ANBI 139

Evolution of Human Disease

**Lecture 8: Epidemiological Transitions - Paleopathology**

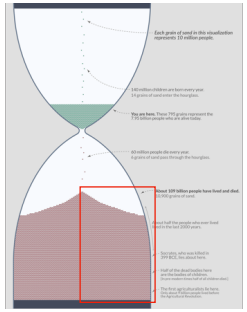
Pascal Gagneux

February 2, 2023

Human vertebrae with tuberculosis lesions from ancient Peru

---

## Major cause of death?



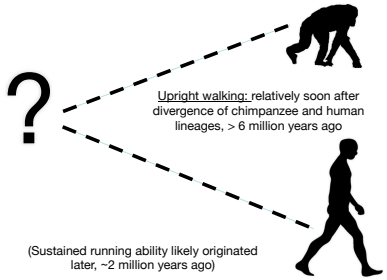
*Aedes spec, Anopheles spec. & Culex spec.*

Humanity today and humanity's past Our World in Data

Over half of the 100 billion people who have ever lived died from mosquito borne disease!

---

## Striding Bipedal Gait: A Uniquely Human Condition

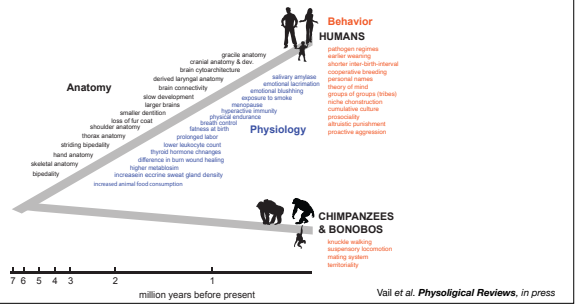



Bipedality is very old and is associated with several human ailments

**Practice question:** What is the evidence that our ancestors were upright by over 5 million years ago?

**Answer:** Fossil skeleton of ape-like species with skeletal adaptation to upright posture (foramen magnum, pelvic and leg bones).

## Some Striking Differences Between Humans and Chimpanzees

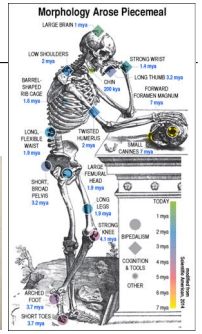



Vail *et al.* ***Physoligical Reviews***, *in press*

Bipedality is very old and is associated with several human ailments

## Striding Bipedal Gait: Biomedical Consequences

- Low Back Pains, Strains, and Injuries
- Spine Deformity Problems
- Herniated Inter-vertebral Discs ("slipped discs")
- Varicose Veins
- Hernias
- Hemorrhoids
- Knee Joint Osteoarthritis
- Obstetric Difficulties (Pelvic Narrowing)

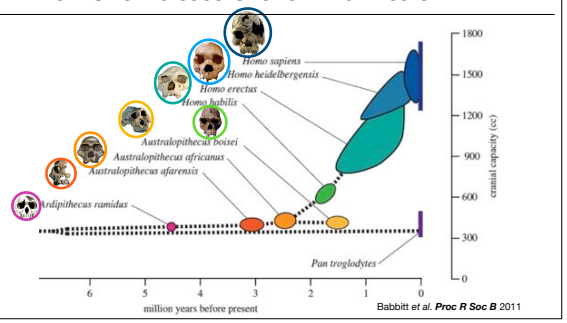



Humans are still paying the price for the switch to bipedal locomotion that occurred over 6 million years ago!

**Practice question:** Name three conditions that represent costly consequences of bipedalism in humans.

**Answer:** Low back pain, obstetrics, hemorrhoids

## Hominin Brain Size Increase Over 6 million Years



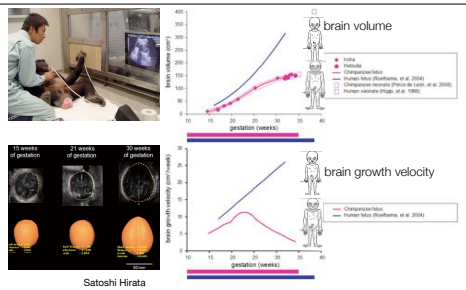

Babbitt *et al.* ***Proc R Soc B*** 2011



The brains of our ancestors tripled in size over that last 2 million years. What drove such a costly expansion?

Did cultural behavior, symbolism, language and complex technology and associated requirements on cognition drive this change?

## How to grow a big brain



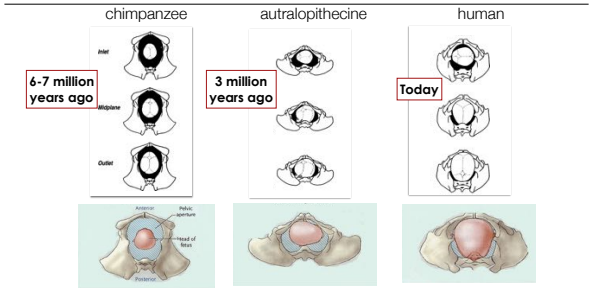

Satoshi Hirata

Sakai et al. **Current Biology**, 2012

Gestational age-related changes in brain volume in chimpanzee (Hatsuka and Iroha) and human fetuses.
Gestational age-related changes in the growth velocity of brain volume in chimpanzee and human fetuses
Chimpanzee brains start slowing down their growth in mid-pregnancy, humans on the other hand continue a high fetal rate for a full year after birth.

---

## Obstetrical dilemma: birthing a big-brained baby




Smith R. Mechanisms of Disease: Parturition. ***N Engl. J Med***. 2007;356:271-283.

Modern humans have evolved such large heads that their bipedal mothers face many difficulties in birthing such large headed babies. Childbirth have become dependent on cultural input, help from relatives or professionals… Cephalo-pelvic disproportion.

**Practice question:** What is cephalon-pelvic disproportion?.

**Answer:** Mismatch between head size of the baby and hip size of the mother.

---

## Pregnancy & Parturition: Human vs. "Great Ape" Differences

Medically mediated human birth

Chimp birth at AtticaPark Athens, Greece

| Feature | Human | Chimpanzee |
|---|---|---|
| Variation in gestation period (days) | ~35 | ~10 |
| Duration of labor (hours) | > 10 HOURS | = 1 HOUR |
| Pain (vocalization, wincing, etc.) | High | Low |
| Time of day for delivery | Unpredictable | Night |

Lieu, J.E., Rubenstein, C.S., and Nowalk, E.R. Normal labor: Mechanism and duration. Obstet Gynecol Clin North Am. 2005;32:145-64

Keeling, M.R., and Roberts, J.R. The Chimpanzee, Volume 5: Histology, Reproduction and Restraint. S. Karger, New York, 1972.

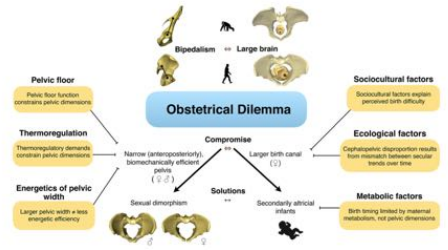
Lehtinen, L., and Cieri, G. Parturition in non-human primates: pain and auditory concealment. Pain. 1990;41:115-122.

Birth in humans has become much more risky for baby and mother due to the large size of the babies head and narrow pelvis of mothers.

**Practice Question:** What are the major differences between birth process in humans and the related great apes?

**Answer:** Humans have much higher variation in gestation time, much longer duration of labor, and birth is associated with much higher levels of pain.

## Obstetrical Dilemma a “cultural construct”?




Haeusler *et al*. The obstetrical dilemma hypothesis: there’s life in the old dog yet
**Biological Reviews** 96 (2021) 2031–2057 © 2021

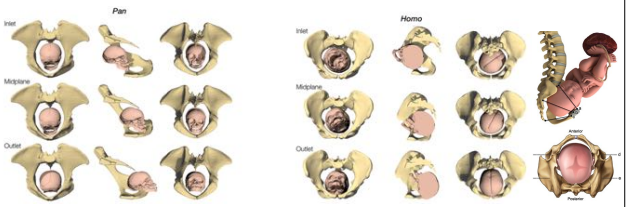
Schematic showing the original obstetrical dilemma hypothesis and complementary or alternative explanations (orange lozenges) as they relate to specific components of the obstetrical dilemma proposed by Washburn (1960). Note that most studies on the pelvic floor, thermoregulation, and energetics to date have focused on pelvic width rather than on the anteroposterior pelvic shortening emphasised by Washburn (1960).

**Practice Question:** What is the notion of an obstetrical dilemma?

**Answer:** The idea that human mother balance the requirement of bipedality with those of birthing a. super large headed baby.

---

## Obstetrical Dilemma not just a “cultural construct”?




Haeusler *et al*. The obstetrical dilemma hypothesis: there’s life in the old dog yet
**Biological Reviews** 96 (2021) 2031–2057 © 2021

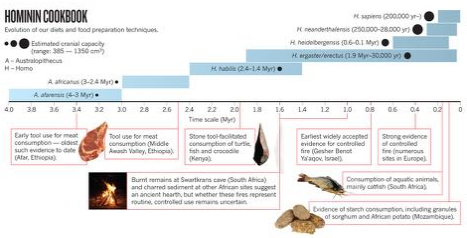
Comparison of the birth mechanism in chimpanzees (left) and modern humans (right), in superior view, longitudinal section, and inferior view at the pelvic inlet, midplane and outlet. In chimpanzees, the fetal head is likely extended throughout the birth process, i.e. in a mentum anterior (chin forward) orientation as it usually occurs in non-human primates, but the fetus can also be born with a flexed head as in humans. In humans, the fetal head is flexed and its orientation adapts to the changing shape of the different pelvic planes.

---

## Examples of Changes in Modern Lifestyle/Biology in Relation to Disease

| Item | Change | Pro | Con |
|---|---|---|---|
| Milk Drinking after infancy | Increased (Lactose Tolerance) | Source of Many Nutrients, e.g. Calcium | Rich source of Saturated Fat |
| Mother/Infant Co-Sleeping | Decreased | Father Does More? | Increased “Sudden Infant Death”? |
| Dietary Soluble Fiber | Reduced | Chewing Easier Food Tastier | Irritable Bowel Colon Cancer |
| Toughness of Food | Reduced | Chewing Easier Less Gingivitis | Dental Crowding Impacted Molars |
| Consumption of Red Meat | Marked Increase | Nutritious, Satisfying | Carcinomas Atherosclerosis |
| Consumption of starch | Marked Increase | Nutritious, Satisfying | Insuline resistance |
| Excessive Focus on Near Objects | Marked Increase Reading/Computers | Cognitive Benefits | Myopia |
| Gut Bacteria/Worms | Reduction | Lower parasite burden | Crohn’s Disease? |
| Hygiene | Improved | Protection from Infections | Increase in Allergies? |

## Hominin Dietary Changes Over Deep Time




Many details still controversial: "The Cooking Hypothesis"

Eisenstein, M. Evolution: The First Supper. *Nature*. 2010;468.S8-S9. 



Dietary changes have also had both immensely positive and very negative effects on human health.

Coevolution of larger brains and dietary changes!

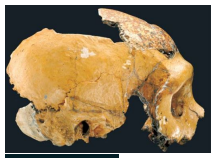
## Post-Paleolithic Changes In Human Diet

Human Diet has undergone major changes during the last 10-20,000 years.

This may help explain the severity and frequency of some modern human diseases

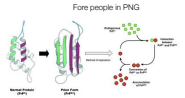
## Eating your neighbor / Cannibalism

Atapuerca, Spain
800 kya



Krapina, Croatia
130 kya

Fore people in PNG



Adaptation to cannibalism?
Prion protein polymorphisms providing protection?
Mead *et al* 2003 ***Science***: yes
Soldevilla *et al* 2006 ***Genome Research***: no

Cannibalism has been documented in several fossil hominids, from Atapuerca, Spain to Krapina, Croatia, it has also been documented for chimpanzees. It appears to be a last resort and is clearly very risky for biological and social reasons. Exocannibalism is the practice of eating members of other social groups, for intimidation or warfare, while endocannibalism is the practice of eating parts of people from one's own group for symbolic reasons.

Cannibalism comes with the threat of its own diseases: the disease Kuru (laughing death) is a form of human spongiform encephalopathy caused by the contagious mis-folded prion glycoprotein. It was discovered in patients among the Fore people of Papua New Guinea, where endocannibalism was practiced until recently as part of funeral rituals (the brain of the deceased is consumed by friends and relatives). This practice has been abandoned.

**Practice question:** What is the difference between endocannibalism and exocannibalsim?

**Answer:** The hundreds of thousands of years that our species spent spent living as foraging small scale communities.

---

## Contrasting European Views on the Past

"No arts; no letters; no society; and which is worst of all, continual fear, and danger of violent death: and the life of man, solitary, poor, nasty, brutish and short."

Thomas Hobbes 1588- 1676

"Civilization is a hopeless race to discover remedies for the evils it produces."

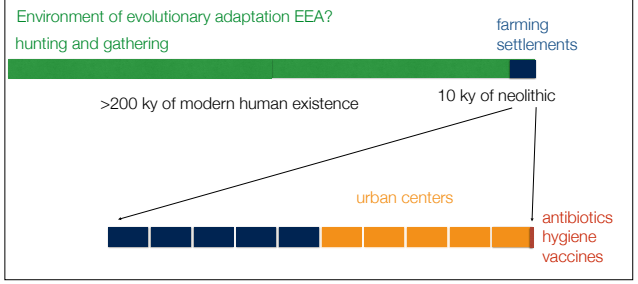
"Nature made me happy and good, and if I am otherwise, it is society's fault."

Jean Jaques Rousseau 1712-1778

Two opposing views of the past, both clearly flawed but still profoundly influencing human attitudes….

---

## Last 200 thousand years




The environment of evolutionary adaptation refers to the extremely long time span during which humans lived in small scale societies and by gathering and hunting their food.

Environment of evolutionary adaptation EEA?

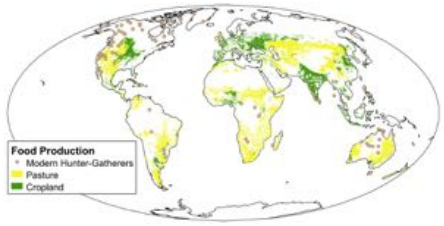


Is there a particular environment that shaped human biology? Could mismatches caused by the many changes in our modern environment be among the causes for disease?

**Practice question:** What is meant by the Environment of Evolutionary Adaptation EEA?
**Answer:** The hundreds of thousands of years that our species spent spent living as foraging small scale communities.

---

Living Foragers and their Plight



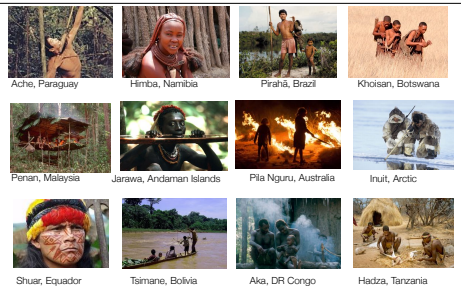

Gatherer-Hunters!

data from Navin Ramankutty and Ohio State University Hunter-Gatherer Wiki

Modern agriculture and hunter-gatherers. Map shows area used for major agricultural and pastoral production in 2000, and locations of societies that have depended on hunting and gathering for a significant portion of their food in the modern era.
data from Navin Ramankutty and Ohio State University Hunter-Gatherer Wiki

---

Last Living Hunter Gatherers/Foragers




All these populations are in the process of losing their traditional ways of life, they represent the last examples of our shared foraging past.

## Pre-agricultural life span was not short!



TABLE 4 Modal ages at death

| Population | Modal age at death | Standard deviation | Percent of adult deaths at mode year | Percent of adult deaths at and above mode |
|---|---|---|---|---|
| Hadza | 76 | 6.0 | 2.5 | 24.1 |
| Hiwi | 68 | 3.3 | 3.3 | 17.9 |
| Ache | 71 | 7.7 | 2.1 | 24.5 |
| Yanomamo Xilixana | 75 | 7.3 | 1.9 | 22.8 |
| Tsimane | 78 | 5.9 | 3.0 | 30.5 |
| !Kung 1963–74 | 74 | 7.8 | 2.7 | 35.4 |
| Ache reservation | 78 | 5.9 | 3.0 | 30.5 |
| Aborigines | 74 | 7.8 | 2.7 | 35.4 |
| Wild chimpanzees | 15 | 16.8 | 4.6 | 100.0 |
| Captive chimpanzees | 42 | 7.5 | 2.6 | 38.5 |
| Sweden 1751–59 | 72 | 7.4 | 2.3 | 24.3 |
| United States 2002 | 85 | 1.7 | 3.5 | 35.3 |

NOTE: The extent of variation around the mode is usually defined as four standard deviation units around the mode (Cheung et al. 2005).

Longevity Among Hunter-Gatherers: A Cross-Cultural Examination Gurven and Kaplan 2 0 0 7 ***Population and Development Review***

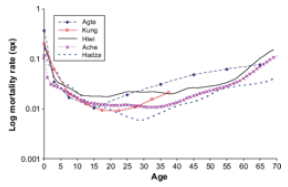
There have always been old people around!

**Practice question:** What is the modal (most common among adults) age of death in living hunter gatherer societies??

**Answer:** 70 plus years!.

---

## But Infant mortality was very high!




Hill, Kim & Hurtado, Ana & Walker, Robert. (2007).
High Adult Mortality among Hiwi Hunter-Gatherers: Implications for Human Evolution. ***Journal of human evolution***. 52. 443-54.

**Practice question:** If life expectancy is around 35 years for most hunter gatherers, how can there be substantial numbers of 70 year olds in those societies?

**Answer:** Very high infant mortality brings down the life expectancy.

---

## Epidemiological Transitions (A.R. Omran 1971)

Age of low-density hunter gatherer life:
few famines
balanced nutrition
long inter-birth intervals

Age of pestilence and famine

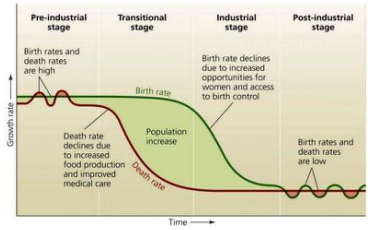
Age of receding pandemics

Age of generative and man-made diseases

**Practice question:** Why is Omran's concept of the earliest stage of epidemiology as one of "pestilence and famine" not necessarily correct?

**Answer:** Because prior to agriculture in the last 10 ky low-density hunter gatherer life included:
few famines
balanced nutrition
long inter-birth intervals
lower threats of widespread epidemics

## Epidemiologcal Transitions

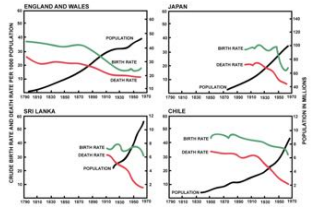



Omran, A.R. The epidemiologic transition: A theory of the epidemiology of population change. ***Milbank Q.*** 1971, 49, 509-538.

Birth rate and death rates have both changed during transitional and industrial stages.

## Epidemiological Transitions

Shift from high mortality due to acute infections to death via chronic, non-infectious degenerative disease




Harper and Armelagos ***Int. J. Environ. Res. Public Health*** 2010

## Three Epidemiological Transitions?

| Transition | Paleolithic Baseline | First Transition | Second Transition | Third Transition |
|---|---|---|---|---|
| **Time Period** | Pre-Neolithic Cultures; More recent hunter-gatherer cultures with little outside contact | Neolithic cultures-Early Modern Times in Western Europe and United States; Still characterizes many low-income countries | Early Modern times to 20th century in Western Europe, United States; Occurred more recently in some other high-income countries and is in progress in lower income countries | End of the 20th century to the present, global |
| **Characteristics** | • Pre-agricultural<br>• Low mortality and fertility rates<br>• Small population size<br>• Varied diet | • Agricultural<br>• High mortality and fertility rates<br>• Large population size<br>• Diet heavily reliant on crops | • Agricultural<br>• Low mortality and initially high then low fertility rates<br>• Large population size<br>• Increased life expectancy<br>• Varied diet, overnutrition common<br>• Discovery of antimicrobials and vaccines, improved hygiene | • Agricultural<br>• Large population size<br>• Declining life expectancy?<br>• Failure of antimicrobials<br>• Rapid spread of novel infections<br>• Age of onset of chronic diseases delayed in high-income countries |

Harper and Armelagos ***Int. J. Environ. Res. Public Health*** 2010

Driven by cultural changes? From foraging to farming/herding, from farming to industry, from traditional medicine to modern pharmaceuticals including vaccines, anti-bacterial (antibiotic), anti-helmintic, anti-protozoan, and anti-viral drugs.

## Three Epidemiological Transitions?

| Transition | Paleolithic Baseline | First Transition | Second Transition | Third Transition |
|---|---|---|---|---|
| **Common causes of morbidity and mortality** | Infections such as tapeworms, body lice, pinworms, typhoid, staph, and possibly yaws | • Infections such as malaria, smallpox, measles, tuberculosis<br>• Nutritional deficiencies | • Degenerative diseases such as heart failure, stroke, diabetes, cancer<br>• Allergies, asthma, autoimmune diseases<br>• Sexually transmitted infections such as HSV-2, gonorrhea, HIV | • Those diseases present in the 2nd transition<br>• Antibiotic resistant forms of tuberculosis, strep, staph, *etc*<br>designer pathogens? |

Harper and Armelagos ***Int. J. Environ. Res. Public Health*** 2010

The types of disease threats have changed.

---

## Epidemiological Transitions

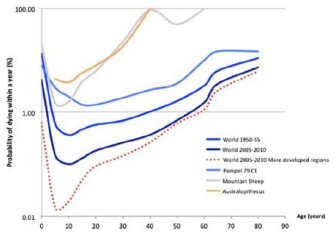
**Heirloom species**:
head and body lice
*M. tuberculosis* (TB)
*Helicobcter pilori*
Yaws (bacterial infection related to syphilis)
*Salmonella typhi*
*Staphylococci* etc

**Souvenir species**:
*Clostridium tetani*
scrub typhus (*Orientia tsutsugamushi)*
*relapsing fever*
*Trichinella*

Harper and Armelagos ***Int. J. Environ. Res. Public Health*** 2010

---

## Probability of dying within a year over deep time & around the world




Saniotis, A., Henneberg, M., 2011. Medicine could be constructing human bodies in the future. ***Medical Hypotheses*** 77 (4),

Postnatal mortality expressed as a probability of dying within a year (logarithmic scale) at various stages of the human biological history.
Data for Australopithecine, mountain sheep (an average mammal), and humans form Pompeii (from Saniotis, A., Henneberg, M., 2011. Medicine could be constructing human bodies in the future. Medical Hypotheses 77 (4), 560e564.), and others (from World Health Organization (WHO) life tables.).

## Population and health (Hans Rosling)



https://www.youtube.com/watch?v=hVimVzgtD6w

How valid is the concept of first world vs “third world”?
This was true in the 1960s, but most human populations now have small families and much longer life expectancies.
Many developing countries have improved the health of their populations. Some by reducing the fertility rate (number of births per woman) first and others by improving hath first.

---

## Double burden of disease

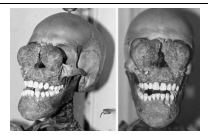

Bygbjerg, I. C. (2012) Double Burden of Noncommunicable and Infectious Diseases in Developing Countries. ***Science***, 337 (6101). p. 1499.

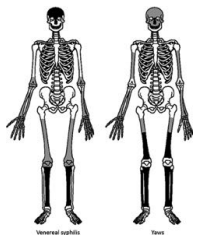
The proportional distribution of disability adjusted life years, contributable to infectious diseases and NCDs for (top) the world, (middle) high-income countries, and (bottom) low-income
countries for 2002 and 2030.

**Practice question:** What is meant by double burden of disease?
**Answer:** Societies where both, communicable (infectious) disease and disease caused by modern lifestyle cooccur!

---

## From Yaws/Pinta to Syphilis?






Treponema pertenue/carateum to Treponema pallidum?

The spirochetes causing yaws, pinta and syphilis cause diagnostic skeletal abnormality and allow to teach these infections in the distant past.
Congenital syphilis, i.e. infection of the fetus from the mother causes characteristic lesions in the skeleton.

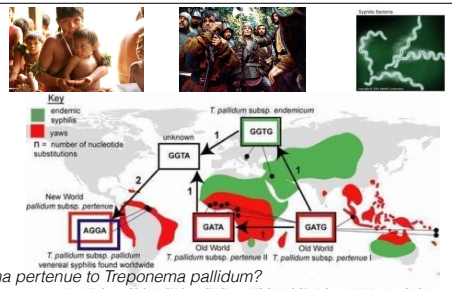
## From Yaws/Pinta to Syphilis?

Treponema pertenue/carateum to Treponema pallidum?

Presentations of spirochete infections by close relatives of the syphilis causing agent.

---

## From Yaws to Syphilis?




*Treponema pertenue to Treponema pallidum?*

Harper KN, Ocampo PS, Steiner BM, George RW, Silverman MS, Bolotin S, Pillay A, Saunders NJ, Armelagos GJ. On the origin of the treponematoses: a phylogeneticapproach. ***PLoS Negl Trop Dis.*** 2008

A network path for four informative substitutions shows that New World subsp. *Treponema pertenue*, or yaws-causing strains, are the closest relatives of modern subsp. *pallidum* strains. On the map green represents endemic syphilis; red, yaws; numbers show the number of nucleotide substitutions.

One hypothesis is that a fairly innocuous skin infection evolved into a devastating sexually transmitted infection via widespread sexual behavior (including violence) at the hand of conquistadores.

**Practice Question:** How could a bacterial infection transmitted by skin contact in South America have evolved into a STI like syphilis?

**Answer:** Sexual exploitation and violence at the hands of the Spanish conquistadores could have selected for sexually transmitted variants that benefit from lesions on genitals fro transmission..

## From Yaws to Syphilis?

Sailors, by the nature of their profession are men without women and are therefore men with many women. We can imagine no group more suitable for guaranteeing that venereal syphilis would have worldwide distribution.

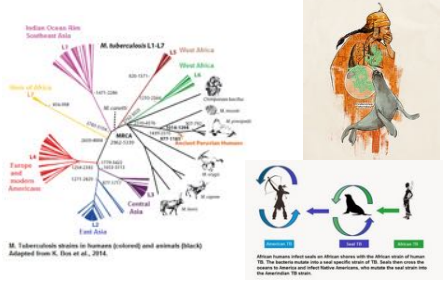
– Alfred Crosby Jr.

*Treponema pertenue* to *Treponema pallidum*?

Could colonial sexual exploitation and violence have contributed to the emergence of a novel STI?

---

## Paleo TB in South America





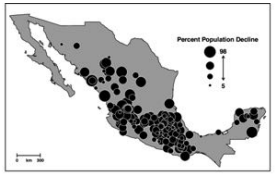

TB arrived in the Americas with humans via the Bering bridge and down into South Americas, but also via seals from Africa.

**Practice Question:** How could TB in pre-columbine South American skeleton be more closely related too TB in seals than any other TB strains?

**Answer:** Intense coastal hunting for seals by paleoamericans could have exposed them to this new strain.

---

## Cocolitzli Epidemic of 1576




Hemorrhagic fever: viral or bacterial?
*Salmonella enterica!*

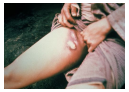
Vågene ÅJ, Herbig A, Campana MG, Robles García NM, Warinner C, Sabin S, Spyrou MA, Andrades Valtueña A, Huson D, Tuross N, Bos KI, Krause J. *Salmonella enterica* genomes from victims of a major sixteenth-century epidemic in Mexico. ***Nat Ecol Evol.*** 2018 Mar;2(3):520-528

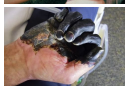
Geographical distribution of mortality in Mexico during the cocoliztli epidemic of 1576. The size of each circle corresponds to the percent population decline between the census of 1570 and the census of 1580.

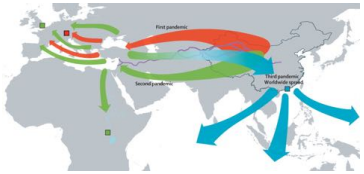
**Practice Question:** How could scientists determine what caused the epidemic of Cocolitli?

**Answer:** Ancient DNA studies of skeletons in mass graves dated to the year of the outbreak.

Bubonic Plague







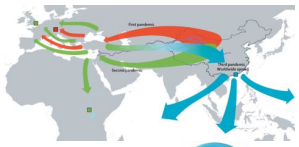

Justinian Plague | Black Death | Hongkong Plague

542 A.D.
Killed million of people in Mediterranean region. It lasted for 60 years.

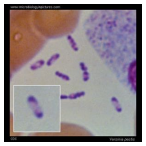
1347 A.D.
Killed people of central Asia and 1/3 of European population. It lasted for 400 years

1894 A.D.
The third pandemic started in 1894 in China and reached to Hong Kong.

The race to isolate the agent causing the plague



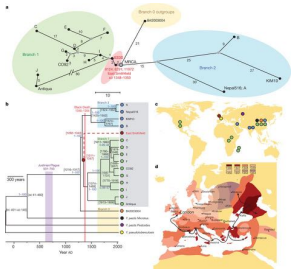

Alexandre Yersin and Shibasaburo Kitasato competed in the race to identify the pathogen in1894



1894 A.D.
The third pandemic started in 1894 in China and reached to Hong Kong.

Bubonic Plague

ancient plague DNA from 660 years ago



Bos *et al.* 2011 ***Nature*** *478*

*Yersinia pestis* pathogen, bacterium invades immune cells and reaches lymph nodes where i massively expands.

**Practice question:** What did the Justinian plague of the 6th century, the Black plague in the 14th century and the Hongkong plague of 1890s have in common?
**Answer:** they were all caused by the bacterium *Yersinia pestis*.

*Yersinia pestis* pathogen thrives at slightly cooler temperatures. The incubators in the Hong Kong hospital controlled by Kitasato were too warm……whereas the temperature at which Yersin examined the tissue from cadavers of plague victims in his hut was just right! Kitasato isolated several bacteria, which turned out to be secondary infections on the cadavers of plague victims.

DNA as time travel machine back to ancient plagues and allows to reconstruct the evolution of their important pathogen!
The plague can safely be thought of as a spill over pandemic, from wild rodents, to large crowded cities.

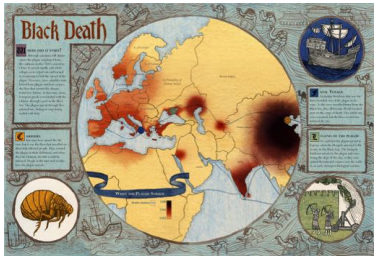
**Practice question:** How can the plague be thought of as a spill over event?
**Answer:** The pathogen lives in wild rodent (marmots, ground squirrels) and trade with their fur led to the importation of the pathogen to trading cities around the Mediterranean.

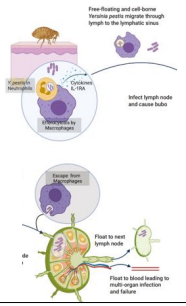
Median network of ancient and modern Y. pestis based on 1,694 variant positions in modern genomes. Coloured circles represent different clades. Gray circles represent hypothetical nodes. b, Phylogenetic tree using 1,694 variable positions. Divergence time intervals are shown in calendar years, with neighbour-joining bootstrap support (blue italic) and Bayesian posterior probability (blue). Grey box indicates known human pathogenic strains. A, NZ ACNQ01000; Nepal516, NC 008149; KIM10, NC 004088; B, NZ AAYT01000; C, NZ ABAT01000; D, NZ ACNS01000; E, NZ AAYS01000; F, NZ AAOS02000; CO92, NC 003143; G, NZ ABCD01000; H, NZ

AAYV01000; I, NC 014029; J, NZ AAYR01000; Antiqua, NC 008150. c, Geographical origin of genome sequences used in a and b. d, Geographical spread of the Black Death from infection routes reported.

---

Bubonic Plague



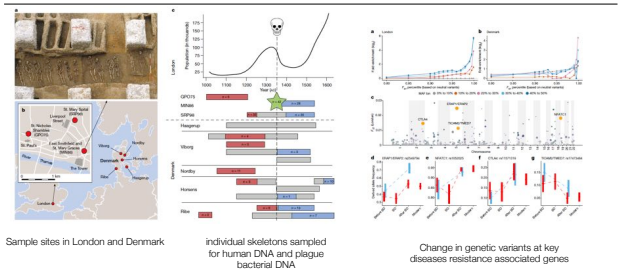




The black death killed off between 1/3 and 1/2 the European population. Massive plague outbreak happened shortly before in China as well!
Reactions to this new infection included mass-murder of Jewish communities around Europe, as Jews were blamed for poisoning wells or any other evil deeds.

Among the social destabilization, the several waves of plague to hit Europe in the 15th century also contributed to lack of faith or trust in the established Christian Clergy which resulted in the reformation (also helped by the translation of the bible into modern languages and dissemination of the texts via printing press, invented in Europe around that time (China had invented printing much earlier, 11th century) but the technology did not disseminate to Europe.

**Practice question:** Name three social consequences of the Black Death in the 14th century?
**Answer:** break down social order, pogroms (violent upheavals) against local Jewish populations, religious upheaval (protestant reformation).

Bubonic Plague (acted as a strong selective pressure)



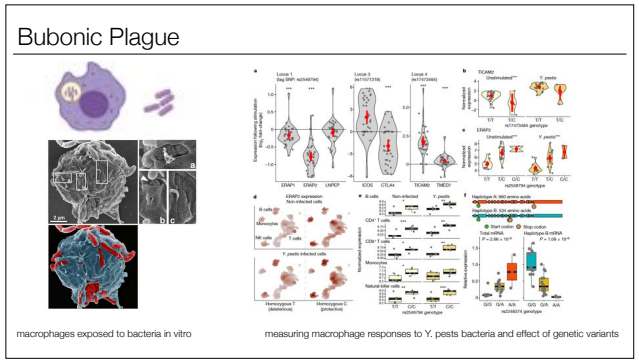
Sample sites in London and Denmark

individual skeletons sampled for human DNA and plague bacterial DNA

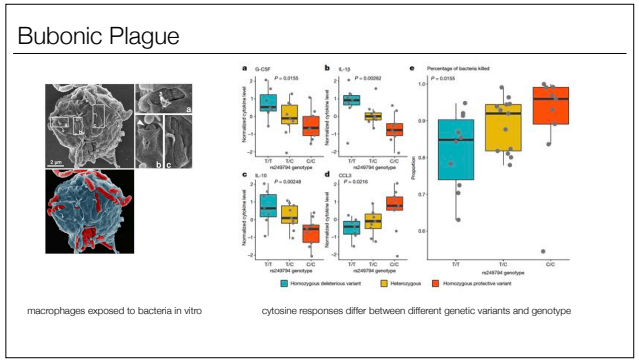
Change in genetic variants at key diseases resistance associated genes

East Smithfield mass burial and sample locations, along with date ranges and final sample numbers used for the present study. a, East Smithfield Black Death mass burial site from 1348–1349 (reproduced with permission of the Museum of London Archaeology, copyright MOLA). b, Site locations and archaeological site codes (in parentheses) for samples from London (inset, afterref. 48, Museum of London Archaeology) and from across Denmark. c, Top, population size estimates for London for around six centuries (data are from refs. 13,49,50) (Supplementary Table 1). Bottom, site locations with associated date ranges. Coloured boxes indicate date range for samples, numbers in boxes indicate samples meeting all criteria for inclusion in final analyses (see main text and Supplementary Information). Number in green star stems from East
Smithfield and the dashed line refers to the time of the Black Death.

Positive selection at immune loci. a,b, Enrichment of highly differentiated sites in functional regions relative to neutral regions when comparing the pre-Black Death (BD) population to the post-BD population in
London (a) and Denmark (b). c, FST between London before and after the Black Death, limited to the 535 sites that show qualitative patterns consistent with natural selection (namely allele frequency changes in the same direction in both London and Denmark after the Black Death, and the opposite direction for individuals who died during the Black Death (Supplementary Table 4)). Manhattan plot showing loci with patterns indicative of positive selection. Point size and colour intensity (which alternates by chromosome) represents the –log10 P value comparing populations in London before and after the
plague, points coloured in orange represent the four positions and their associated genes, which are highly differentiated in Denmark as well. d–g, Patterns of allelic change over time for the four strongest candidates for positive selection. Error bars represent the standard deviation based on bootstrapping individuals from that population and each time point 10,000 times. Allele frequencies for London are shown in red and for Denmark are shown in blue. Modern allele frequencies are derived from 1000 Genomes data for Great Britain in London51.




Positively selected loci are associated with changes in gene regulation upon Y. pestis stimulation. a, Normalized log2 fold-change of genes within 100 kb of candidate variants in response to incubation of primary macrophages for four hours with heat-killed Y. pestis. Dark grey dots correspond to the fold-change observed for each of the 33 individuals tested; red dots and bars represent the mean ± standard deviation. With the exception of LNPEP, all associations are significant (10% false discovery rate). b,c, Effect of rs1747384 genotype upon TICAM2 expression (b) and rs2549794 genotype upon ERAP2 expression (c), split by macrophages stimulated for four hours with heat-killed Y. pestis and unstimulated macrophages. Red dots and bars represent the mean ± standard deviation. d, Comparison of ERAP2 expression among non-infected and infected cells with live Y. pestis for five hours, profiled using scRNA-sequencing data in individuals with homozygous rs2549794 genotypes. Colour intensity reflects the level of ERAP2 expression, standardized for unstimulated or infected cells. Major PBMC cell types are labelled and can be found clearly coloured in Extended Data Fig. 7; CD4+ and CD8+ T cells were analysed separately. NK, natural killer. e, Effects of rs2549794
genotype upon ERAP2 expression, split by infected and non-infected conditions, for each cell type. f, Illustration of the two haplotype-specific ERAP2 spliced forms for Haplotype A and Haplotype B with start (green) and stop (brown) codons. Below we show the effect of rs2248374 genotype upon total mRNA expression of ERAP2 (left) and the specific expression of the isoform (Haplotype B) encoding the truncated version of ERAP2 (right). For all panels: ***P < 0.001; **P < 0.01; *P < 0.05.

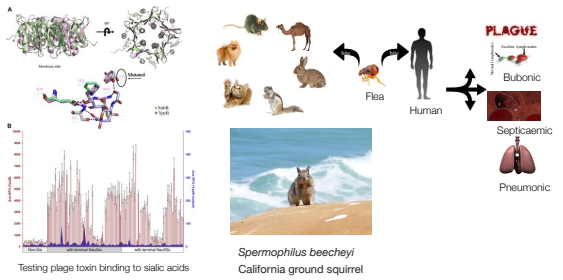



ERAP2 genotype is associated with cytokine response to *Y. pestis* stimulation. a–d, Effect of genotype upon cytokine levels for granulocyte colony-stimulating factor (G-CSF) (a), interleukin-1β (IL-1β) (b), interleukin 10 (IL-10) (c) and C-C motif chemokine ligand 3 (CCL3) (d). Remaining cytokines showed no significant effects and are included in Supplementary Table 7. e, Boxplots showing the percentage of bacteria killed (y axis) by macrophages infected for 24 h as a function of ERAP2 genotype (x axis). The percentage of bacteria killed was calculated as the CFU2 h – CFU24 h/CFU2 h, where CFU is colony-forming unit. The P value results from a linear model examining the
association between ERAP2 single nucleotide polymorphism genotypes (SNP) (coded as the number of protective rs2549794 alleles found in each individual: 0, 1 or 2) and the percentage of bacteria killed.

**Practice question:** How can scientists test the effect of a genetic mutation involve red in. immune cell activation against the plague?
**Answer:** By testing immune cells with different genotypes with regard to their activation to plague bacteria in a dish in the lab.

---

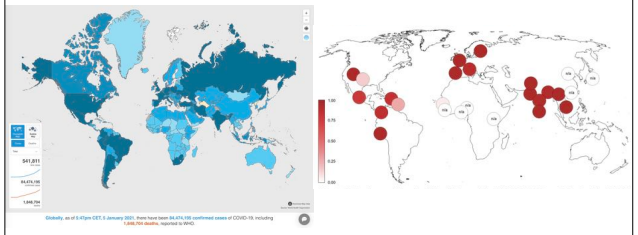
Bubonic Plague: bacterial Toxin binds what?




A toxin made by Yersinia pests bacteria is highly specific for a broad range of sialic acids and causes damage in most mammal species.
**Practice question:** Is infection by the plague strictly transmitted by fleas?
**Answer:** No the plague can become pneumonic, i.e. transmitted directly from one human to the next (airborne).

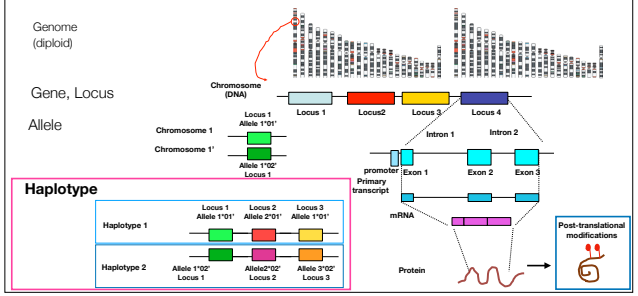
---

COVID-19 Cases vs Genomic Risk



Left: COVID rates across the world in 2021
Right: frequency of COVID severe symptom Risk associated haplotype

## **Module 1**: haplotypes and linkage

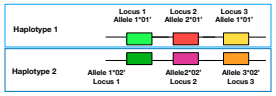



Some key terms used in genetics: **genome**, **gene**, **locus** ("site" in Latin), **allele**, **haplotype, promoter**, **exon**, **intron**, **mRNA**, **post-translational modification,**
Haplotypes are long stretches of DNA that carry unique combinations of genetic variants (alleles). **Post-translational modifications** of proteins include the addition of **glycans** (mono, oligo- or polysaccharides, i.e. glycosylation), or **phosphate** (phosphorylation), **lipids** (acylation) etc… Among other things, these modification regulate the function of proteins.

---

## Haplotype

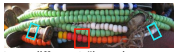
Haplotypes
in a diploid individual




Unique
combination of
**linked alleles**

"Beads on a String", recombination can disrupt haplotypes.

The further apart on the string, the more likely to be recombined during meiosis.



In genetics, the unit for measuring genetic linkage between two different "beads on the string" is the **centimorgan** (cM).

One **centimorgan** is the distance that has a **1% probability of recombination**, it corresponds roughly to 1 million basepairs in humans.

The human genome is ~ 3000 cM long ( 4460 cM in females / 2590 cM in males ).

The human female genome is 4460 cM long, while the male genome is only 2590 cM long. How could genome size differ between males and females? (see below)

---

## Linkage & Linkage Disequilibrium

When stretches of DNA stay together more than expected

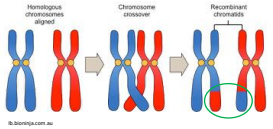
Pascal Gagneux, PhD  October, 3, 2022 Lecture #37

**Beads on a string** as the overarching analogy of genetic variants found along a chromosome.
Eat chromosome corresponds to a distinct "string" of DNA, tightly wrapped around **histones** and **adapter proteins** (forming **chromatin**).

## What Is A Haplotype?

A group of alleles across the same chromosome inherited from a single parent

- Rarely gets broken apart and recombined during meiosis




Example of a haplotype:

Y chromosome is passed paternally

Does not cross over with the X

Is affected by mutations

Fun Fact: terms like *haplotype and haploid* (a single set of unpaired chromosomes) share an etymology

- *Haploos* (Greek): simple/single + oid

**Practice question:** What is a haplotype in genetics?

**Answer:** A unique combination of genetic variants (alleles) along the same string of DNA on a given chromosome.

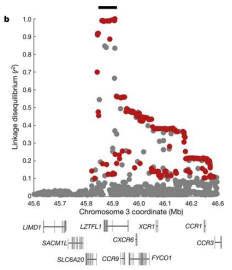
---

## A Neanderthal-Derived Haplotype as **Risk Factor** for COVID-19

Functional feature is currently unknown

Genes highly implicated for risk:

- LZTFL1: encodes regulates membrane on cilia. Expressed in lungs, testes, thyroid, and 24 other tissues.
- CCR9: encodes G protein-coupled receptor. Expressed in small intestine, colon, duodenum, and 6 other tissues.




Genes on the Neanderthal haplotype in people at higher risk for serious COVID19 disease.

---

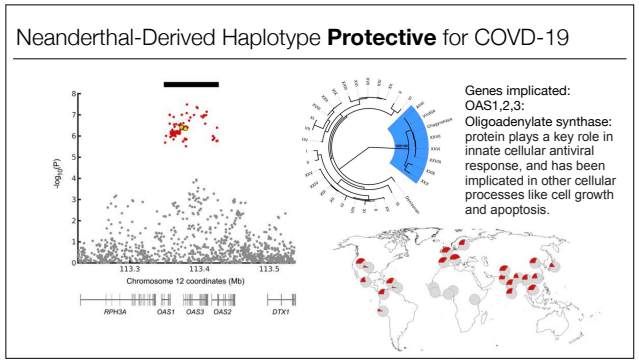
## Why is a Neanderthal-Derived Haplotype a **Risk Factor** for COVD-19?

Functional feature is currently unknown

Genes highly implicated for risk:

- LZTFL1: encodes regulates membrane on cilia. Expressed in lungs, testes, thyroid, and 24 other tissues.
- CCR9: encodes G protein-coupled receptor. Expressed in small intestine, colon, duodenum, and 6 other tissues.

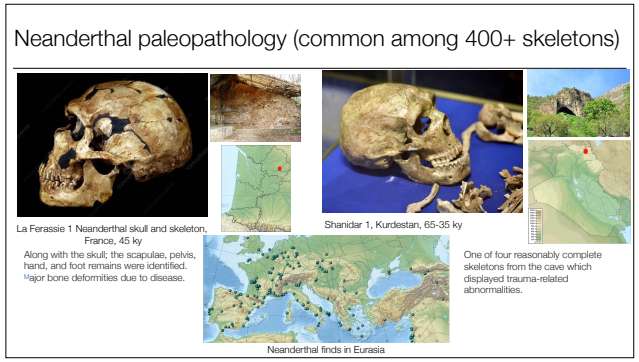
Genes on the neanderthal haplotype in people at higher risk for serious COVID19 disease.




Genetic variants associated with COVID-19 hospitalization at the OAS locus. Variants marked in red have P values less than 1e-5. In Europeans, they are in LD with the index variant (r2 ≥ 0.8), forming a haplotype (black bar) with the genomic coordinates chr12: 113,350,796 to 113,425,679. P values are from the HGI (24), excluding the 23andMe data for which only sparse SNP data are available. The x axis gives hg19 coordinates; genes in the region are indicated below. The three OAS genes are transcribed from left to right. Yellow dots indicate rs10735079 (right, the GenOMICC index SNP) and rs1156361 (left, typed by the Human Origins Array).

**Practice question:** Does Neanderthal DNA in modern humans protect from or put people at higher risk fro COVID?
**Answer:** Both, depending on which chromosome the DNA is on.

---



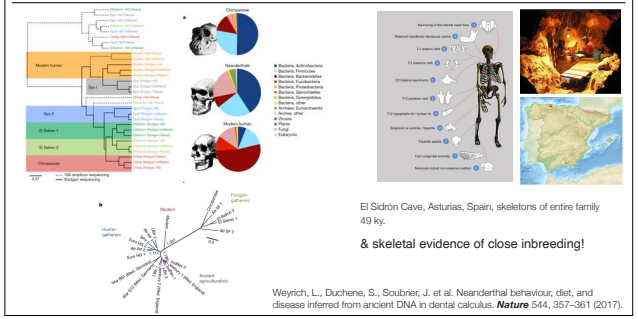

Neanderthals suffered a high rate of traumatic injury, with an estimated 79–94% of specimens showing evidence of healed major trauma, of which 37–52% were severely injured, and 13–19% injured before reaching adulthood.
One extreme example is Shanidar 1, who shows signs of an amputation of the right arm likely due to a nonunion after breaking a bone in adolescence, osteomyelitis (a bone infection) on the left clavicle, an abnormal gait, vision problems in the left eye, and possible hearing loss[231] (perhaps swimmer's ear).

In 1995, Trinkaus estimated that about 80% succumbed to their injuries and died before reaching 40, and thus theorised that Neanderthals employed a risky hunting strategy ("rodeo rider" hypothesis).
However, rates of cranial trauma are not significantly different between Neanderthals and Middle Palaeolithic modern humans (although Neanderthals seem to have had a higher

mortality risk),
A 2016 study looking at 124 Neanderthal specimens argued that high trauma rates were instead caused by animal attacks, and found that about 36% of the sample were victims of bear attacks, 21% big cat attacks, and 17% wolf attacks (totalling 92 positive cases, 74%). There were no cases of hyaena attacks, although hyaenas still nonetheless probably attacked Neanderthals, at least opportunistically.
Such intense predation probably stemmed from common confrontations due to competition over food and cave space, and from Neanderthals hunting these carnivores.

---

Neanderthal paleopathology aDNA in Dental calculus



El Sidrón Cave, Asturias, Spain, skeletons of entire family 49 ky.

& skeletal evidence of close inbreeding!

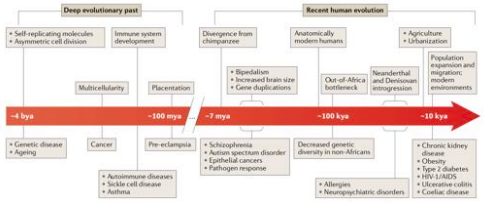
Weyrich, L., Duchene, S., Soubrier, J. et al. Neanderthal behaviour, diet, and disease inferred from ancient DNA in dental calculus. ***Nature*** 544, 357–361 (2017).

Dental caries associated bacteria and evidence for exchange of bacteria with modern humans.

**Practice question:** How can scientists get information about Neanderthal microbiome?
**Answer:** By extracting ancient DNA from dental calculus of Neanderthal fossils s old as 40,000 years.

Bacterial community composition at the phyla level of oral microbiota from chimpanzee, Neanderthal and modern human samples.
a, Oral microbiota from shotgun sequencing datasets of a wild-caught chimpanzee (top), Neanderthals (n = 3; middle) and a modern human (bottom) are presented at the phyla level. Names of the phyla were simplified for clarity, and unidentified reads were excluded. Gram-positive (blue) and Gram-negative (red) phyla are differentiated by colour.
b, UPGMA clustering of Bray–Curtis distances are displayed for 22 oral metagenomes, revealing a strong correlation with meat consumption. The scale bar represents differences in Bray– Curtis distances. The UPGMA clustering reveals four distinct groupings: Forager-Gatherers, Hunter-Gatherers, Ancient Agriculturalists, and the Modern human. Definitions for abbreviations can be found in the Supplementary Table 1: Spy and El Sidron, Neanderthals; Afr SF, African forager; LBK, Early European farmer; Afr PP, African Pastoralist period; Euro HG, European hunter–gatherer; Jewbury, UK Medieval; War, German (published German Medieval data sets from ref. 12) Medieval; and modern, modern human (C10).

Evolutionary events in both the deep evolutionary past and recent human evolution shape the potential for disease

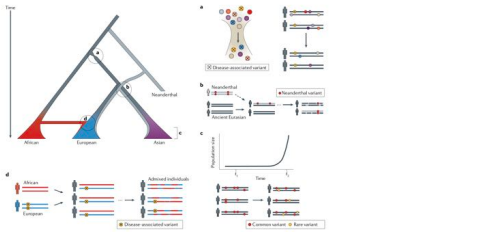



Benton, M.L., Abraham, A., LaBella, A.L. *et al.* The influence of evolutionary history on human health and disease. ***Nat Rev Genet*** 22, 269–283 (2021).

Evolutionary events in both the deep evolutionary past and recent human evolution shape the potential for disease. A timeline of evolutionary events (top) in the deep evolutionary past and on the human lineage that are relevant to patterns of human disease risk (bottom). The ancient innovations on this timeline (left) formed biological systems that are essential, but are also foundations for disease. During recent human evolution (right), the development of new traits and recent rapid demographic and environmental changes have created the potential for mismatches between genotypes and modern environments that can cause disease. The timeline is schematic and not shown to scale. bya, billion years ago; kya, thousand years ago; mya, million years ago.

---

Evolutionary events in both the deep evolutionary past and recent human evolution shape the potential for disease



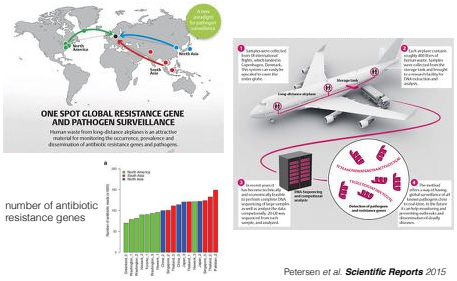

Benton, M.L., Abraham, A., LaBella, A.L. *et al.* The influence of evolutionary history on human health and disease. ***Nat Rev Genet*** 22, 269–283 (2021).

Effects of recent demographic events in human history on genetic mechanisms underlying disease. **Ancient human migrations**, **introgression events** with other archaic hominins and **recent population expansions** have all contributed to the introduction of variants associated with human disease. Schematic of human evolutionary history, where the branches represent different human populations and the branch widths represent population size (top left).

Letter labels refer to the processes illustrated in parts a–d. a | Human populations migrating out of Africa maintained only a subset of genetic diversity present in African populations. The resulting out- of- Africa bottleneck is likely to have increased the fraction of deleterious, disease- associated variants in non- African populations. Coloured circles represent different genetic variants. Circles marked with X denote deleterious, disease- associated variants. b | When anatomically modern humans left Africa, they encountered other archaic hominin populations. Haplotypes introduced by archaic introgression events (illustrated in grey) contained Neanderthal- derived variants (denoted by red circles) associated with increased disease risk in modern populations. c | In the last 10,000 years, the burden of rare disease-associated variants (denoted by yellow circles) has increased due to rapid population expansion. d | Modern human individuals with admixture in their recent ancestry, such as African Americans, can have differences in genetic risk for disease, because of each individual's unique mix of genomic regions with African and European evolutionary ancestry. For example, each of the three admixed individuals depicted have the same proportions of African and European ancestry, but do not all carry the disease- associated variant found at higher frequency in European populations (illustrated by
yellow circles). Summarizing clinical risk for a patient requires a higher resolution view of evolutionary ancestry along the genome and improved representation of genetic variation from

diverse human populations.

## Metagenomics of global poop (on airlines and on UCSD campus)






Petersen *et al.* ***Scientific Reports*** *2015*

Modern surveillance of novel dangerous pathogens introduced via air traffic: Sequence DNA in the sewage of airplanes!

A. Adjusted number of resistance reads (DNA sequences known to encode resistance to antibiotic drugs) identified in the flight samples. Green: North America, red: South Asia, blue: North Asia.

## Summary

The disease landscape has dramatically changed over time for humans.

Three major epidemiological transition are often proposed:
from hunter gatherer to settled farmers, from farming to industrial societies, and from industrialized societies to modern, globalized metropolitan societies.

There may well have been earlier transitions associated with carnivory and the use of home bases.

Developing nations face double burdens of infectious and non-communicable disease.

Reconstructing distant epidemics/pandemics is mired in difficulties.

Traces in skeletal remains and ancient DNA studies are starting to shed light on diseases such as syphilis, the plague and TB.

We are in the midst of a further epidemiological transition: antibiotic resistance, emerging infectious diseases, and human made pathogens…..