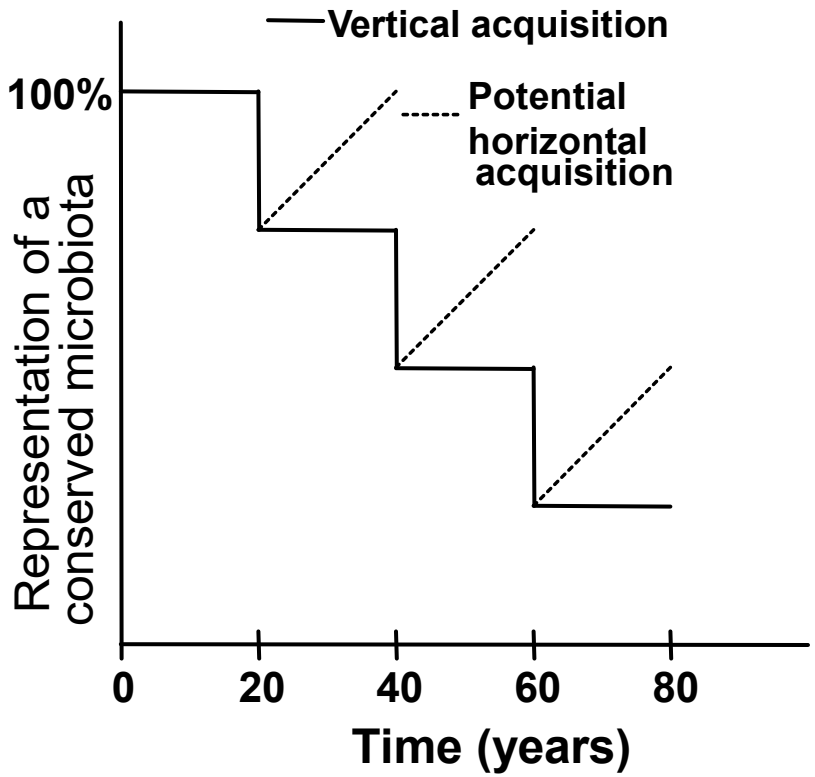
# Theory of *Disappearing Microbiota*



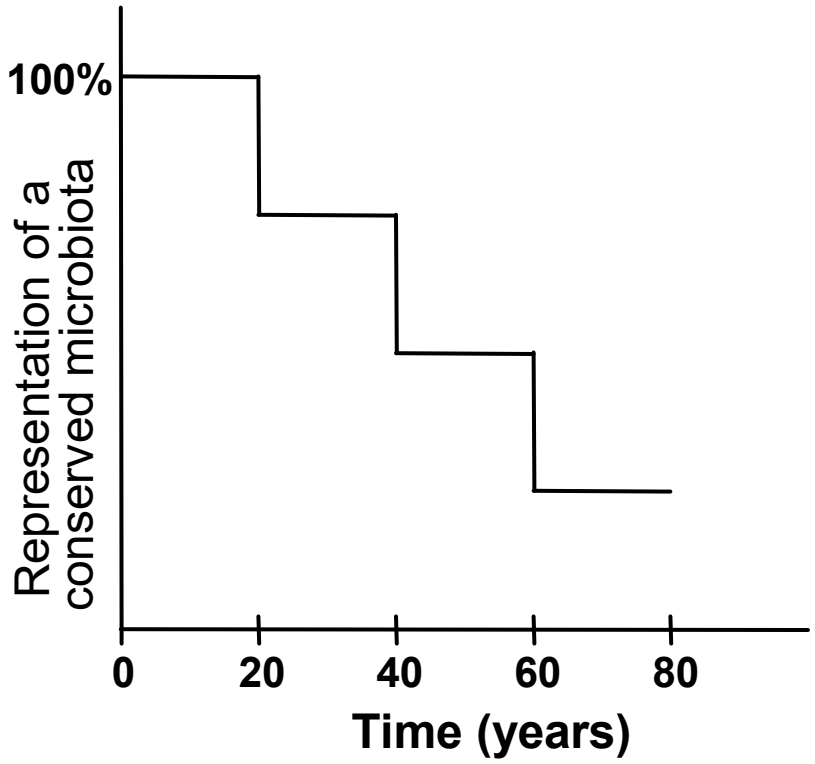

- Changed human ecology has altered transmission and maintenance of ancestral microbes, which affects the composition of the microbiota.
- The microbes, both good and bad, usually acquired **early in life** are especially important, since they affect a developmentally critical stage.

*Lancet* 1997; *Gut* 1998; *Perspect Biol Med* 2002; *Scientific American* 2005; *EMBO Reports* 2006; *Nature Rev Microbiol* 2009; *Nature* 2011; *Nature Rev Immunol* 2017; *Cell* 2018

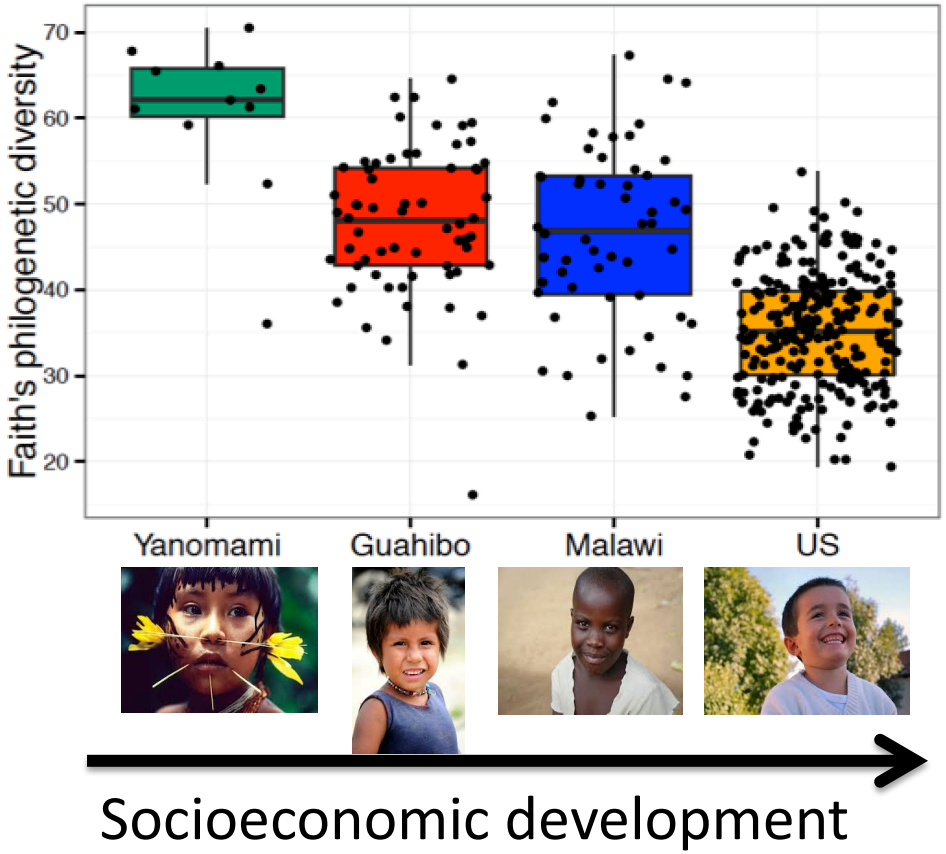
# The effect of maternal status on the resident microbiota of the next generation




*Nature Rev Microbiol* 2009;7:887



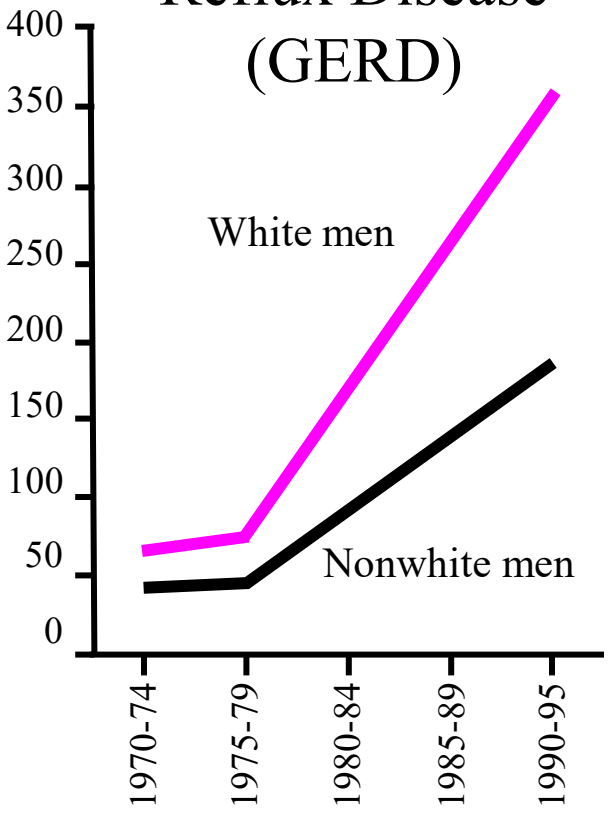

Diversity of the intestinal microbiota in four populations



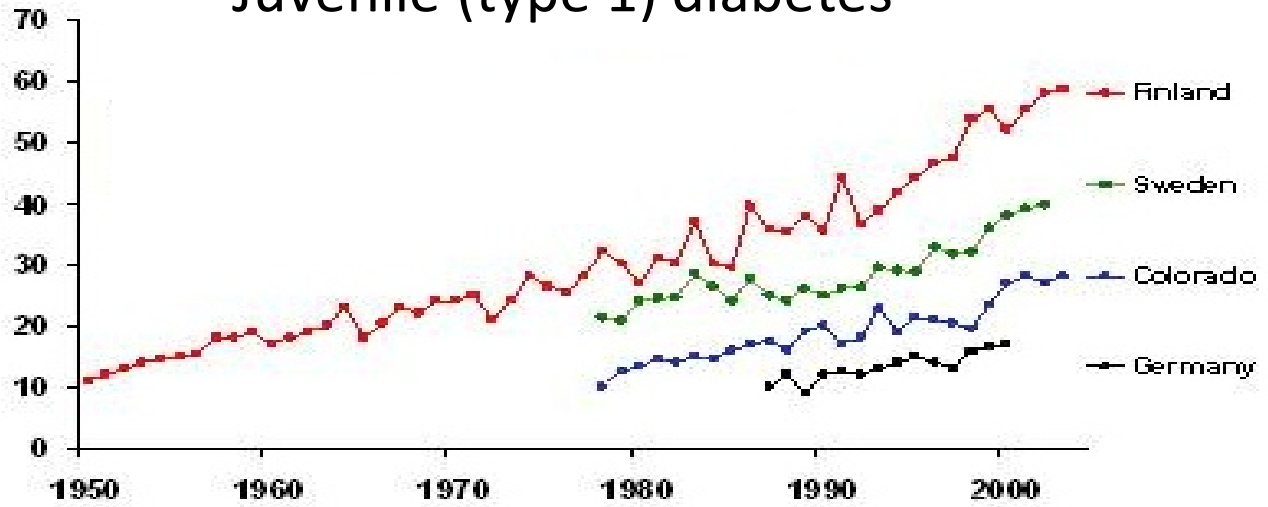

J Clemente *et al*. *Science Advances* 2015

Chronic diseases increasing in recent decades

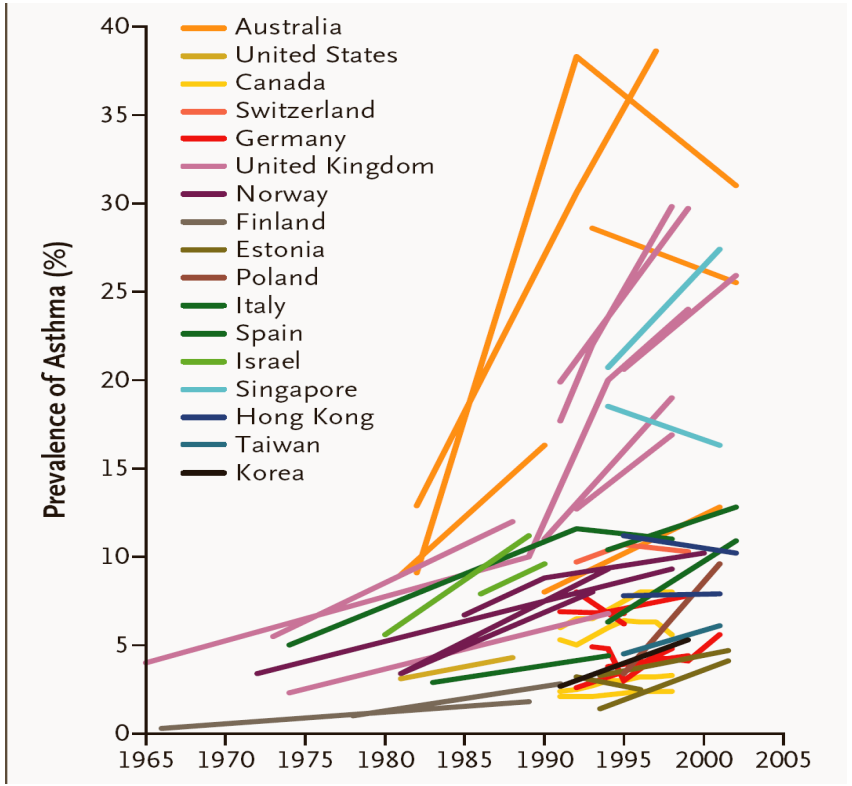
## Reflux Disease (GERD)




## Juvenile (type 1) diabetes




## Asthma



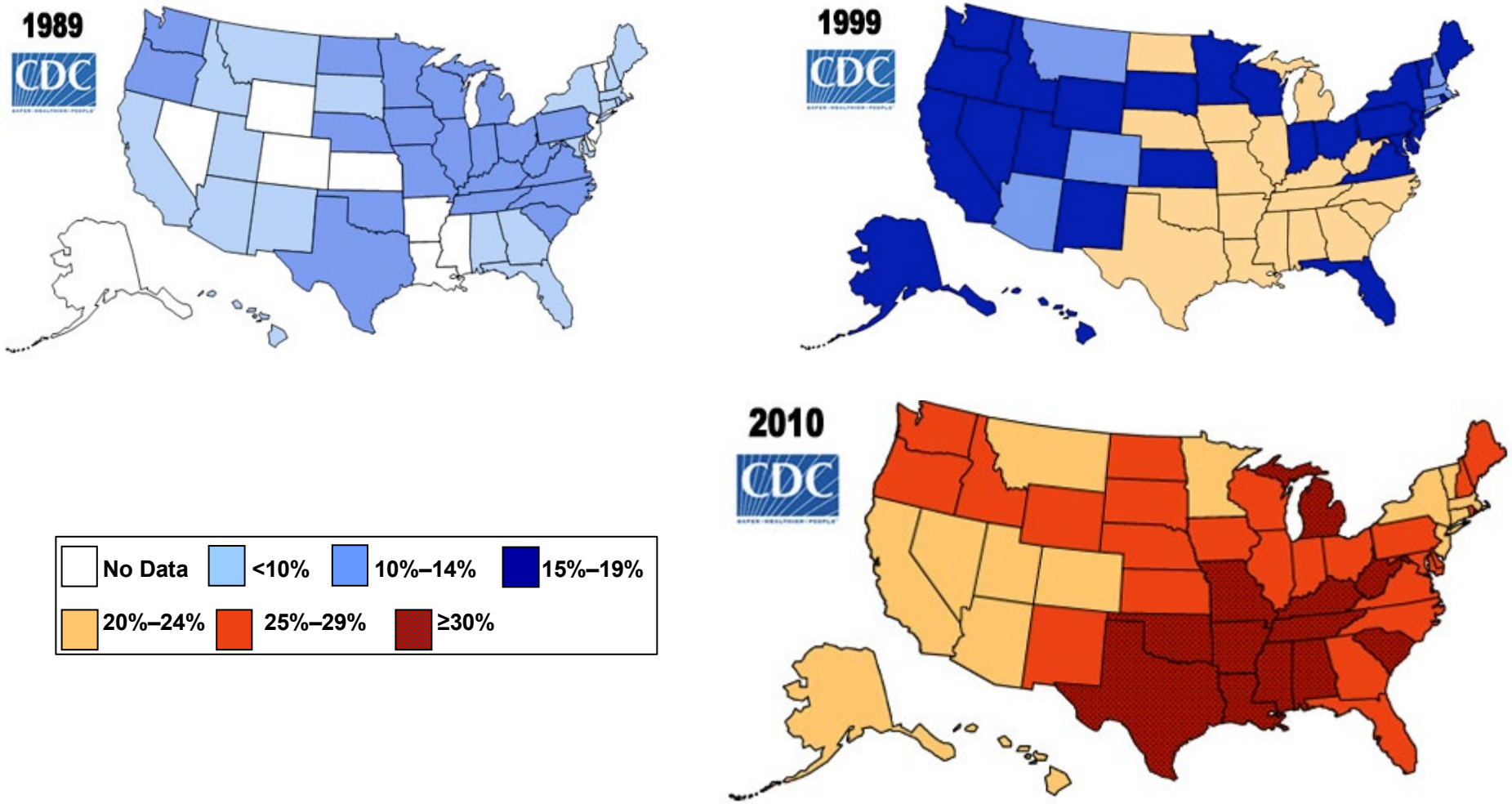

Sources:

*Ann NY Acad Sci* 2008 12:1150

*N Engl J Med* 2006;355:2226

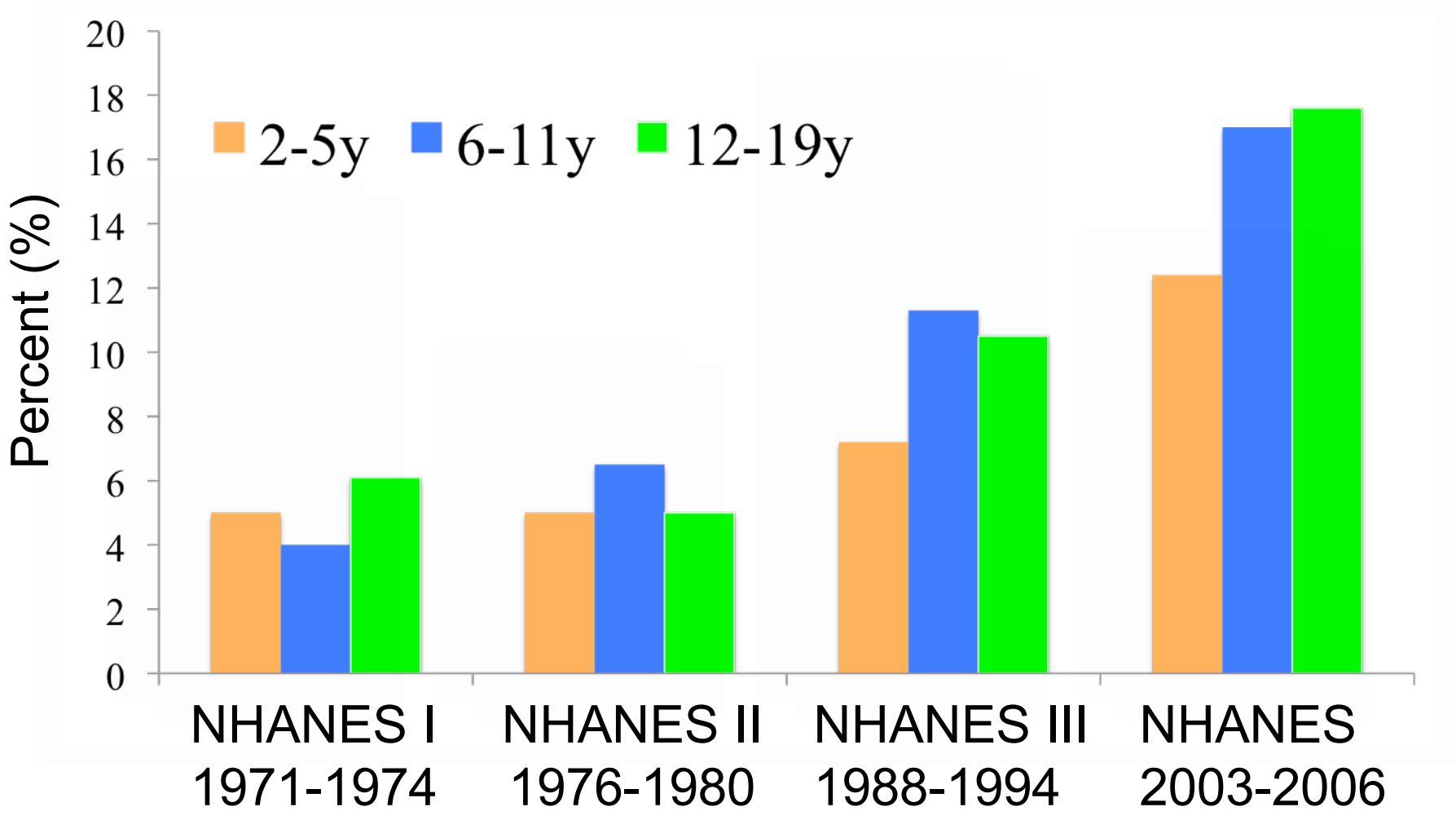
*Gut* 1997;41:594

# Obesity trends in US adults: changing physiology



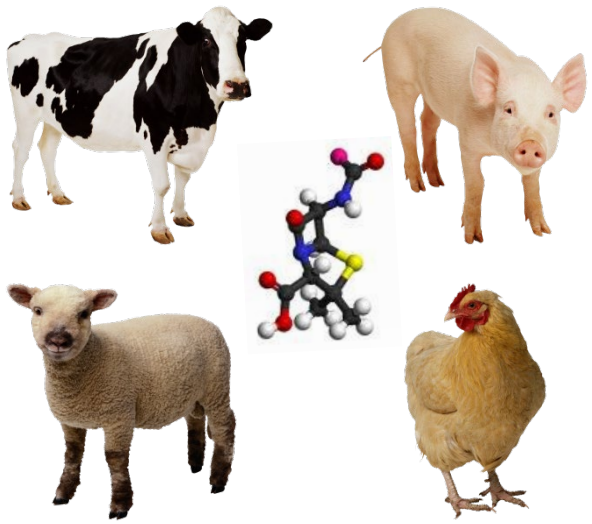

Source: *CDC Behavioral Risk Factor Surveillance System*

# Obesity trends among U.S. children and adolescents

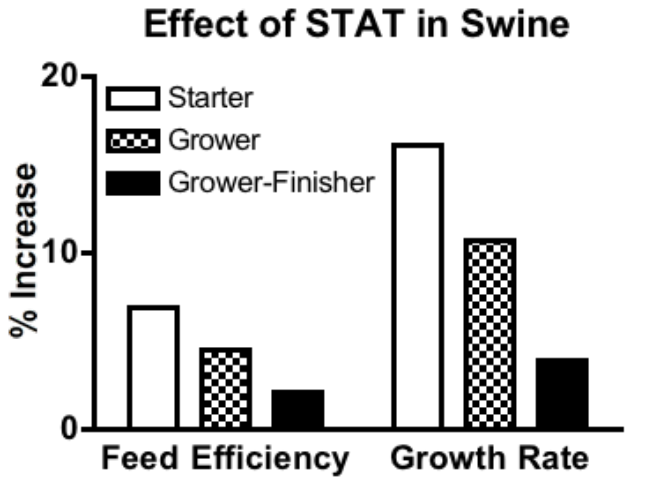



*Sex- and age-specific BMI > 95$^{th}$ %ile, based on CDC growth charts*

# Antibiotics used in farm animals to promote their growth

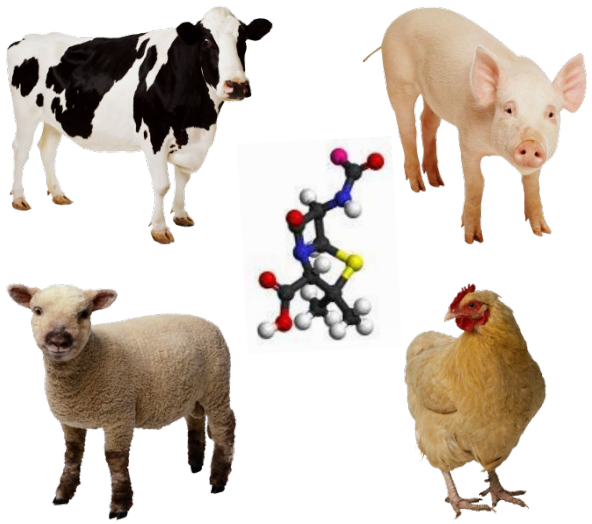


| Antibiotic | Class | Target |
|---|---|---|
| Bambermycin | Glycolipid | Cell wall |
| Virginiamycin | Streptogrammin | Protein synthesis |
| Avilamycin | Orthosomycin | Protein synthesis |
| Bacitracin | Cyclic peptide | Cell wall synthesis |
| Monensin | Ionophore | Cell membrane |
| Carbadox | Quinoxaline | DNA Synthesis |




(Adapted from Zimmerman, J Animal Sci, 1986)

# Using mice to examine the effects of antibiotics



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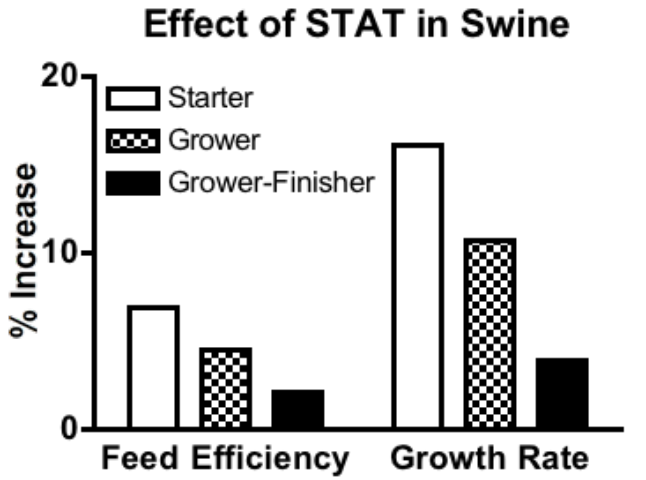
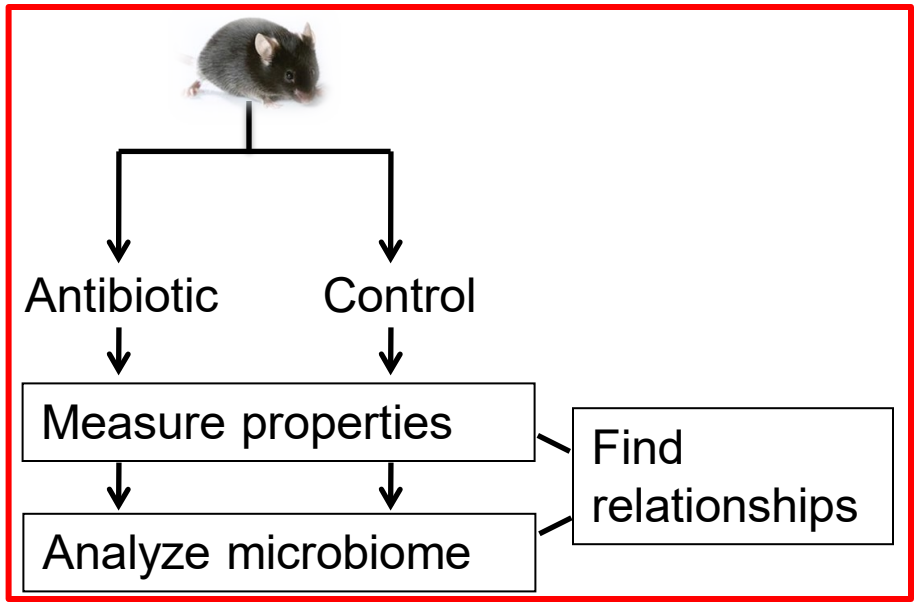
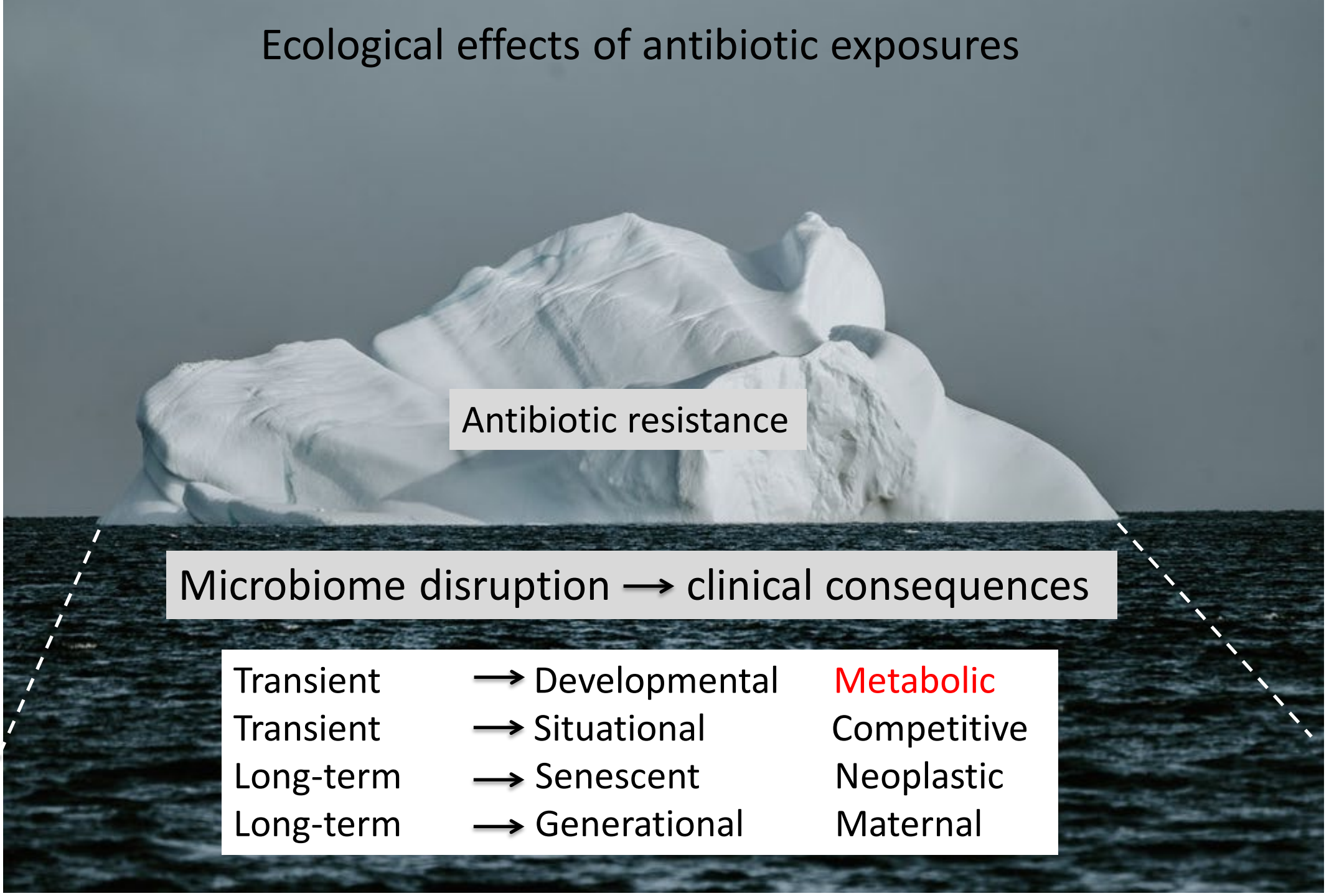


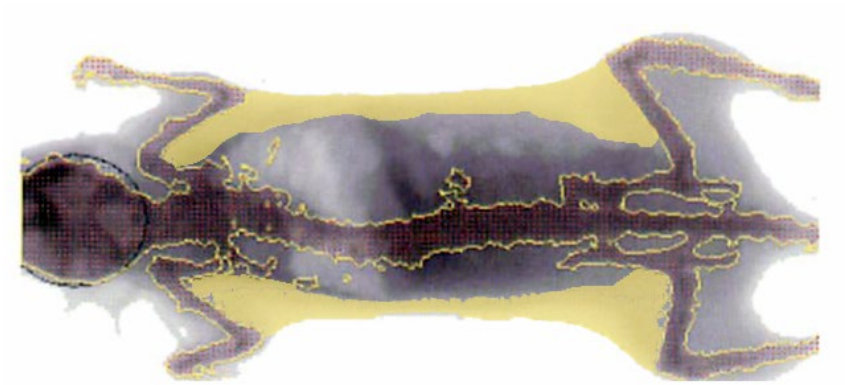

(Adapted from Zimmerman, J Animal Sci, 1986)



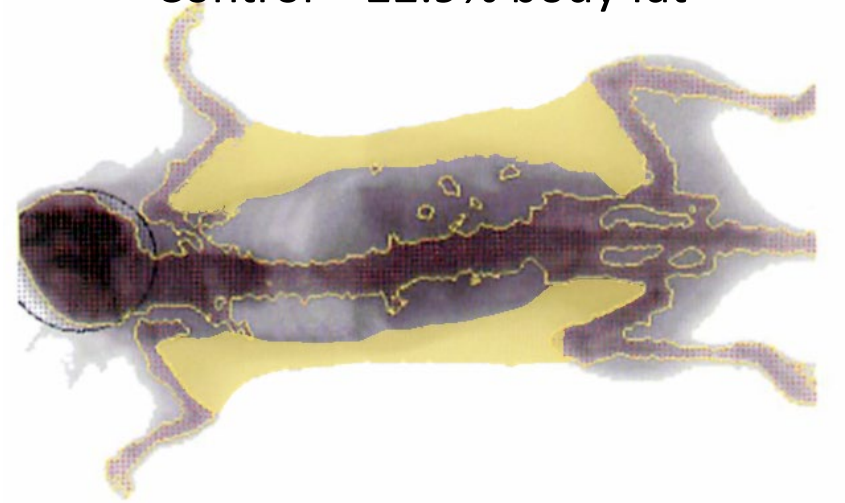
# Ecological effects of antibiotic exposures



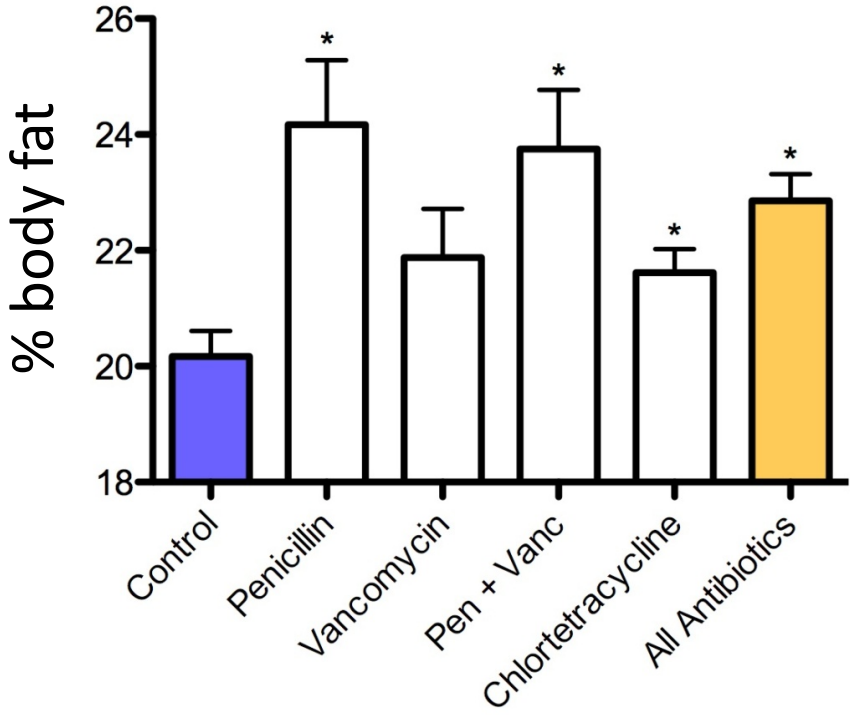
# Body fat in antibiotic-exposed and control 10-week old mice



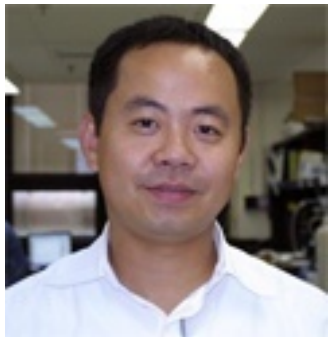
Control – 22.9% body fat



Antibiotic – 32.0% body fat




*p<0.05

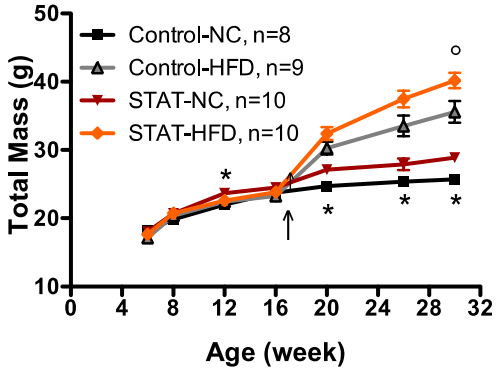


Ilseung Cho

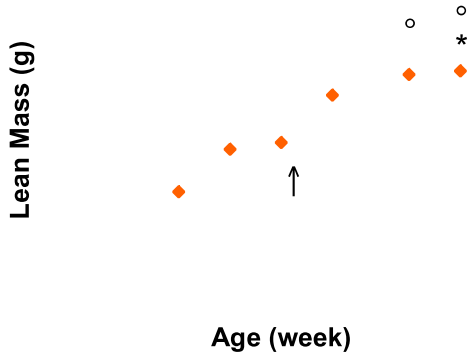
I Cho *et al. Nature* 2012; 488:621-6

# HFD and antibiotic both contribute to body fat


**Male**

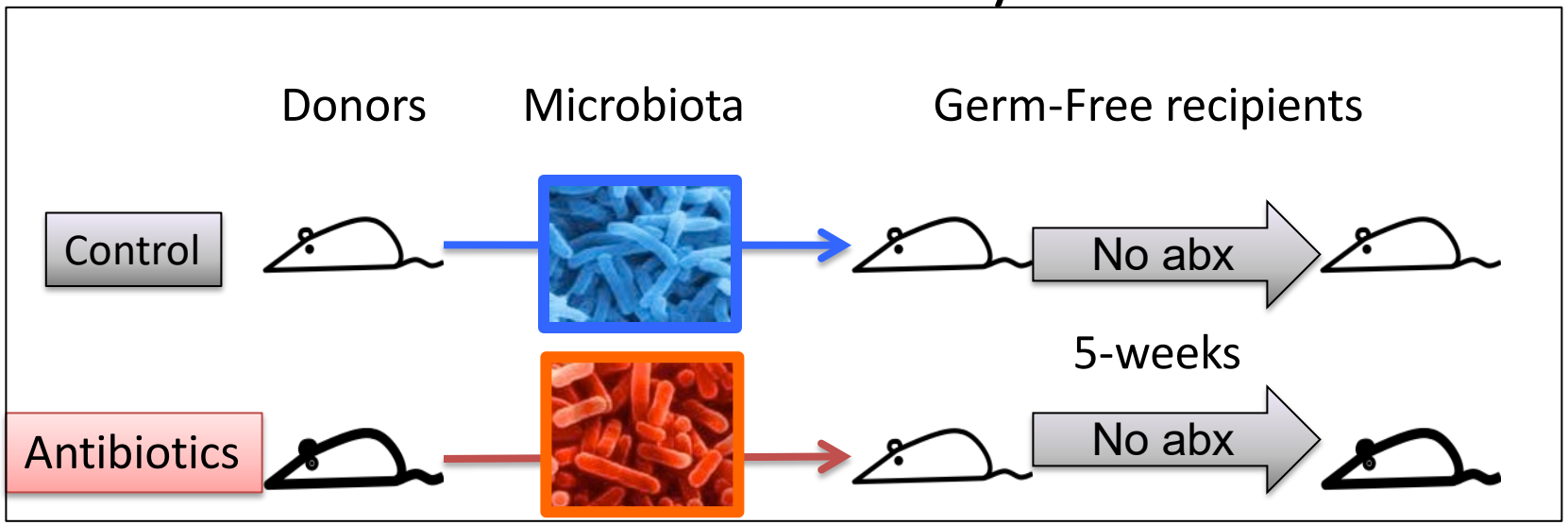


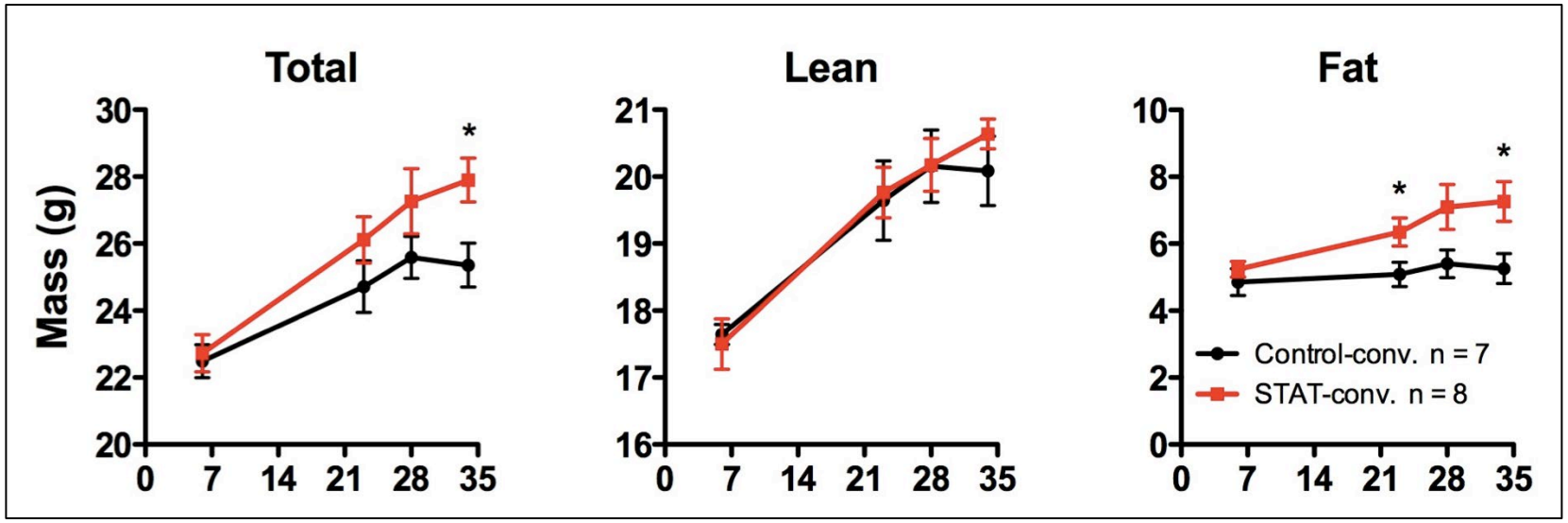

**Female**

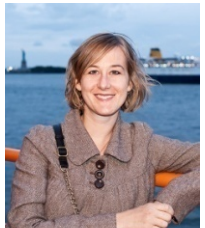



↑ High fat diet introduced  * $p < 0.05$ NC  ° $p < 0.05$ HFD

# Is microbe-induced obesity transferable?



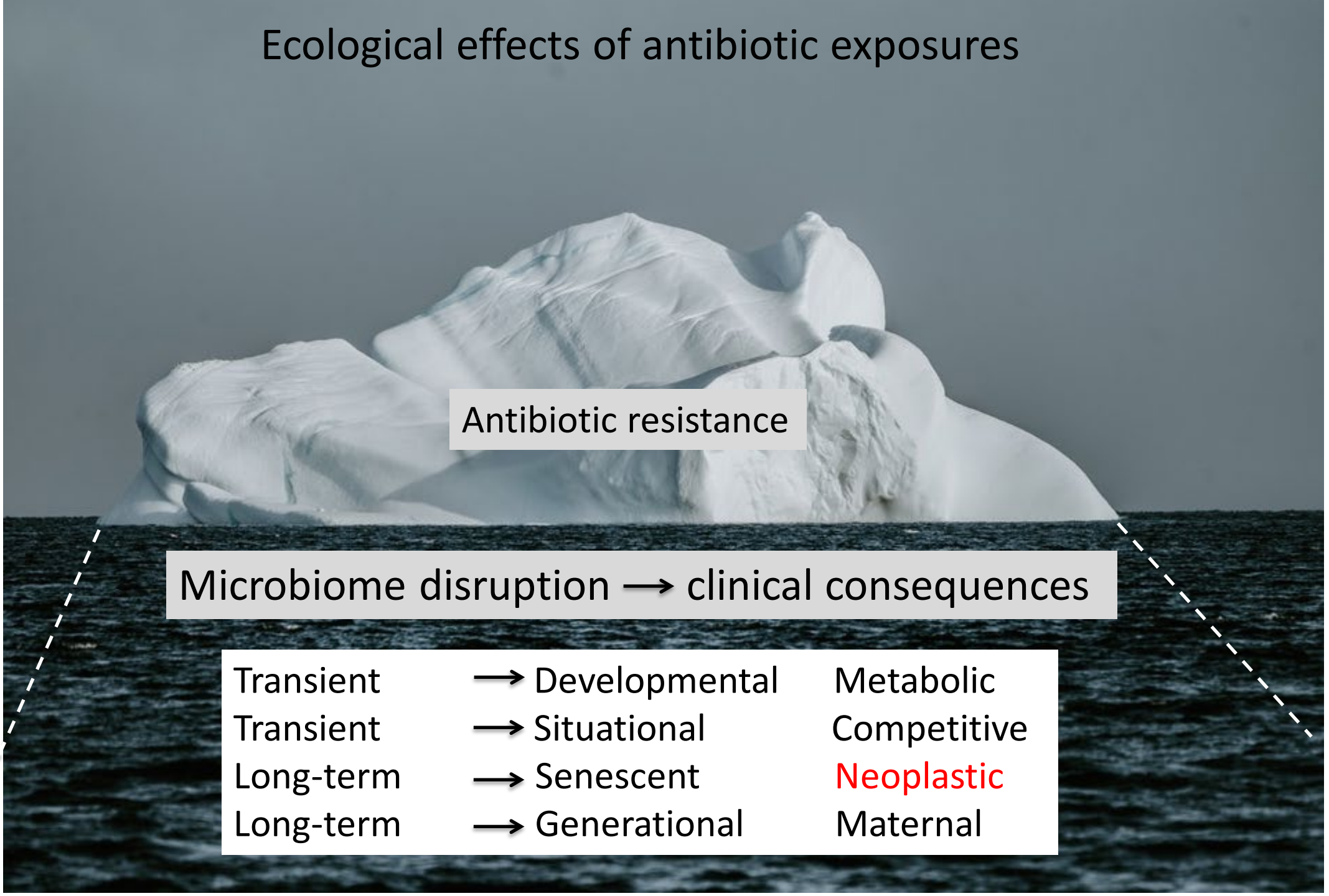



Body composition - Days post-transfer

L Cox *et al.* *Cell* 2014; 158: 705-21.

# Ecological effects of antibiotic exposures



ORIGINAL ARTICLE

# Long-term use of antibiotics and risk of colorectal adenoma

Yin Cao,[1,2,3] Kana Wu,[3] Raaj Mehta,[1,2] David A Drew,[1,2] Mingyang Song,[1,2,3] Paul Lochhead,[1,2] Long H Nguyen,[1,2] Jacques Izard,[4] Charles S Fuchs,[5,6,7] Wendy S Garrett,[8,9,10] Curtis Huttenhower,[9,11] Shuji Ogino,[8,12,13] Edward L Giovannucci,[3,12,14] Andrew T Chan[1,2,9,14]

▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2016-313413).

For numbered affiliations see end of article.

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Revised 7 February 2017
Accepted 9 February 2017

## ABSTRACT

**Objective** Recent evidence suggests that antibiotic use, which alters the gut microbiome, is associated with an increased risk of colorectal cancer. However, the association between antibiotic use and risk of colorectal adenoma, the precursor for the majority of colorectal cancers, has not been investigated.

**Design** We prospectively evaluated the association between antibiotic use at age 20–39 and 40–59 (assessed in 2004) and recent antibiotic use (assessed in 2008) with risk of subsequent colorectal adenoma among 16 642 women aged ≥60 enrolled in the Nurses' Health Study who underwent at least one colonoscopy through 2010. We used multivariate logistic regression to calculate ORs and 95% CIs.

**Results** We documented 1195 cases of adenoma. Increasing duration of antibiotic use at age 20–39 ($p_{trend}$=0.002) and 40–59 ($p_{trend}$=0.001) was significantly associated with an increased risk of colorectal adenoma. Compared with non-users, women who used antibiotics for >2 months between age 20

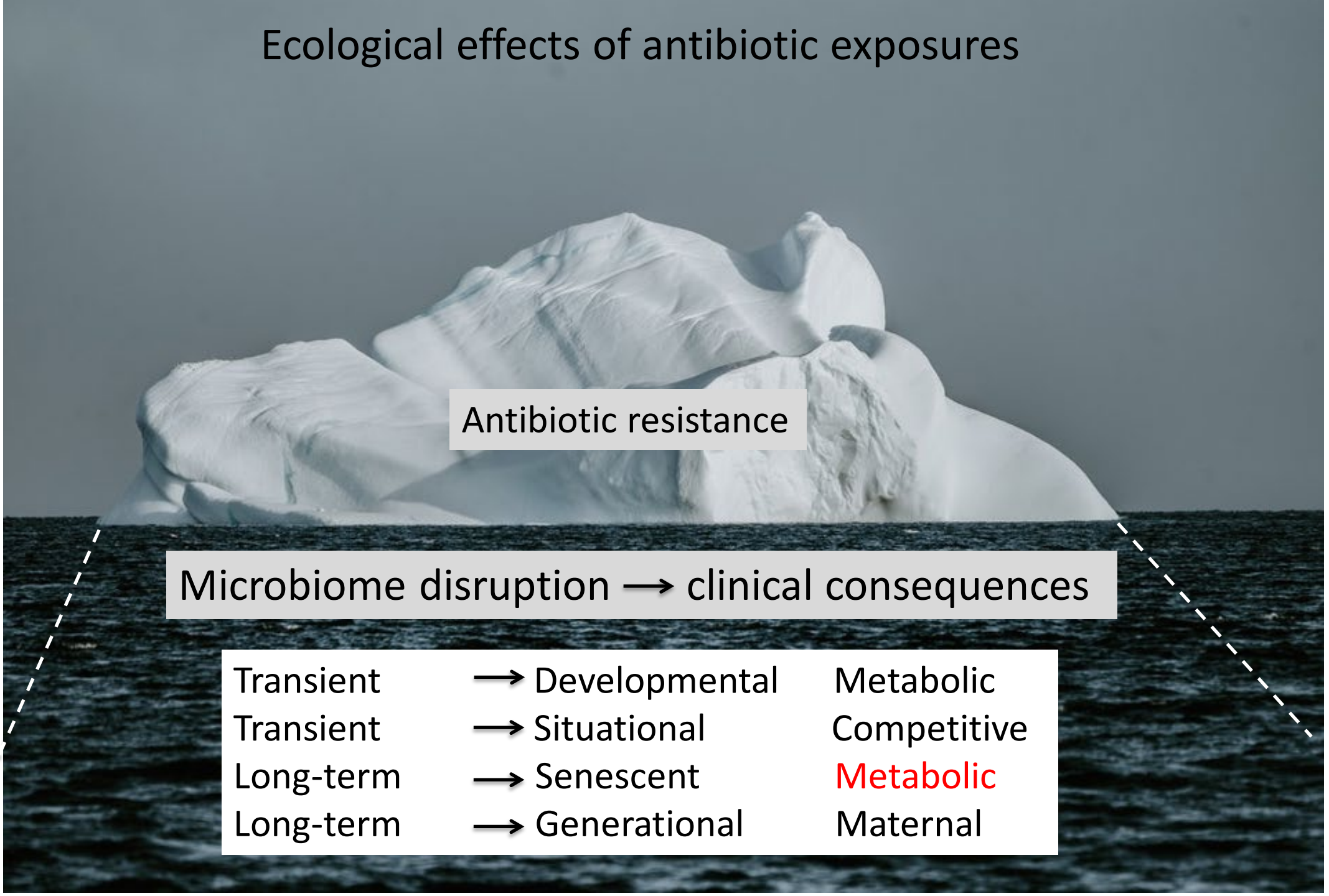
## Significance of this study

### What is already known on this subject?

- Increasing data have supported a role for the gut microbiota in colorectal carcinogenesis.
- Limited studies from cancer registries and healthcare claims with short-term follow-up suggest an association between antibiotic exposure and colorectal cancer.
- The association between antibiotic use and risk of colorectal adenoma, the precursor for the majority of colorectal cancers, has not been investigated.

### What are the new findings?

- Exposure to antibiotics earlier in life (age 20–39 and 40–59) was significantly associated with an increased risk for colorectal adenoma after age 60.


Ecological effects of antibiotic exposures
Antibiotic resistance
Microbiome disruption ⟶ clinical consequences
Transient ⟶ Developmental Metabolic
Transient ⟶ Situational Competitive
Long-term ⟶ Senescent Metabolic
Long-term ⟶ Generational Maternal

# Use of Antibiotics and Risk of Type 2 Diabetes: A Population-Based Case-Control Study

Kristian Hallundbæk Mikkelsen, Filip Krag Knop, Morten Frost, Jesper Hallas, and Anton Pottegård

Center for Diabetes Research (K.H.M., F.K.K.), Gentofte Hospital, University of Copenhagen, Hellerup; Novo Nordisk Foundation Center for Basic Metabolic Research (K.H.M., F.K.K.), Department of Biomedical Sciences, University of Copenhagen, Denmark; Department of Medicine (M.F.), Kolding Hospital, Kolding, Denmark; Endocrine Research Unit (M.F.), University of Southern Denmark, Odense, Denmark; and Clinical Pharmacology (J.H., A.P.), Department of Public Health, University of Southern Denmark, Odense, Denmark

**Context and objective:** Evidence that bacteria in the human gut may influence nutrient metabolism is accumulating. We investigated whether use of antibiotics influences the risk of developing type 2 diabetes and whether the effect can be attributed to specific types of antibiotics.

**Methods:** We conducted a population-based case-control study of incident type 2 diabetes cases in Denmark (population 5.6 million) between January 1, 2000, and December 31, 2012. Data from the Danish National Registry of Patients, the Danish National Prescription Registry, and the Danish Person Registry were combined.

KH Mikkelson et al. *J Clin Endocrinol Metab* 2015

# Oral Antibiotic Exposure and Kidney Stone Disease

Gregory E. Tasian,[1,2,3] Thomas Jemielita,[4] David S. Goldfarb,[5] Lawrence Copelovitch,[6] Jeffrey S. Gerber,[2,3,7] Qufei Wu,[3] and Michelle R. Denburg[2,3,6]

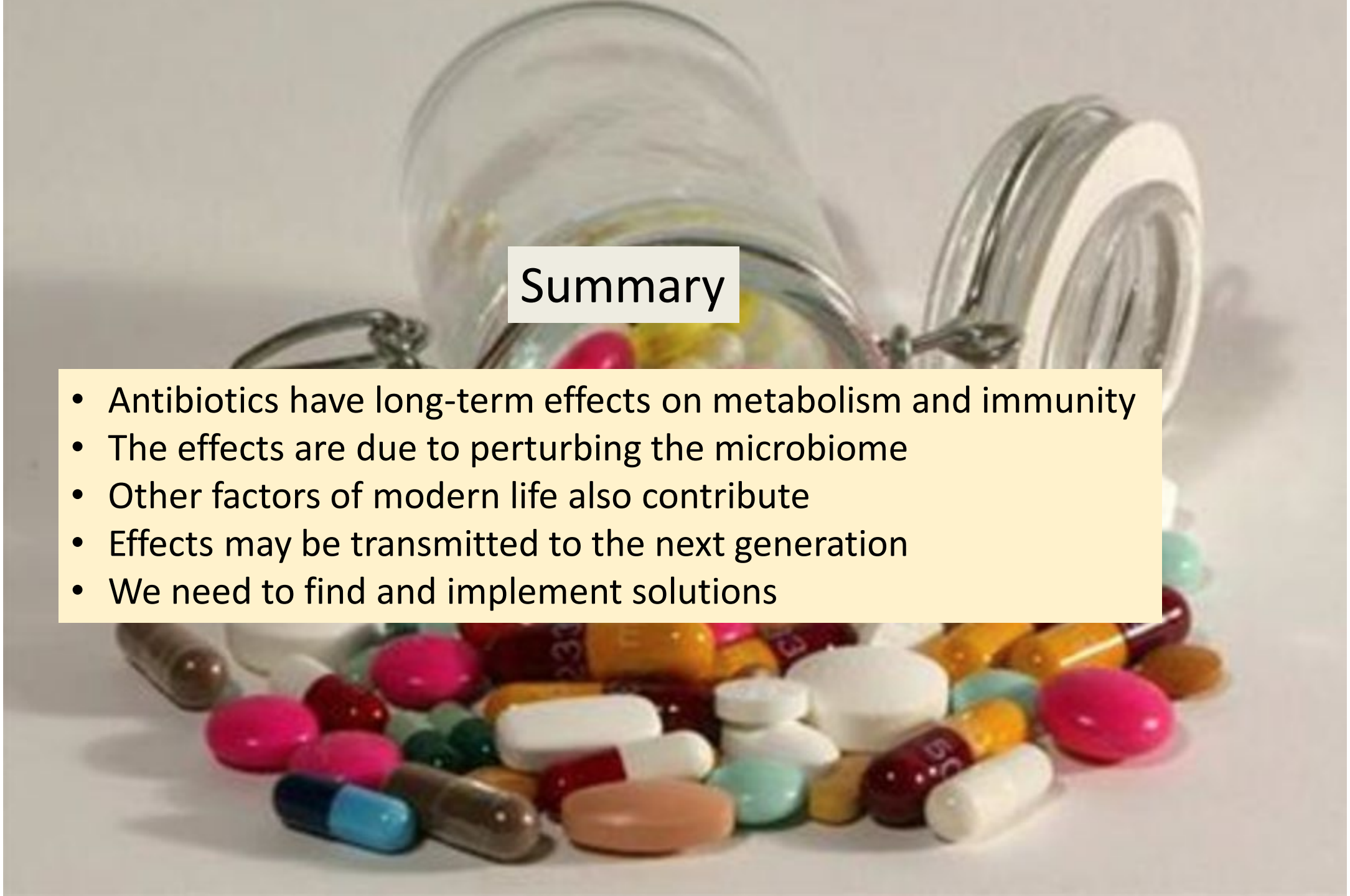
[1]Division of Pediatric Urology, Department of Surgery, and [2]Center for Pediatric Clinical Effectiveness, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; [3]Department of Biostatistics, Epidemiology, and Informatics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania; [4]Biostatistics and Research Decision Science, Early Oncology Department, Merck & Co., Inc., North Wales, Pennsylvania; [5]Division of Nephrology, Department of Medicine, New York University Langone Medical Center, New York, New York; and Divisions of [6]Nephrology and [7]Infectious Diseases, Department of Pediatrics, The Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania

## ABSTRACT

**Background** Although intestinal and urinary microbiome perturbations are associated with nephrolithiasis, whether antibiotics are a risk factor for this condition remains unknown.

**Methods** We determined the association between 12 classes of oral antibiotics and nephrolithiasis in a population-based, case–control study nested within 641 general practices providing electronic health record data for >13 million children and adults from 1994 to 2015 in the United Kingdom. We used incidence density sampling to match 25,981 patients with nephrolithiasis to 259,797 controls by age, sex, and practice at date of diagnosis (index date). Conditional logistic regression models were adjusted for the rate of health care encounters, comorbidities, urinary tract infections, and use of thiazide and loop diuretics, proton-pump inhibitors, and statins.

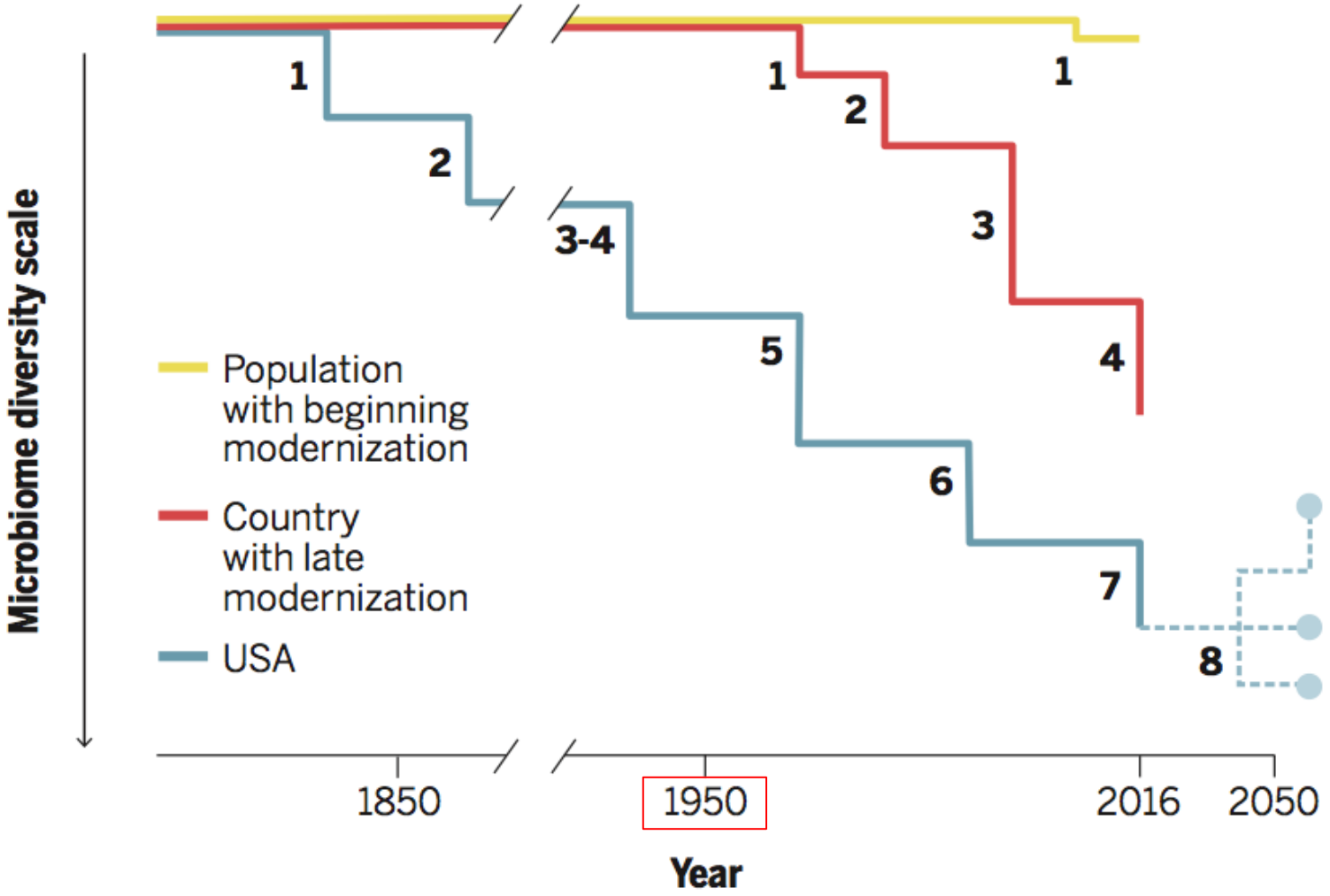
GE Tasian *et al*. *JASN* 2018; 29:1731-40.



# Summary

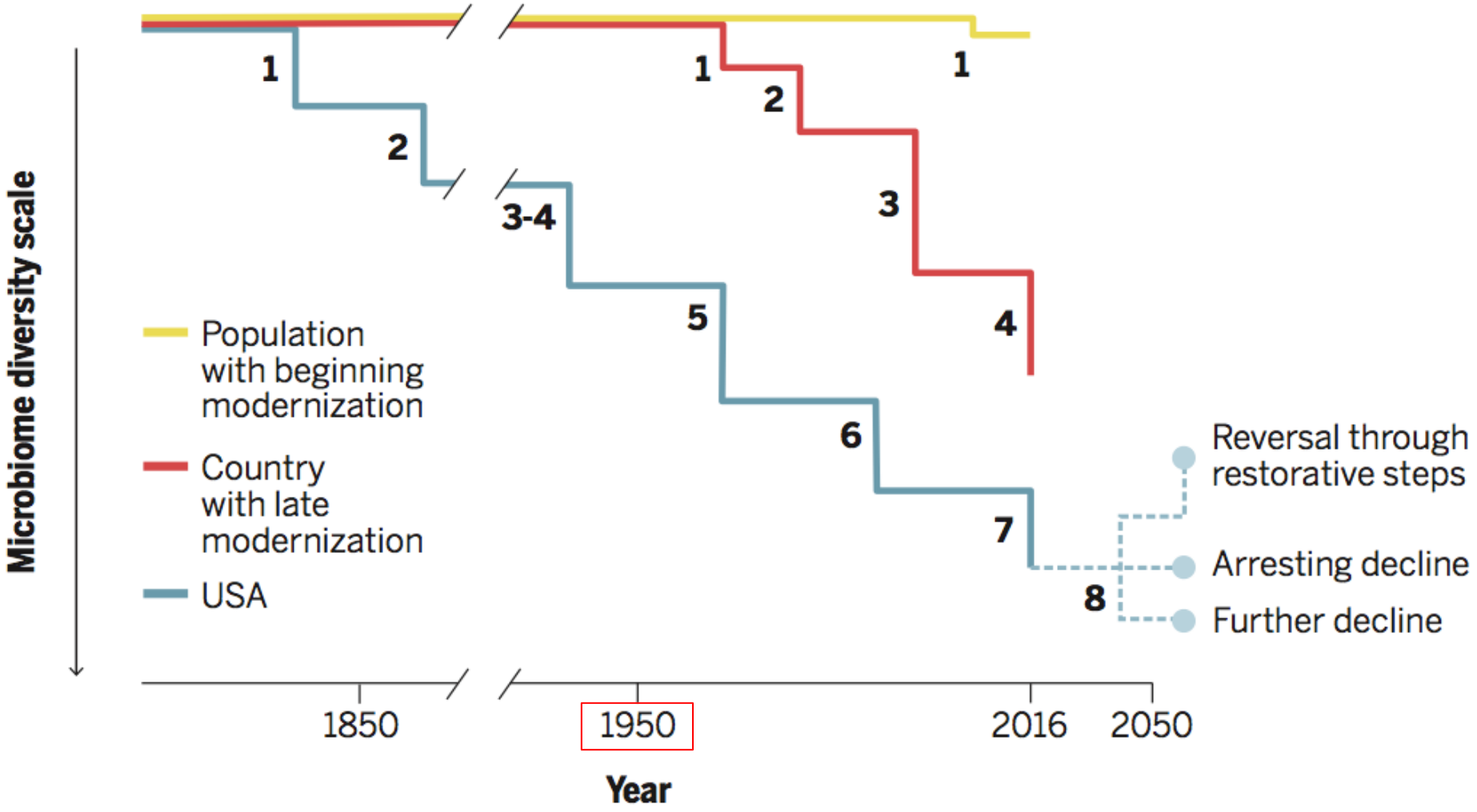
- Antibiotics have long-term effects on metabolism and immunity
- The effects are due to perturbing the microbiome
- Other factors of modern life also contribute
- Effects may be transmitted to the next generation
- We need to find and implement solutions

# Diversity loss in the microbiome in 3 model locales

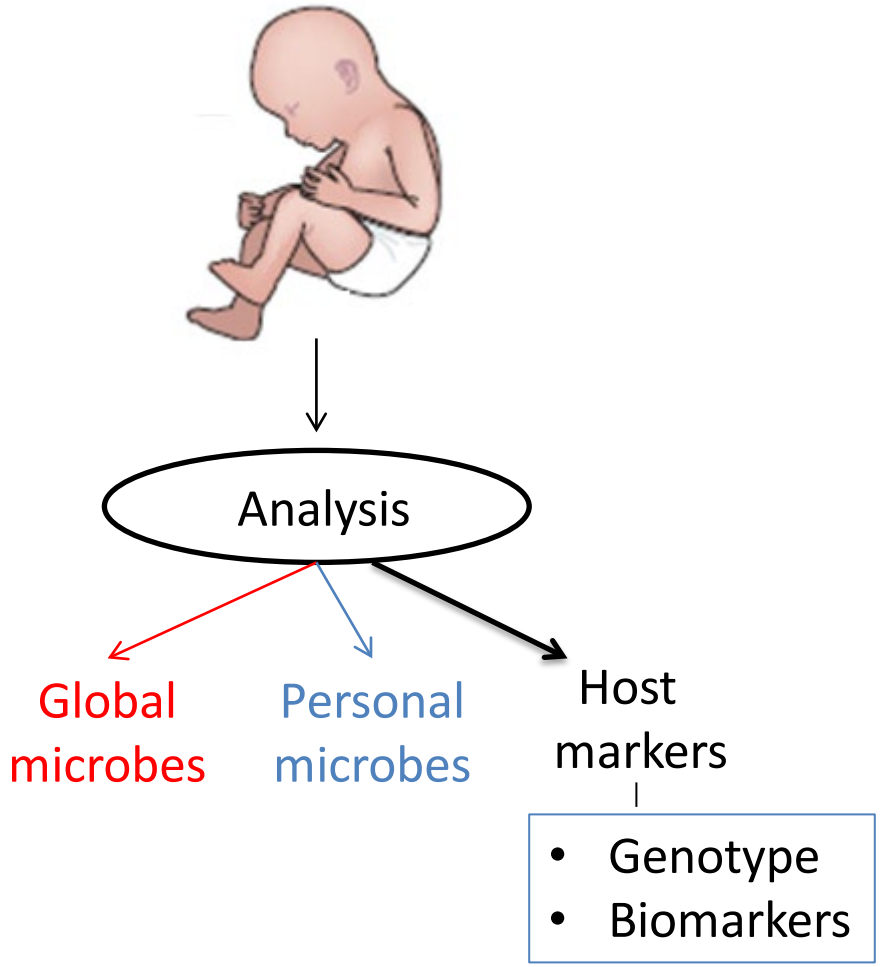



*Science* 2016

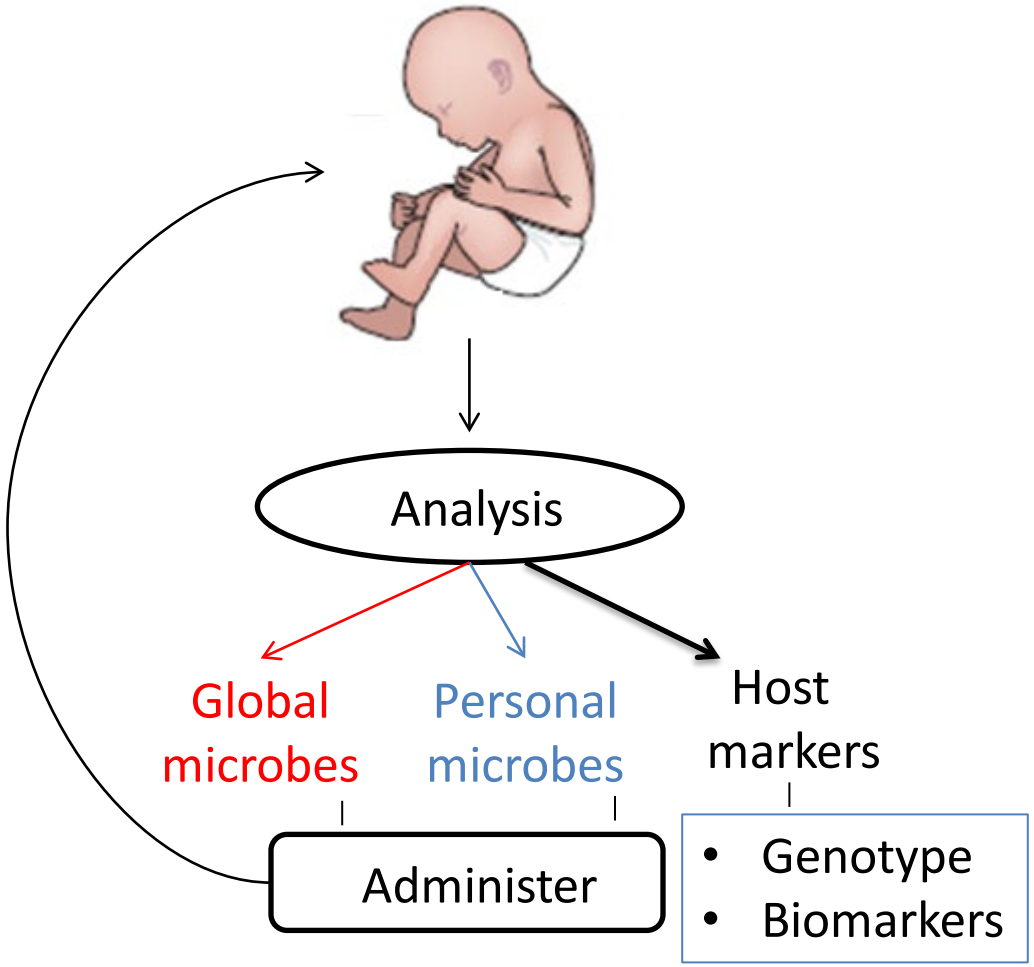
# Next steps for the microbiome?

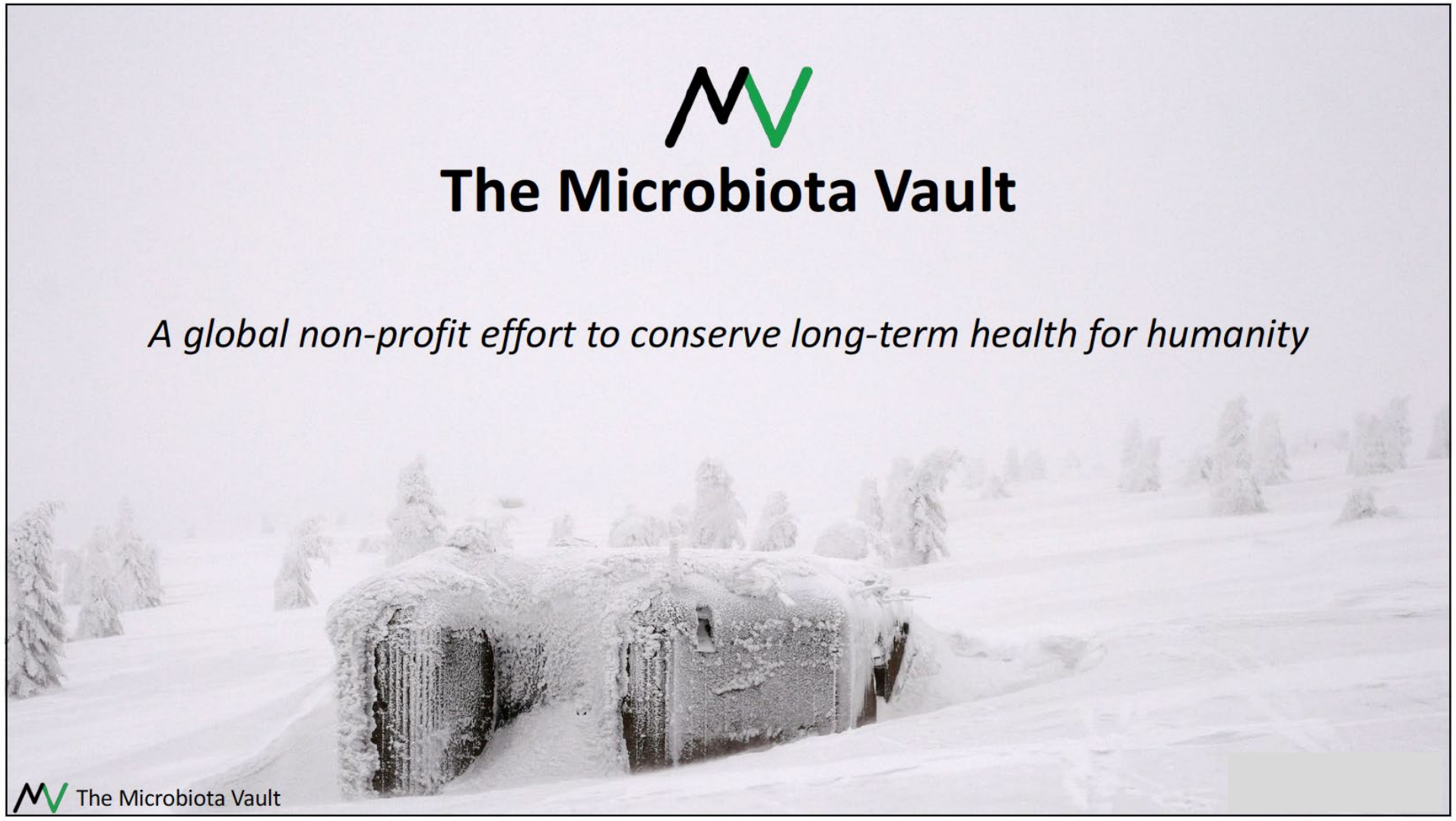


# Medicine of the future: new analyses of child health



# New approach to optimize child health?






www.microbiotavault.org

MG Dominguez Bello *et al*. *Science* 2018;362:33