



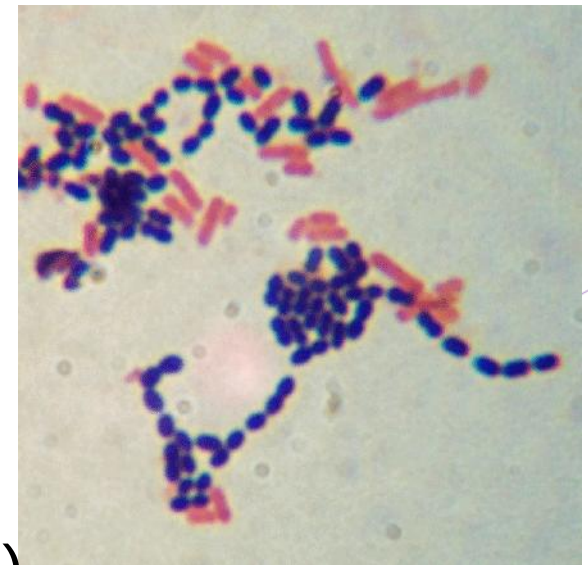
El Microbioma Humano: Nuevos Conceptos

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Universidad de New York Escuela de Medicina
Langone Medical Center**

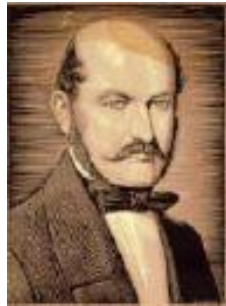
Octubre 22, 2012

La época de Oro de la Bacteriología



Robert Koch (1843-1910)

SON LOS MICROBIOS PATOGENOS DIFERENTES?



Ignaz
Semmelweis



Louis
Pasteur



Joseph
Lister



Robert
Koch

LA TEORIA DEL GERMEN
DE LA ENFERMEDAD
FINALES 1800s

SI

Bail c1900
Rosenow

Virulinas
Agresinas
CAPSULES
TOXINS

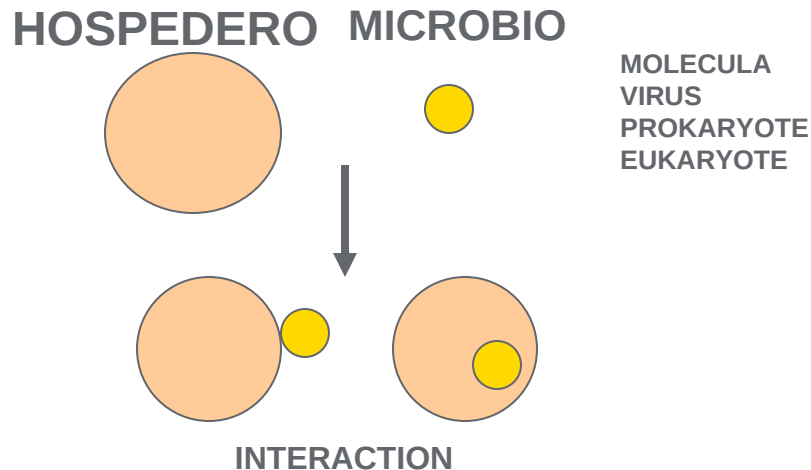
NO

‘No hay diferencias fundamentales entre
patógenos y no patógenos
Bordet c1912

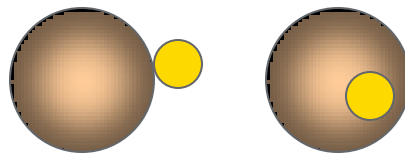
1. Virulencia no es estable
2. Inmunización previene virulencia

MARCO DAÑO-RESPUESTA

1. Dos participantes



2. RESULTADO IMPORTANTE= DAÑO AL HOSPEDERO



3. DAÑO PUEDE VENIR DEL HOSPEDERO, MICROBIO O AMBOS

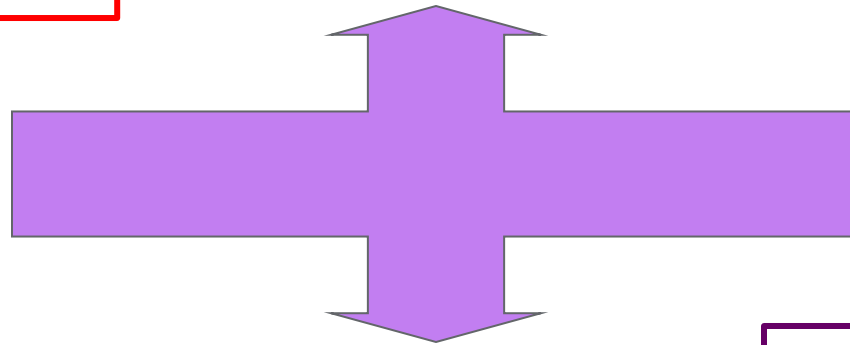
Interaccion Microbio-Hospedero

Produce:

Toxinas, invade células
Produce daño tisular
Enfermedad y muerte

Inmunidad natural
Respuesta inmune :
Humoral y celular

Microbio



Hospedero

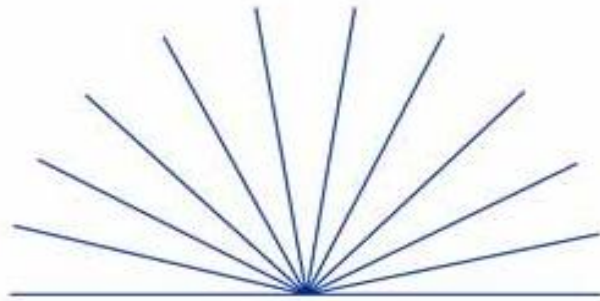
Contribuye a:

Nutrición de hospedero
Balance energético
Desarrollo y mantenimiento
de una respuesta inmune
robusta

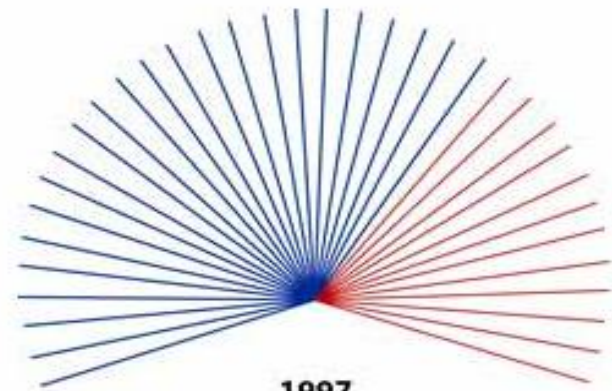
Provee:

Nutrientes esenciales
Asegura su transmisión
Asegura su
mantenimiento en la
misma especie del
hospedero

Known Bacterial Phylogenetic Divisions

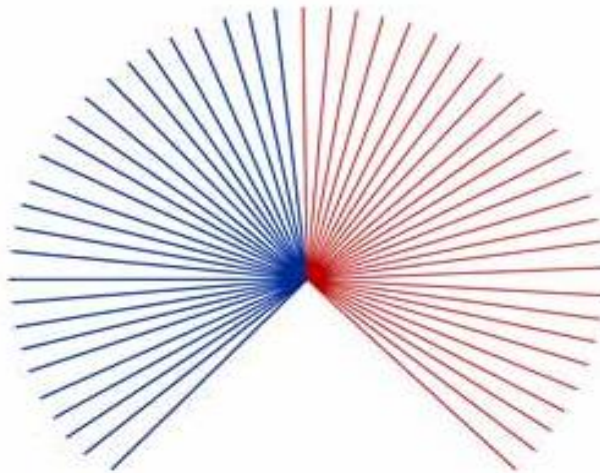


1987
(12 divisions; 12 cultured / 0 uncultured)

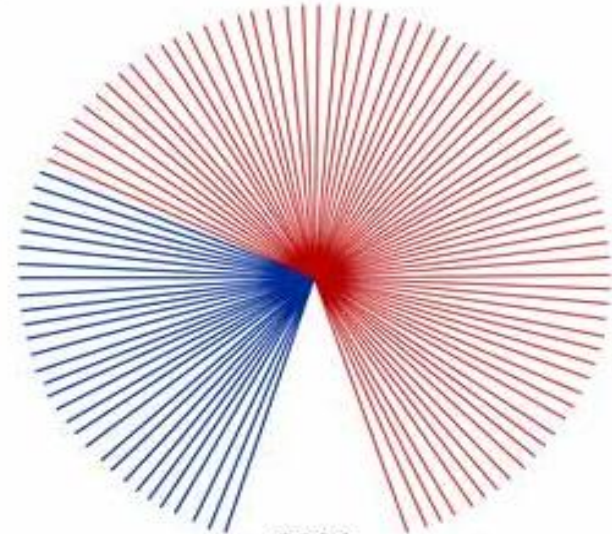


1997
(36 divisions; 24 cultured / 12 uncultured)

— Cultured
— Uncultured

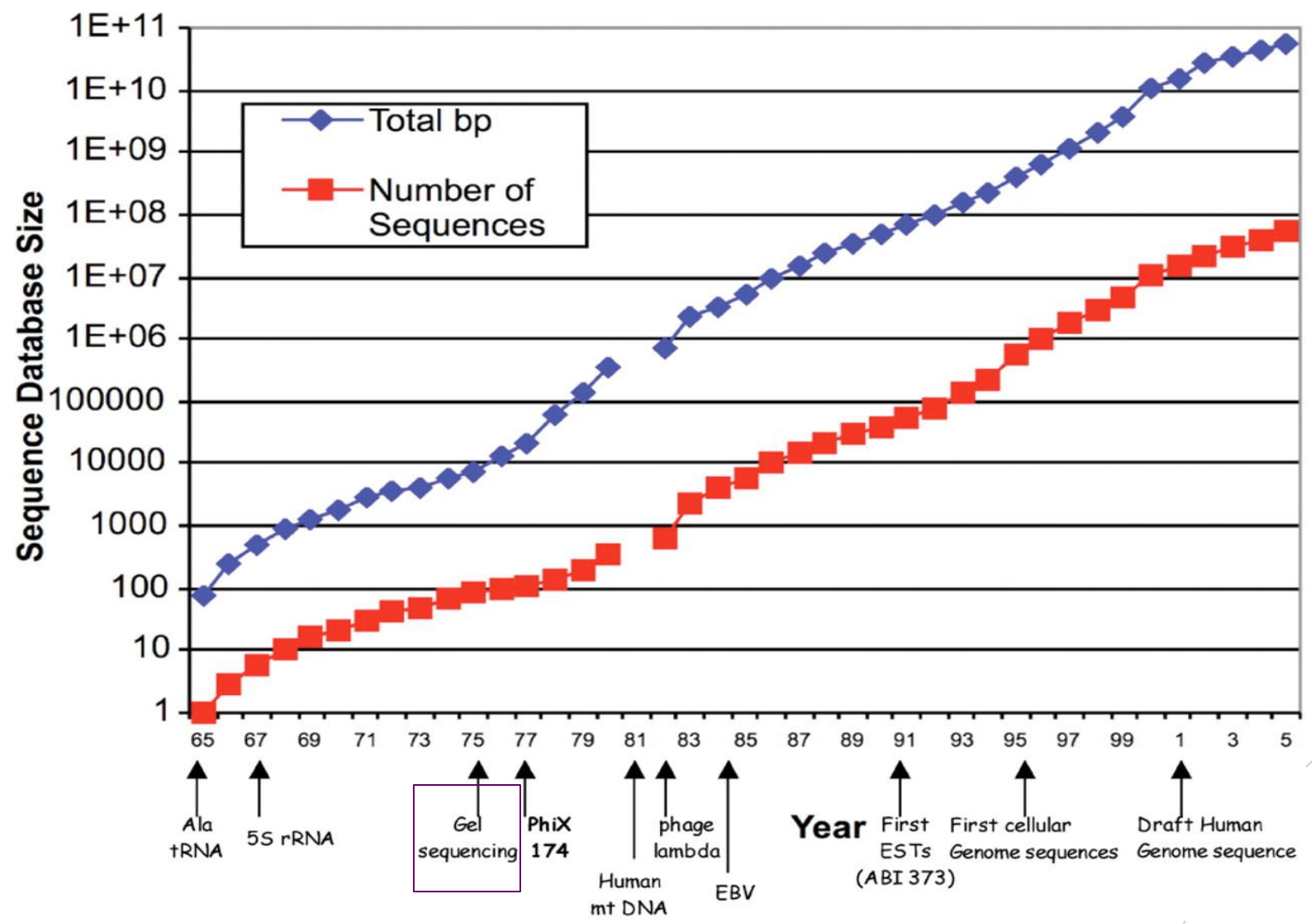


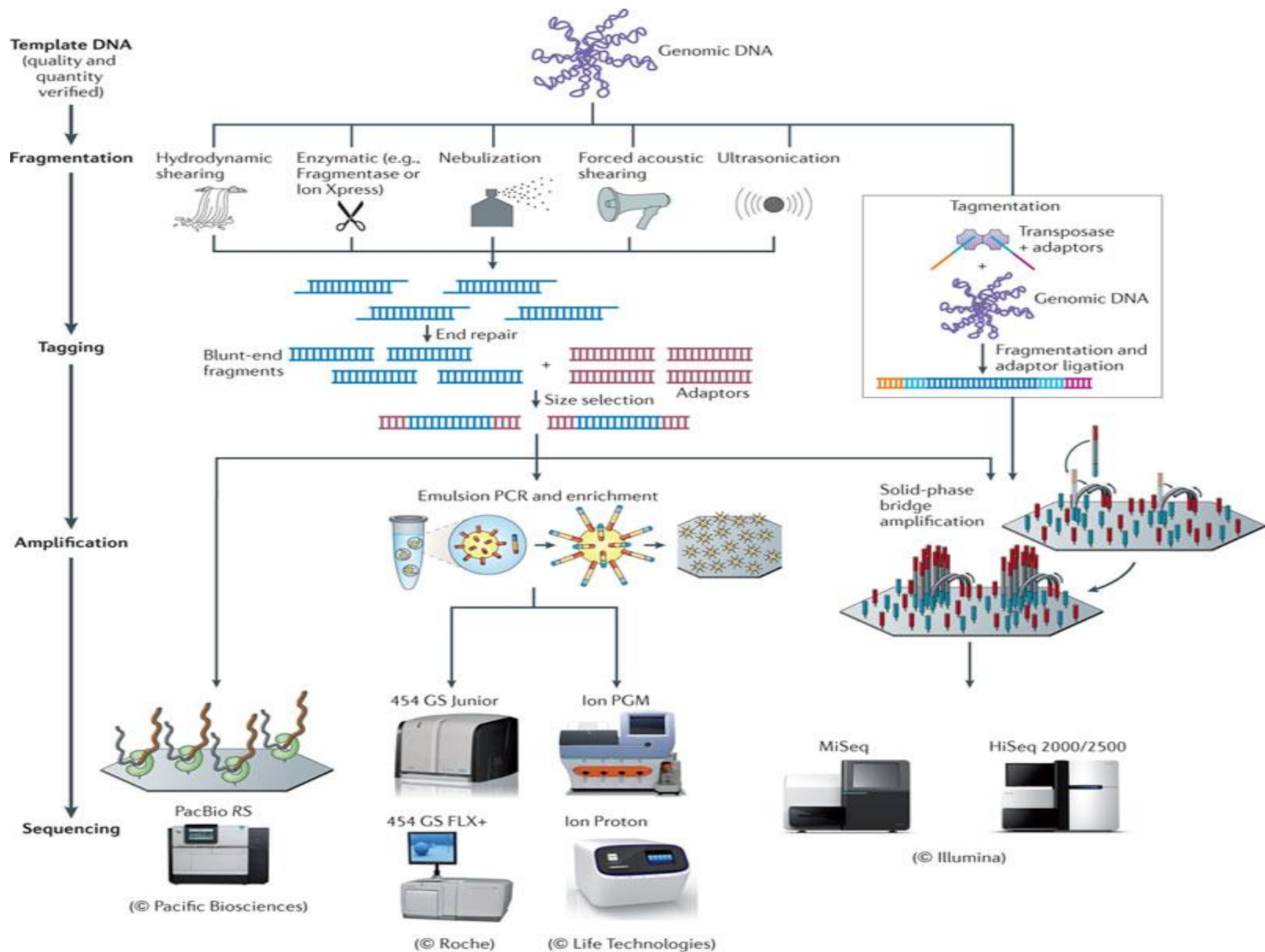
2003
(53 divisions; 26 cultured / 27 uncultured)



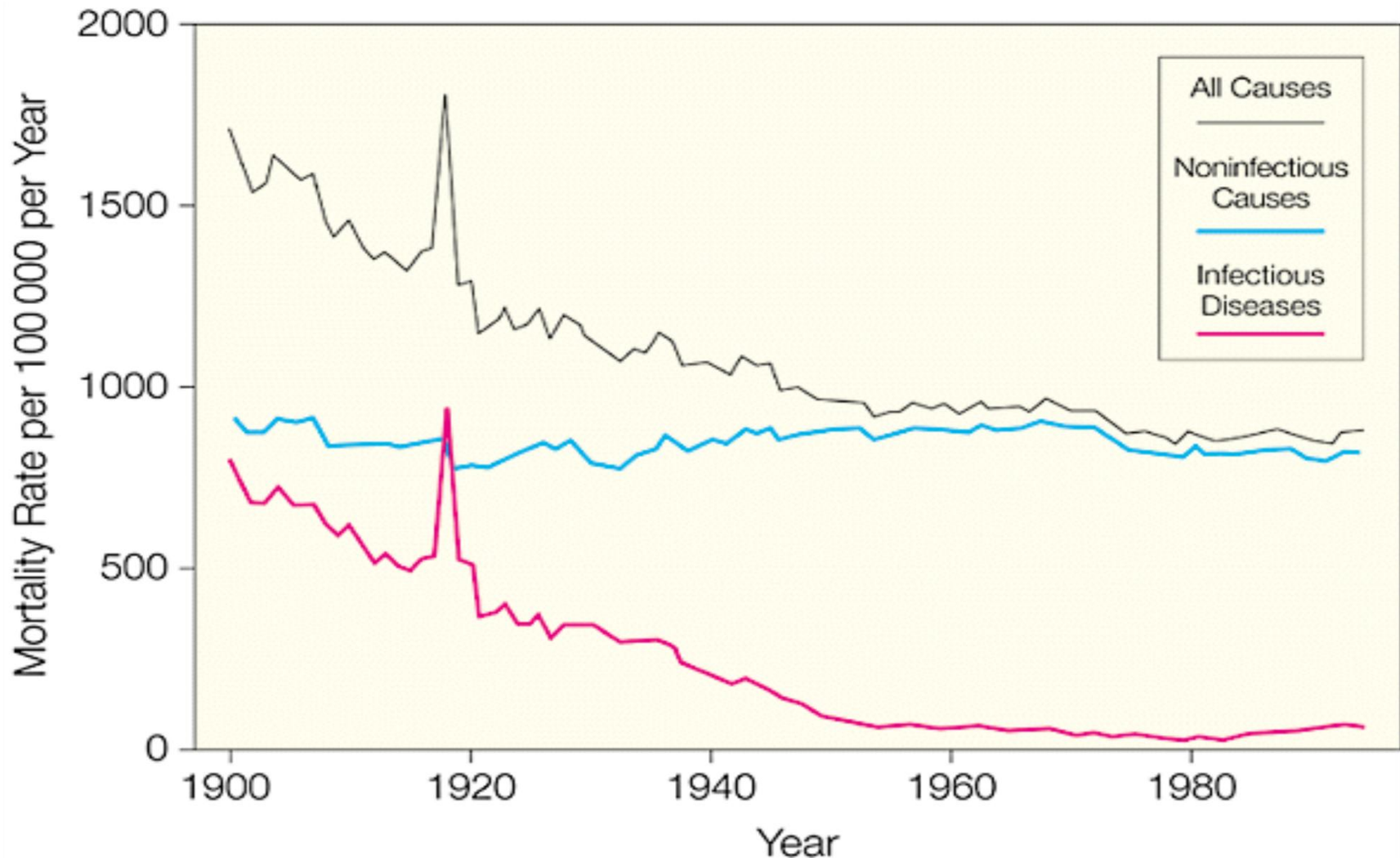
2006
(~100 divisions; 30 cultured / ~70 uncultured)

Aumento en el Numero de Nucleotidos Secuenciados

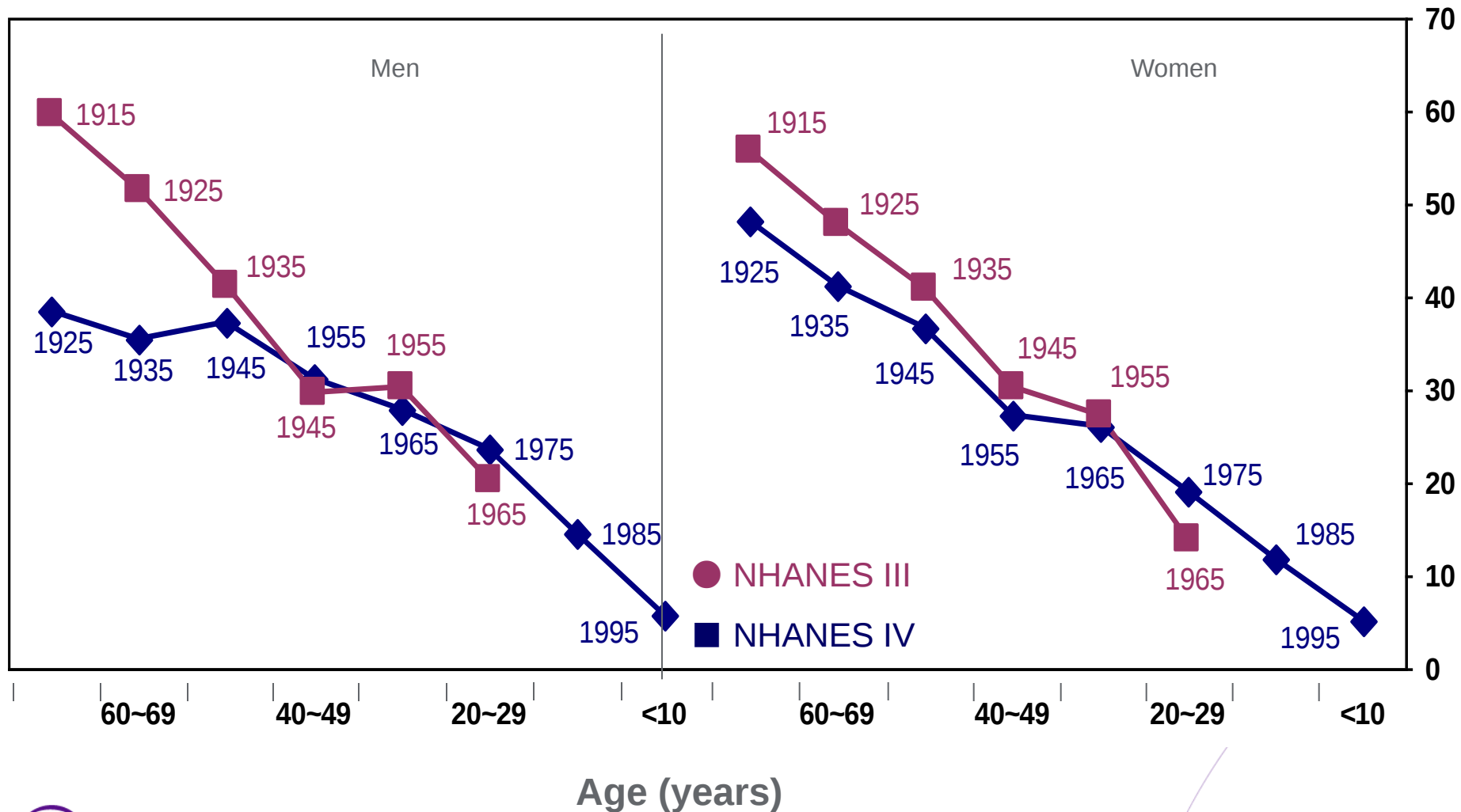




Tendencia en la mortalidad a las enfermedades Infecciosas en los EUA durante el siglo XX

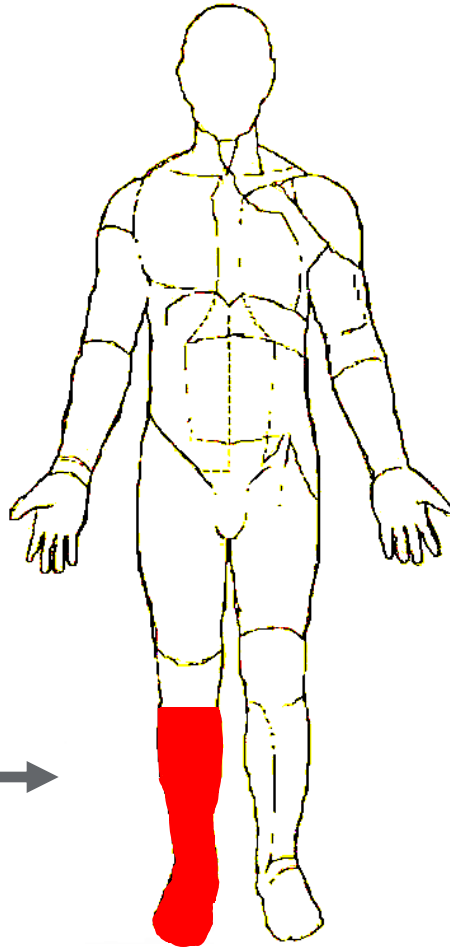


Prevalencia de *H. pylori* en los EUA, por Edad y Año de Nacimiento



Quiénes somos?

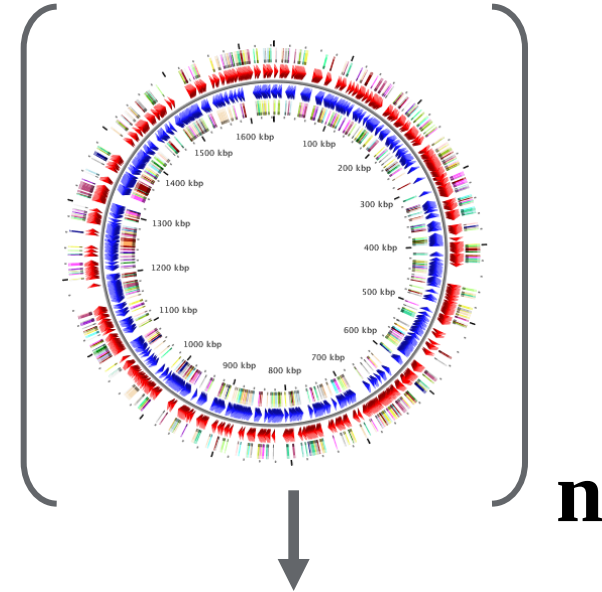
10^{13} Celulas
humanas



10^{14} células
microbianas



+



GENOMA

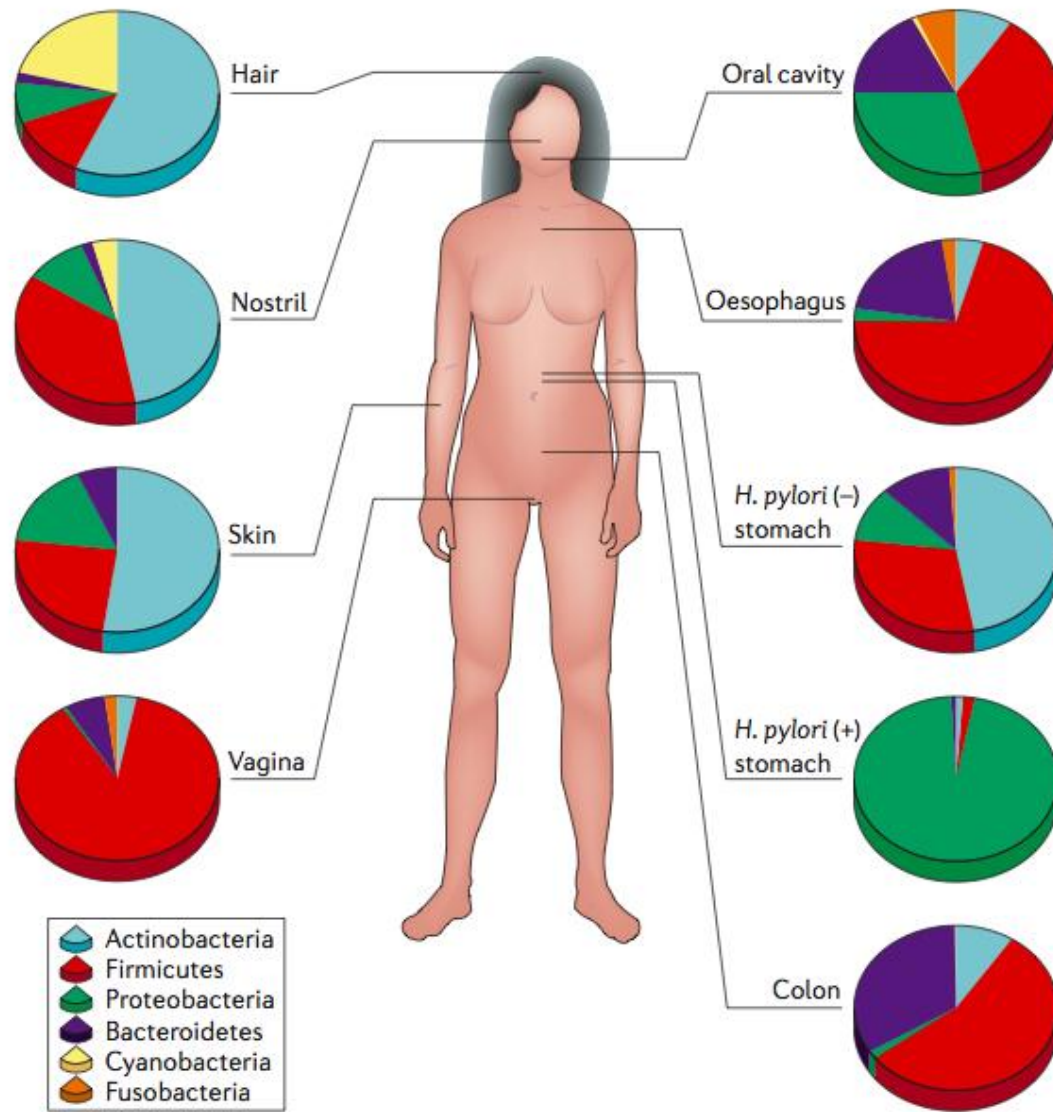


MICROBIOMA

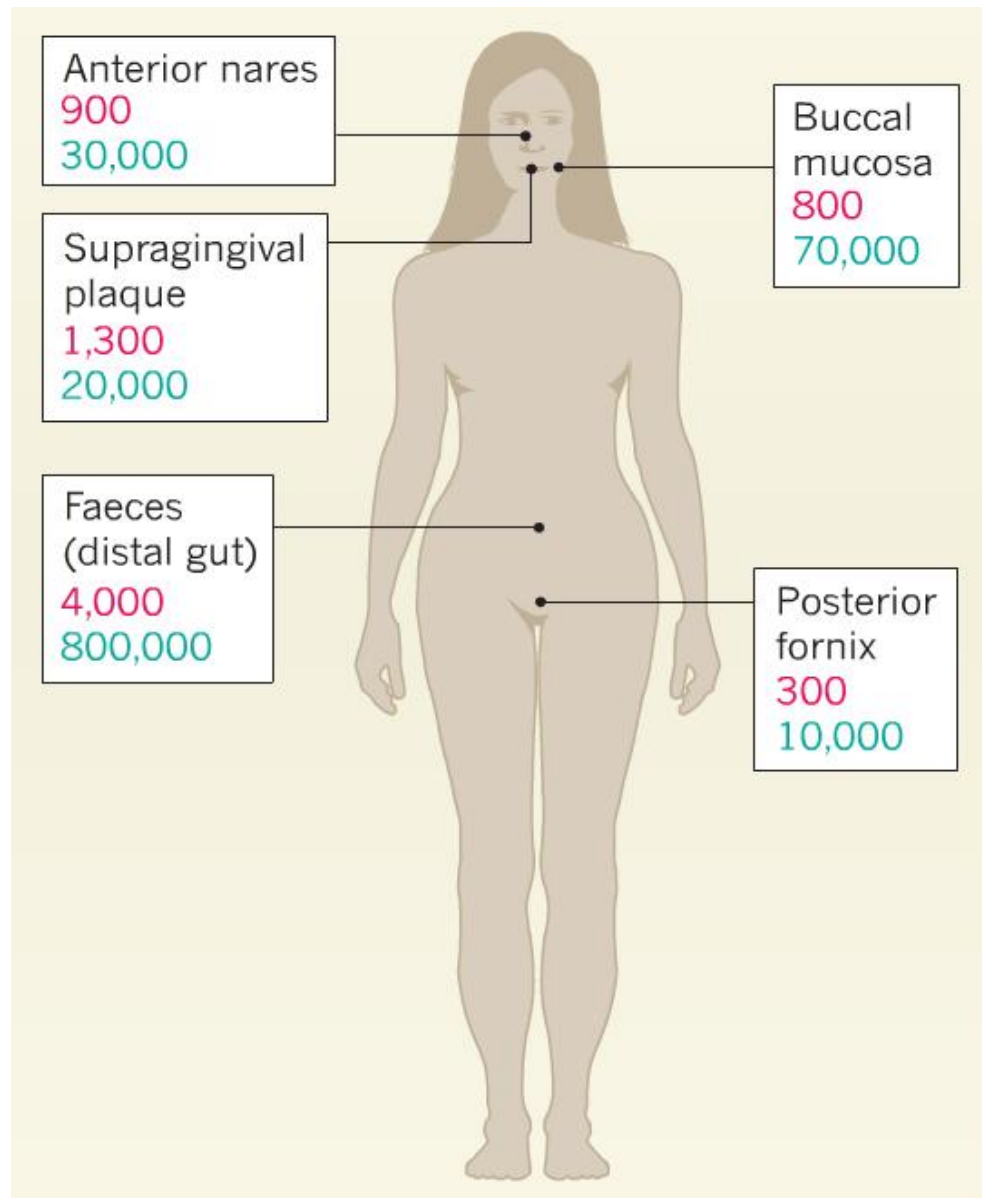
Metabolome

EMBO Rep 2006;7:956.
Nature 2007;449:843.
PNAS 2010; 107:6125.

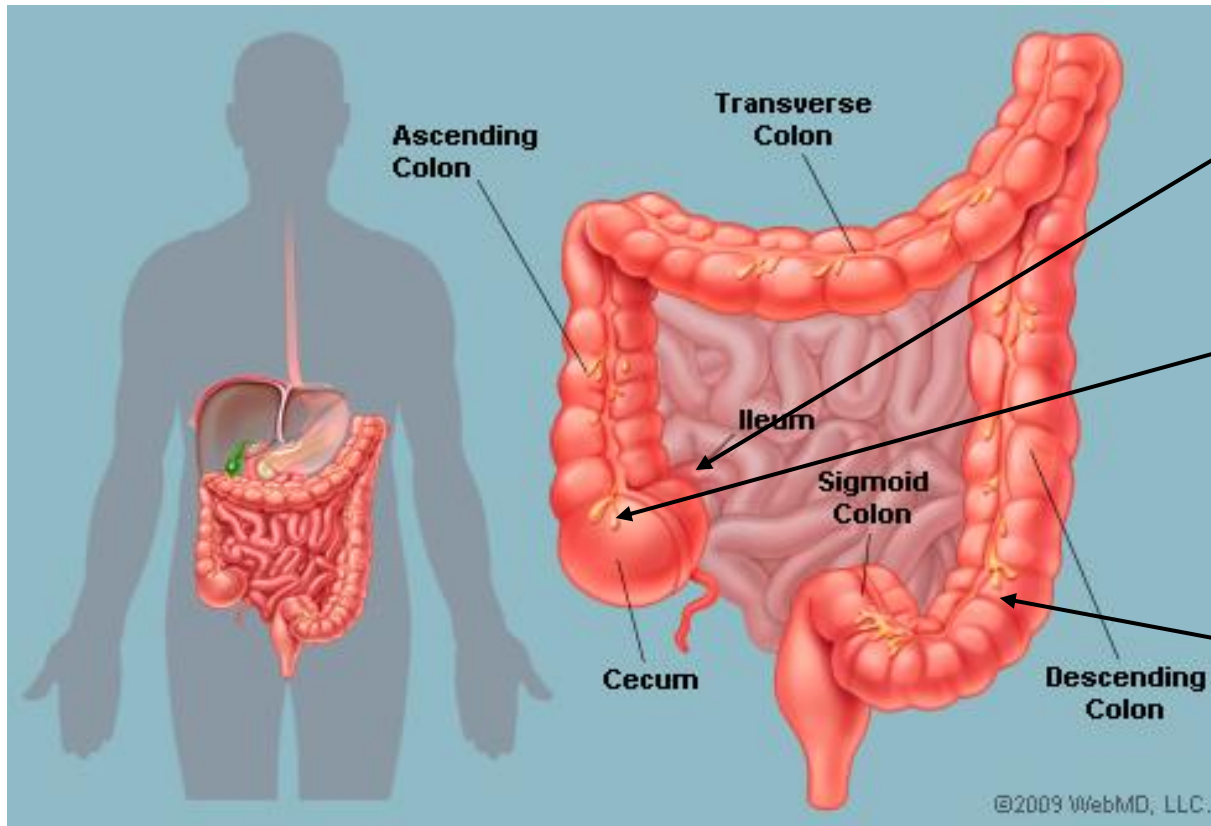
Diversidad del Microbioma en el Cuerpo Humano



- 242 healthy human adults
- 15 sites for men
- 18 sites for women
- Skin 4 sites
- Mouth and throat 9 sites
- Vagina 3 sites
- Feces
- Nostrils



Concentración de Bacterias en el Tubo Digestivo



Ileum: 10^5 to 10^9 cfu/g

Proximal Colon:
 10^{10} to 10^{11} cfu/g

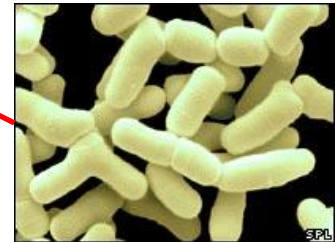
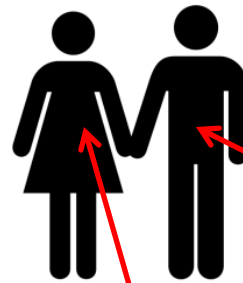
Distal Colon
 10^{12} to 10^{14} cfu/g

The principal sites of colonic fermentation are the cecum and proximal colon.

Un colon Sano tiene mas Bacterias que Seres Humanos sobre la Tierra



Earth: population 7,070,037,517



Human gut microbiome:

10,000,000,000,000 bacteria

Digest

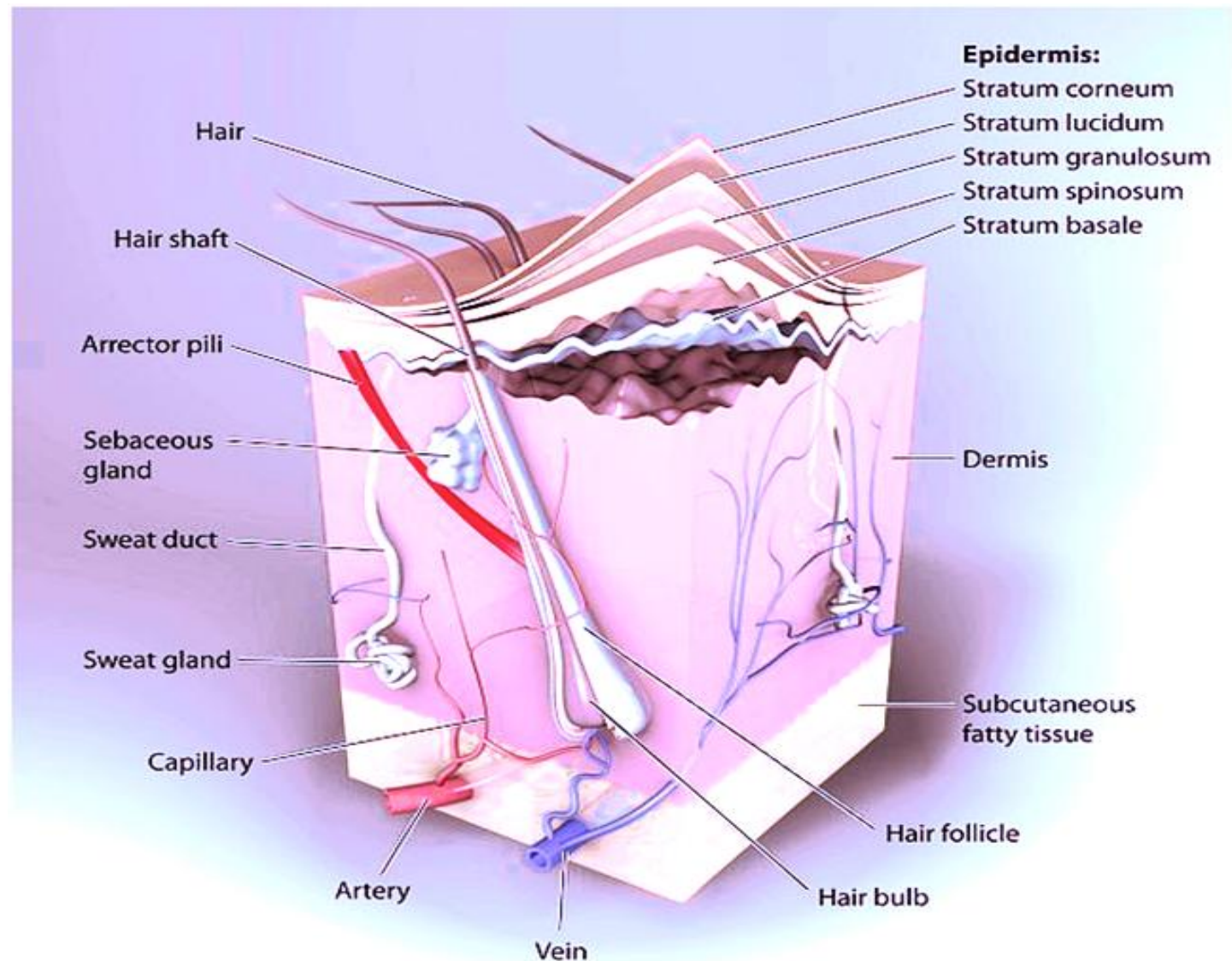
Detoxify

Synthesize

Que es Disbiosis?

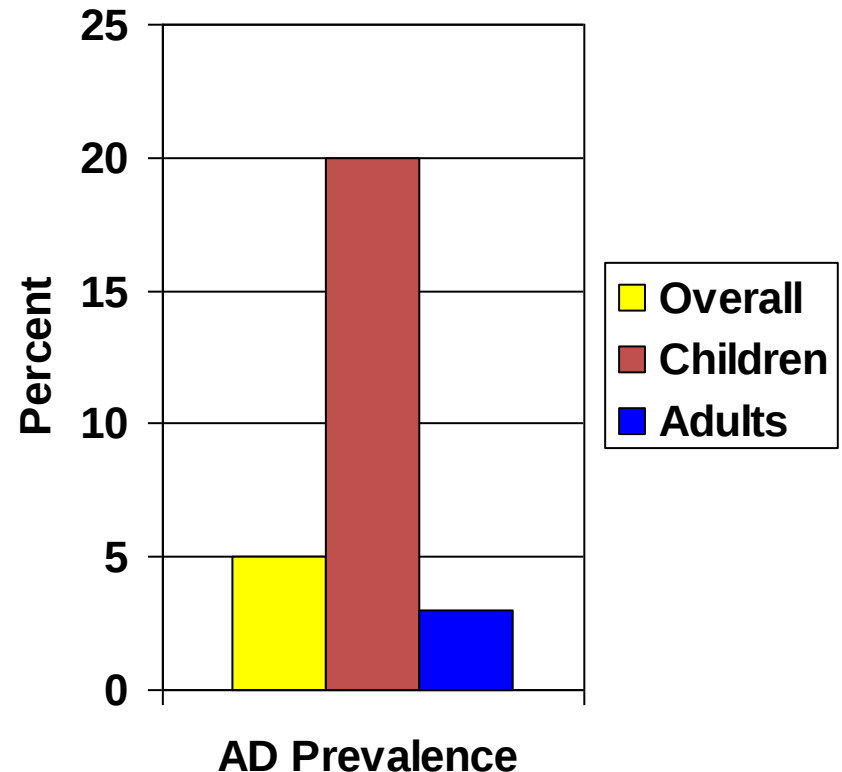
Un cambio subitito en la comunidad de bacterias comensales que puede resutar en una enfermedad inflamatoria no solo en el intestino pero tambien en otros organos a sitios distantes.

Piel



Dematitis Atopica: Prevalencia

- Worldwide health problem¹
- Affects 17.8 million children and adults in US, or about 6% of population²
- Childhood lifetime prevalence: 10%-20%^{1,2}
- Prevalence is increasing especially in industrialized countries¹
- Significant adverse impact on quality of life of affected children & families³



¹Asher MI, et al. *Lancet*. 2006;368:.

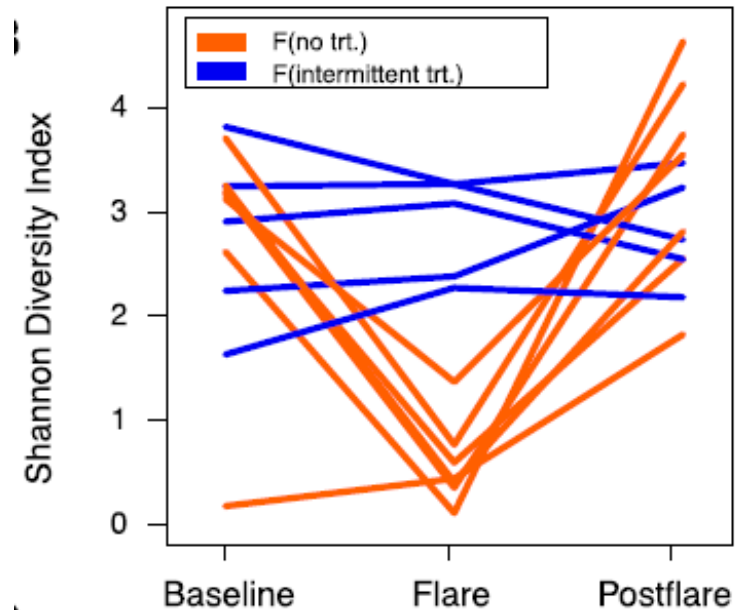
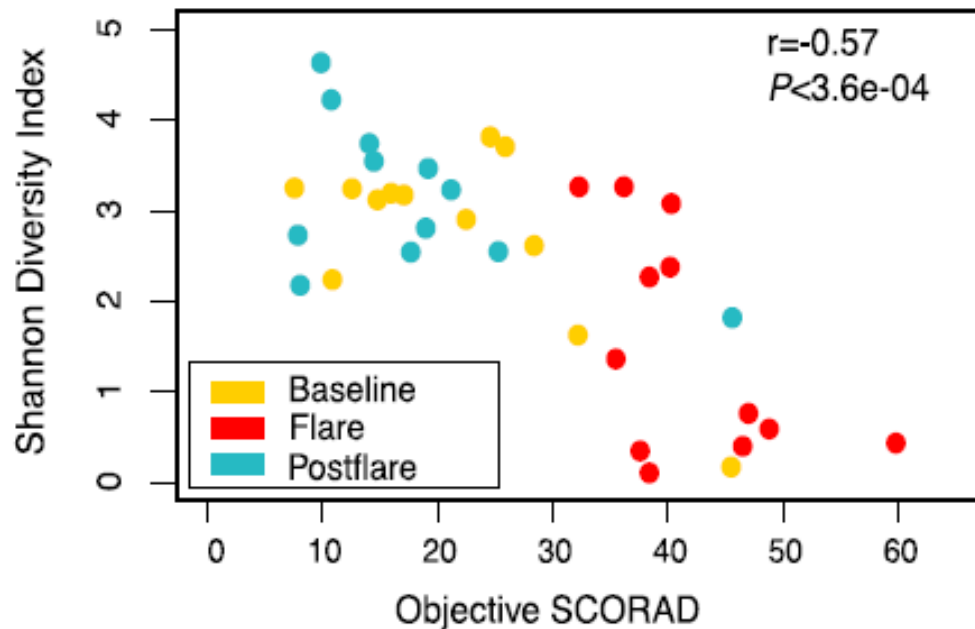
²Hanifin JM et al. *Dermatitis*. 2007.

³Simpson EL, et al. *Med Clin North Am*. 2006;90:149-167

Genomic approach to skin microbiome in atopic dermatitis

- 12 pediatric patients (2-15 yr) moderate to severe AD
- Baseline → “Stable disease state”
- Flare → acute exacerbation
- Post-flare → 10-14 days post treatment
- At each timepoint:
 - L & R antcub (Ac), adjacent volar forearm, L & R popliteal (Pc) nares (culture and DNA extraction)
 - Clinical (overall) SCORAD recorded
- 11 healthy controls sampled at similar intervals

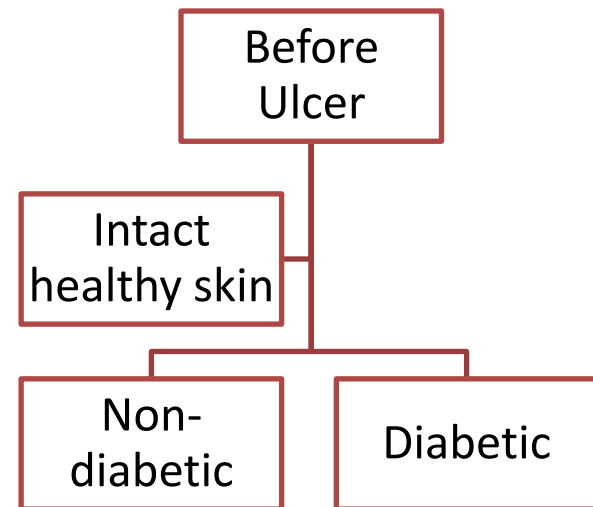
Microbial diversity decreases during AD flares



- Inverse correlation with SCORAD
- Microbial diversity is greatest at baseline and post-flare, and lowest during flares
- No treatment group shows a decrease in diversity during a flare

El Pie del Diabetico

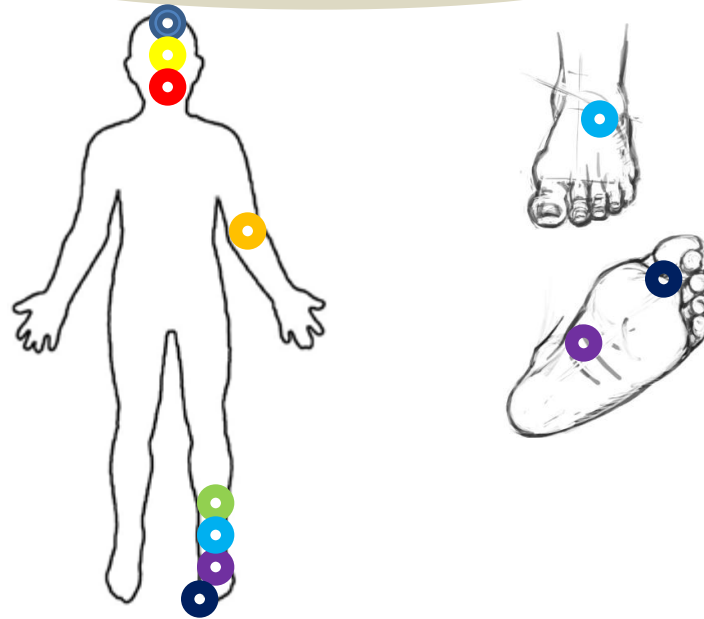
- Diabetic foot ulcers occur in 15% of diabetics, with a yearly incidence of 1-2% of diabetics.
- The pathophysiology is thought to involve neuropathy followed by micro-trauma and formation of ulcers in the skin with subsequent infection.



Variación en el microbioma de la piel entre diabéticos y no-diabéticos

VA Internal Medicine Clinic Patients

Consent and questionnaire



- Forehead
- Nare
- Upper Palate
- Forearm
- Calf
- Dorsal foot
- Plantar arch
- First interdigital space

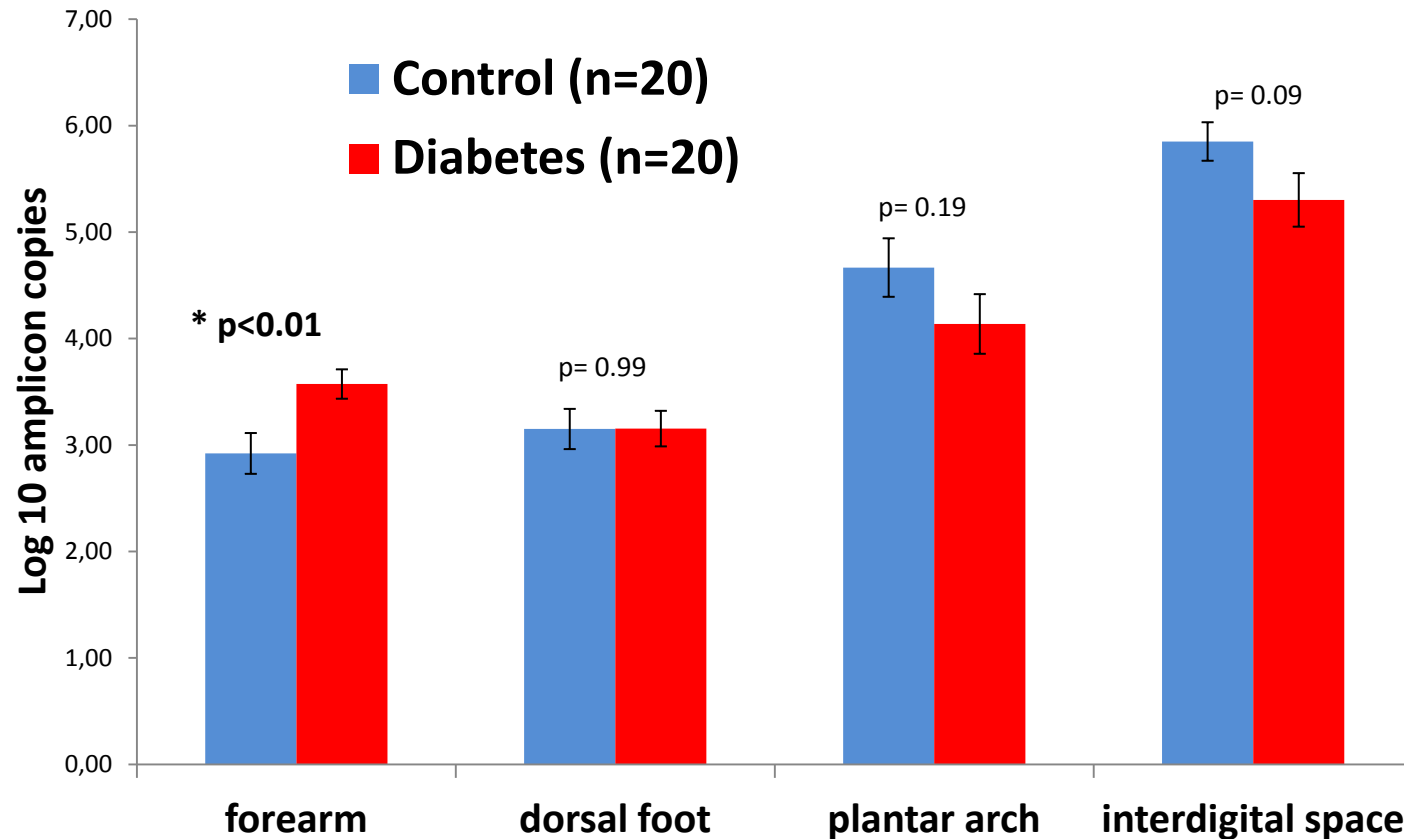
Diabetics
(n=20)

Sites for swab at time
zero and repeat swab
within four months

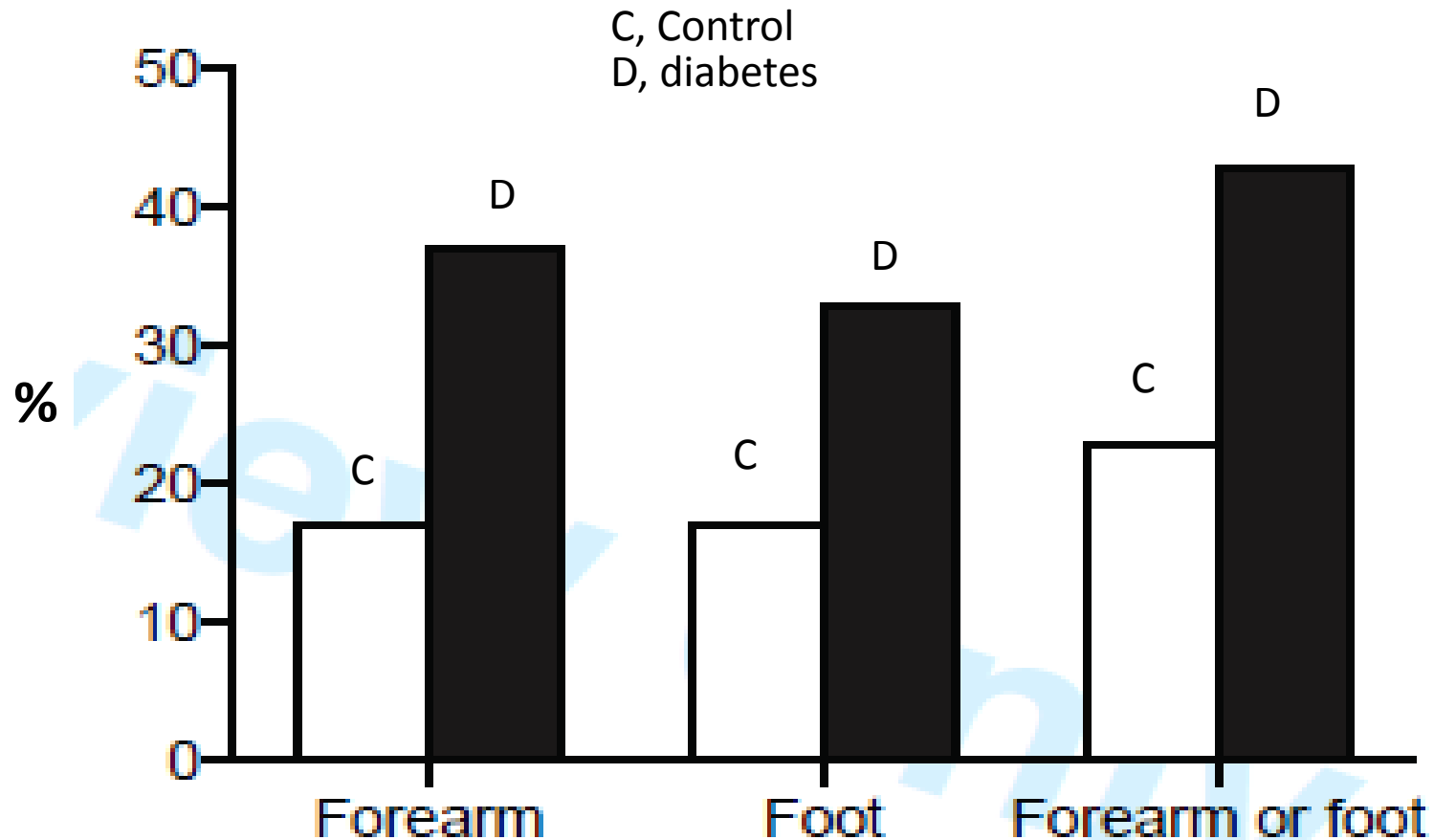
Non-diabetics
(n=20)

Analysis with 454 and qPCR on all samples

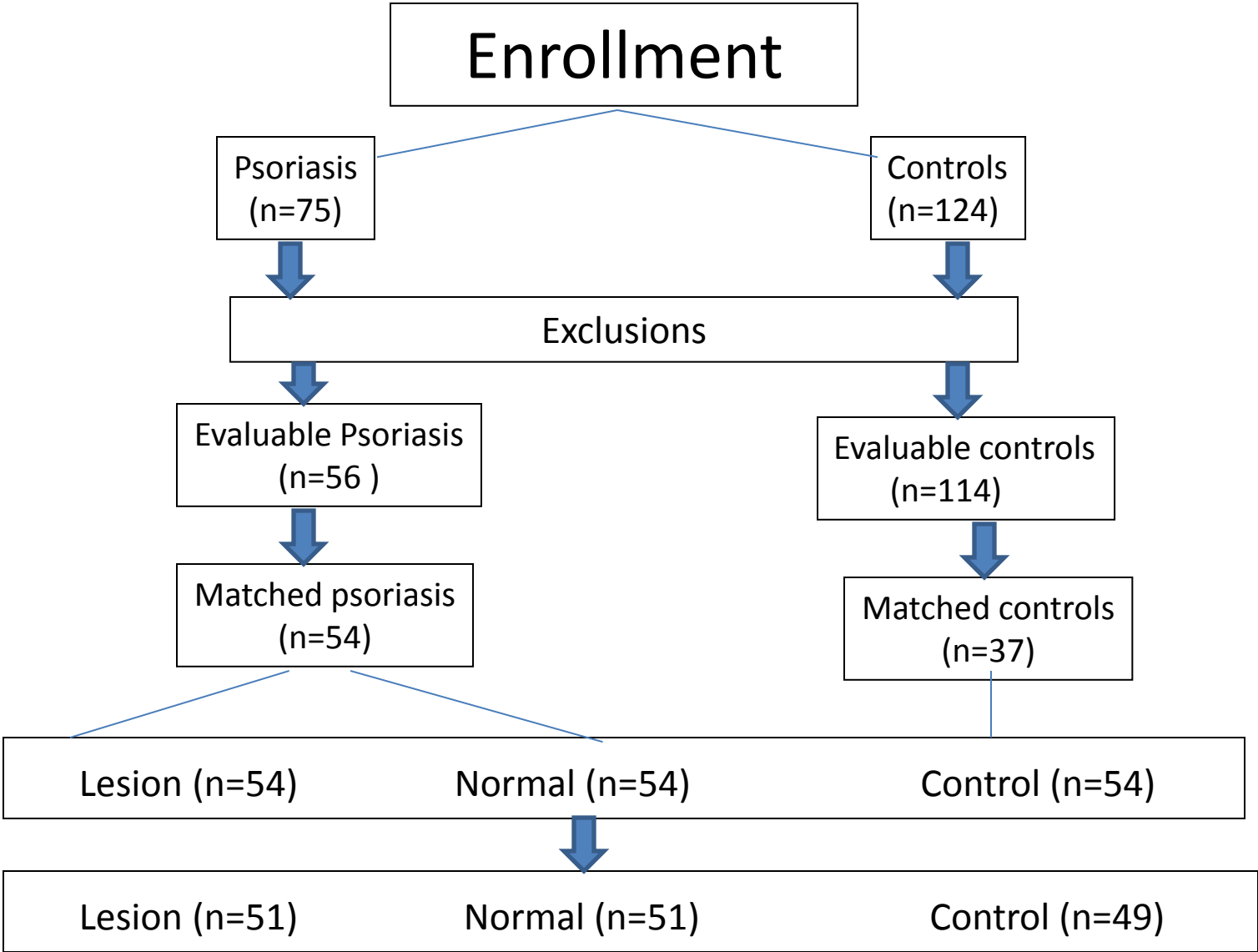
Numero Total de Bacterias en la piel estimado por qPCR en cuatro sitios



Prevalencia de *Staphylococcus aureus*

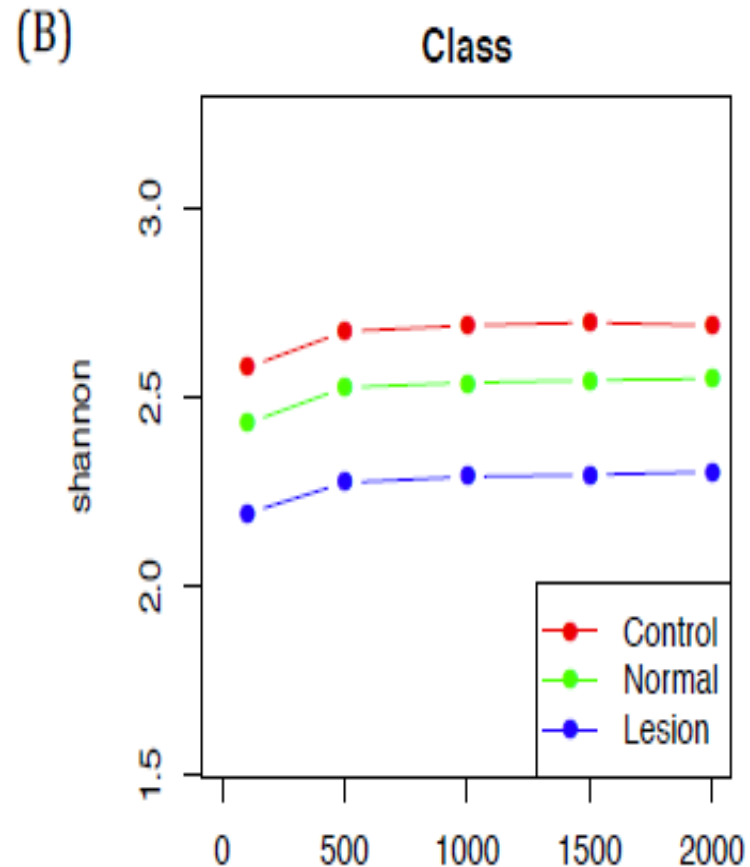
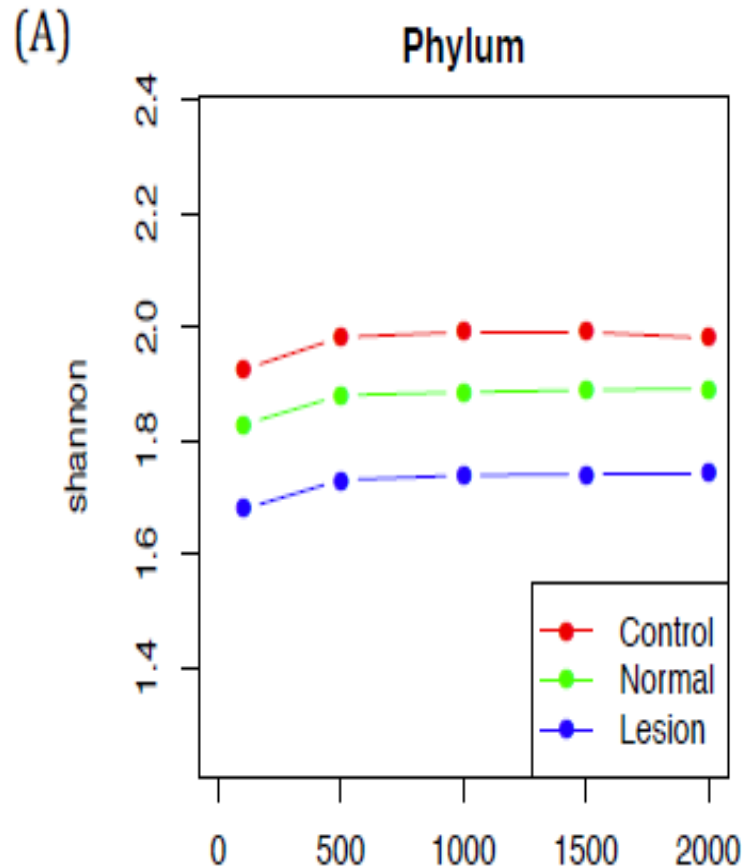


Enrollment and selection of samples for 16S rRNA evaluation.



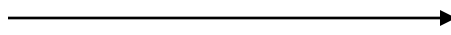
Shannon alpha-diversity of the triplets at baseline

Psoriasis study

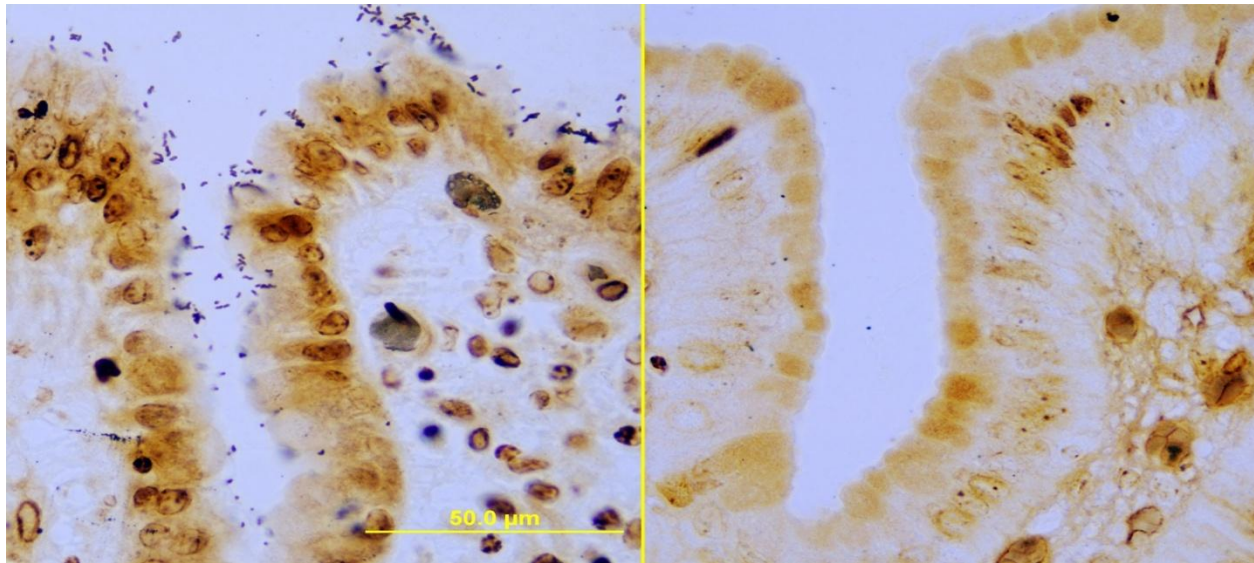


Cambios en la microecología gastrica

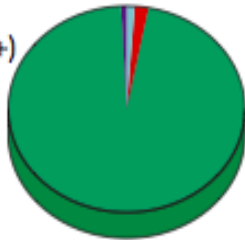
H. pylori⁺



H. pylori⁻



H. pylori (+)
stomach



Consequences:

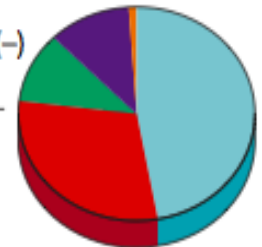
GERD

Esophageal adenocarcinoma

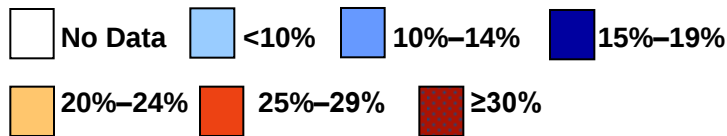
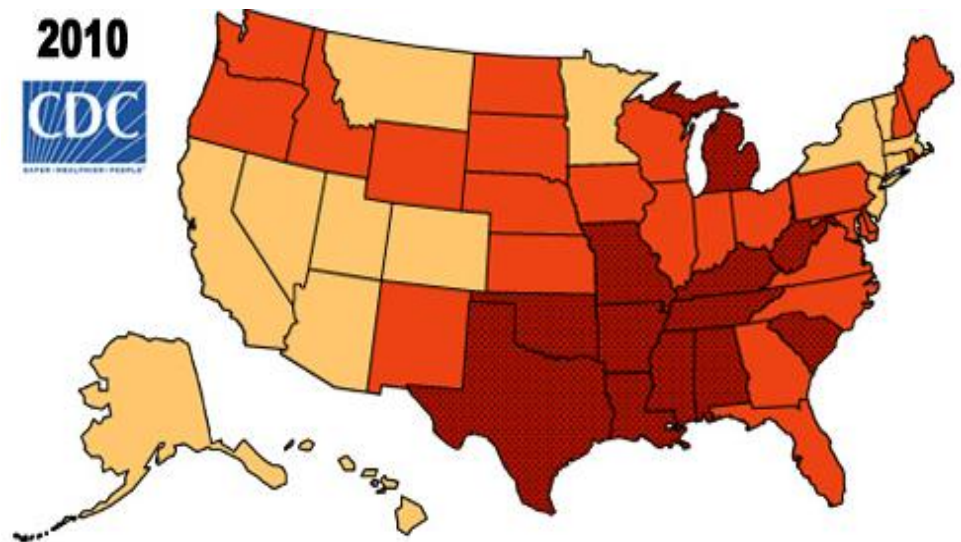
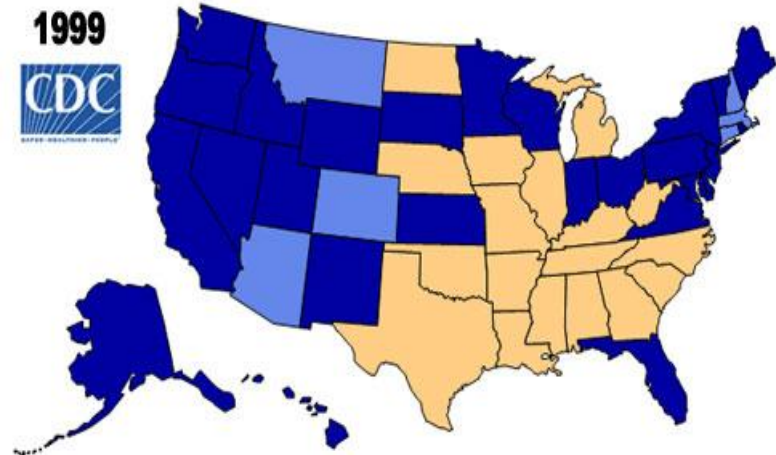
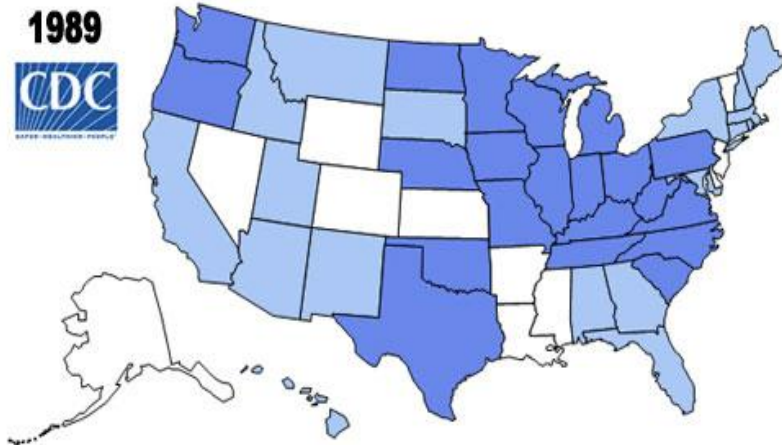
Increase asthma

Obesity

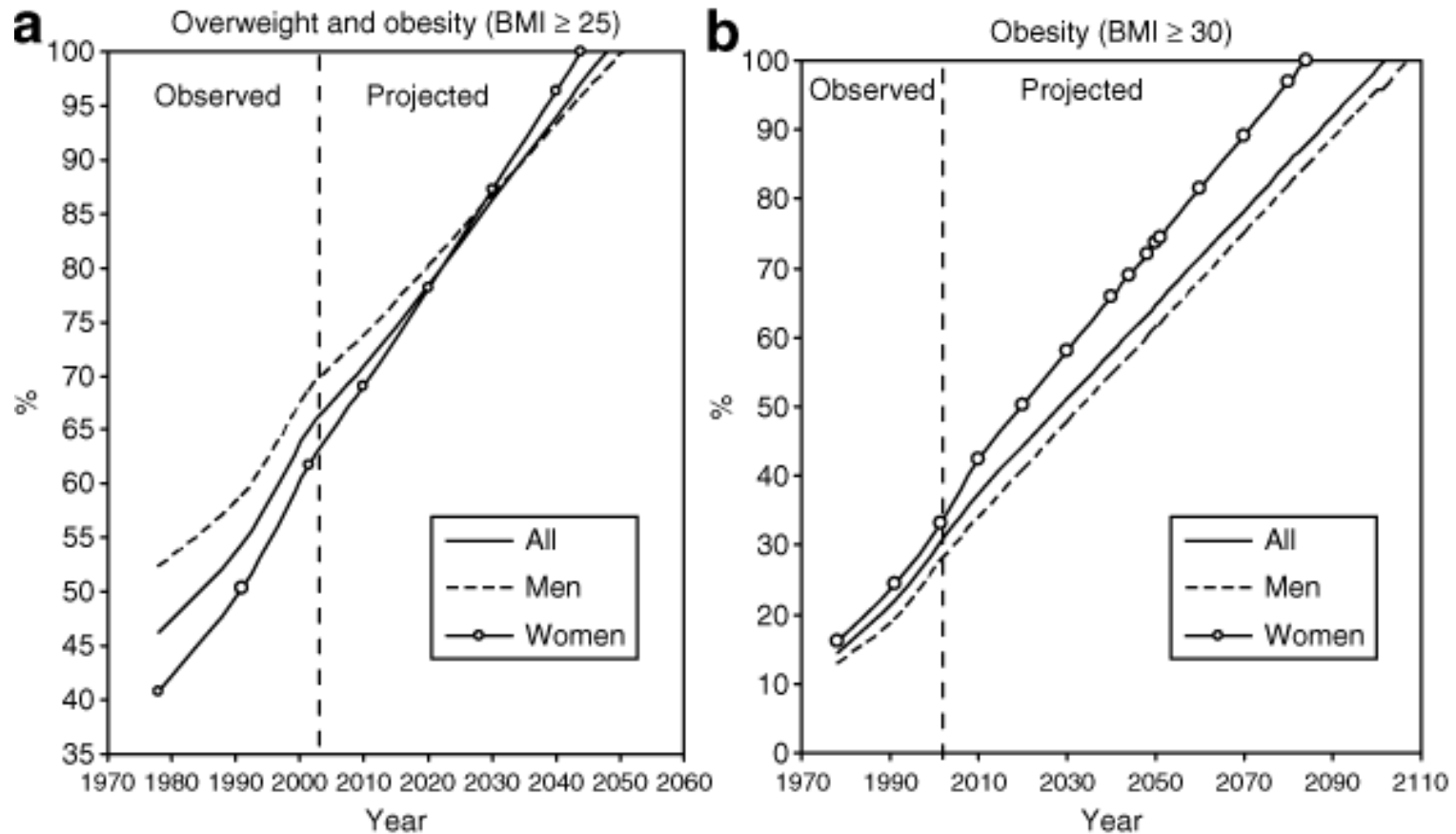
H. pylori (-)
stomach



Tendencia en Obesidad en US adultos 1989-2010

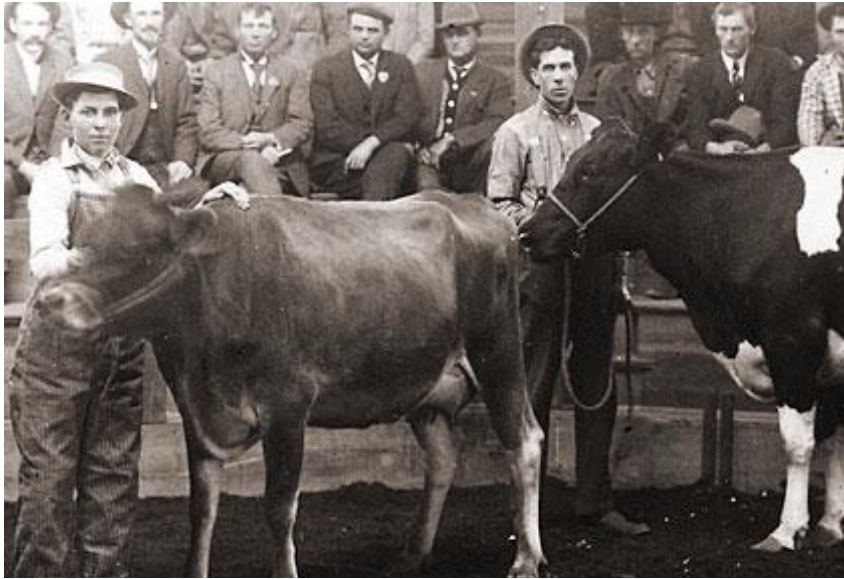


Obesidad es un problema en crecimiento en los EUA

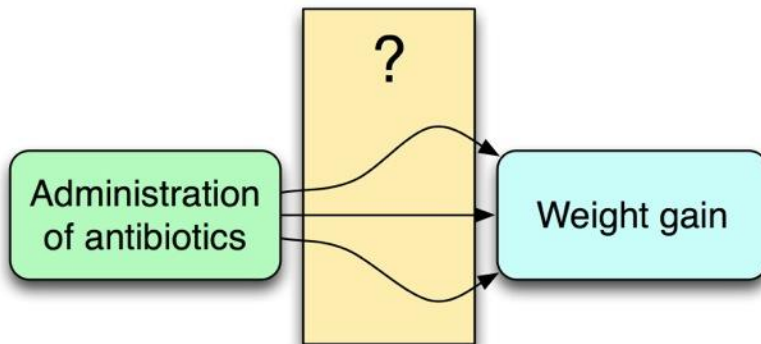


Observed rates 1976-2004.

Antibióticos para promoción de crecimiento



- >50 years of antibiotic use for growth promotion
- Economic benefits
- Low level exposure (subtherapeutic) is sufficient for effect
- Unknown mechanism of action



Annual antibiotic-prescribing in US children (2006-2008), according to condition

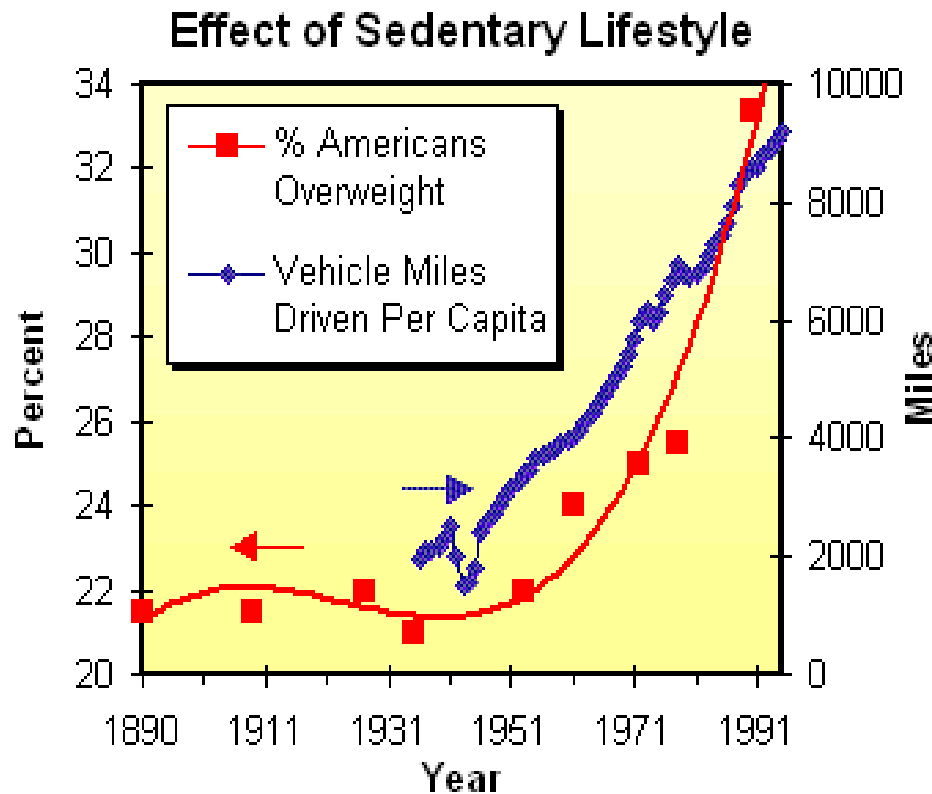
Millions (%)

Condition	Annual number of visits	Visits for which antibiotics are prescribed
Respiratory (ARTIs)	65.6	31.7 (48.4)
Antibiotics are indicated	29.9	21.5 (71.7)
Antibiotics are not indicated	19.5	5.8 (29.6)
Other respiratory conditions	16.2	4.5 (27.8)
Other	158.6	12.2 (7.7)
Skin/cutaneous/mucosal	28.2	5.2 (18.6)
Urinary tract infections	1.4	0.9 (59.3)
Gastrointestinal infections	2.3	0.1 (5.7)
Miscellaneous infections	8.7	0.8 (9.6)
Other	117.9	5.1 (4.3)
Total	224.2	43.9 (19.6)



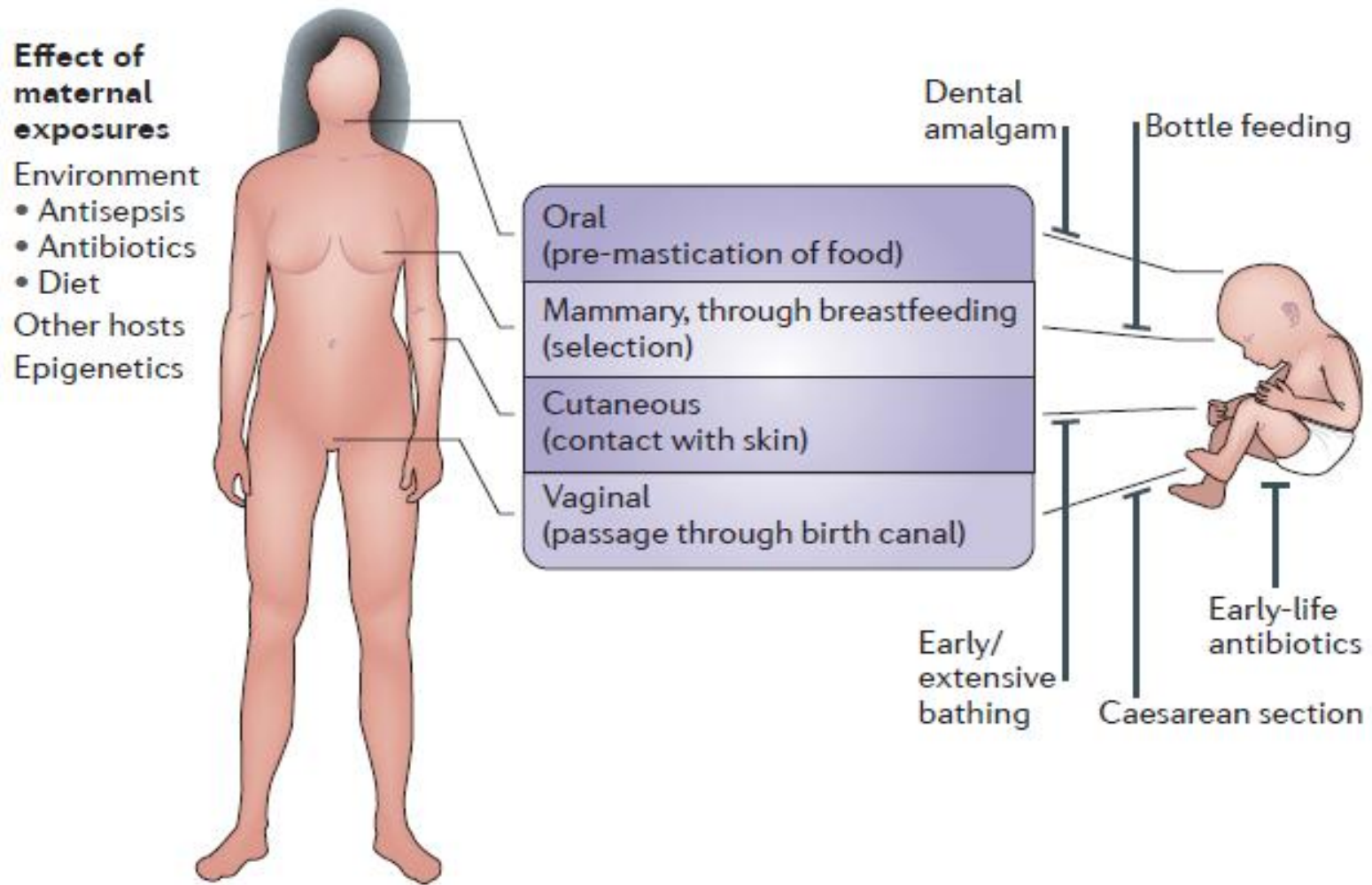
Otros factores que contribuyen a la obesidad

1. Calories-in / calories-out

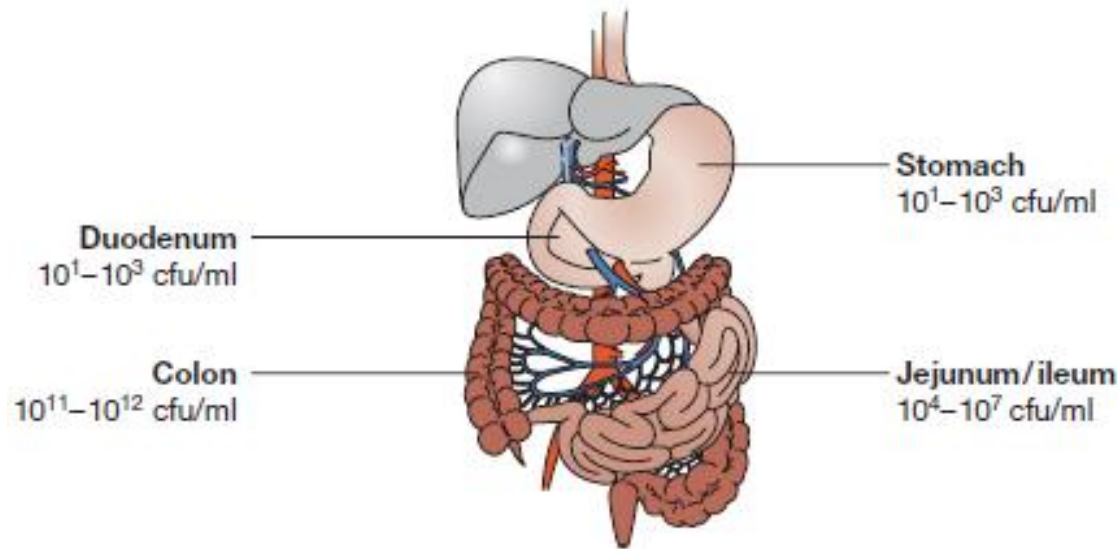


Seafood Sampler:
1964 kcal, 123g fat,
120mg cholesterol,
2893mg sodium.

Madre → Transmisión al niño



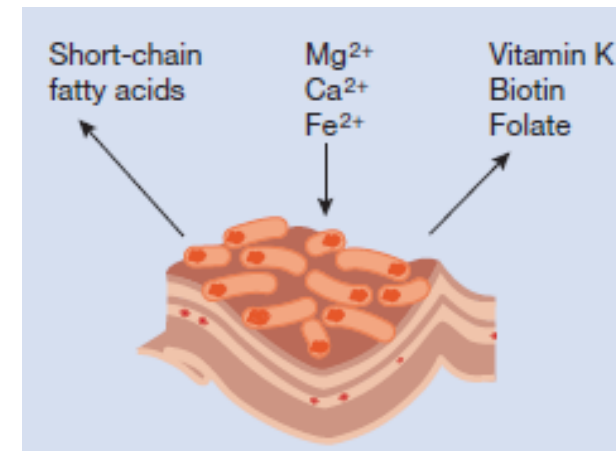
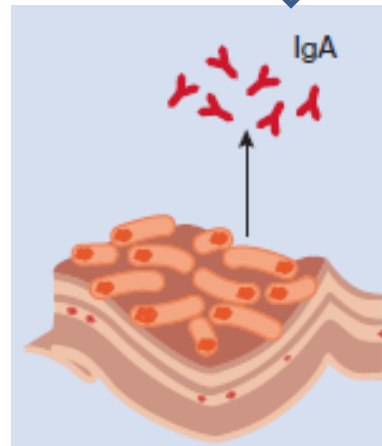
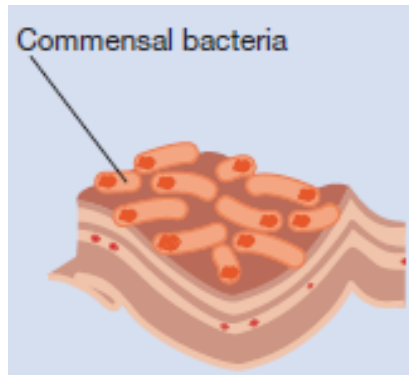
Funciones del Microbioma Intestinal



Structural

Protective

Metabolic



El Microbioma Intestinal como un “Órgano” dentro de otro Órgano



10,000,000,000,000 to 100,000,000,000,000 bacteria
100 x more genes than that of its human host
Metabolically active!

Principales Contribuyentes a la Disbiosis

- Only 20,000 years ago humans were able to control fire and using it for cooking.
- Only 2,000 years ago humans start separating waste water from drinking water (Roman era).
- Only 75 years ago refrigeration was introduced to the public.
- Processed and packing food products started 40 years ago.

Perspectivas

- Aumento en el numero de enfermedades de tipo crónico asociadas a cambios en el microbioma
- Fobia a los microorganismos que se traduce en un nuevo estilo de vida
- Determinacion personalizada del microbioma
- Posibilidad de revertir la teoría de la higiene?

Muchas Gracias!