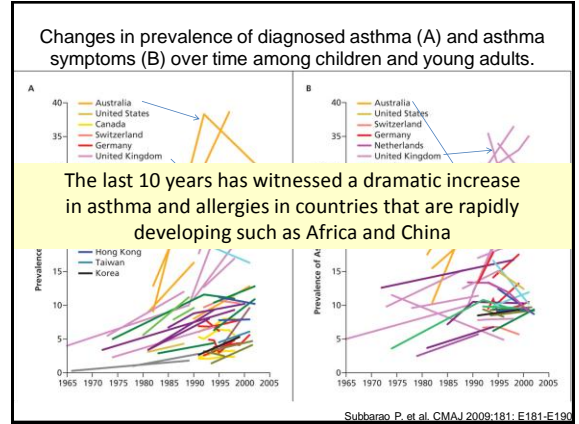





### Understanding the epidemic of asthma and allergy

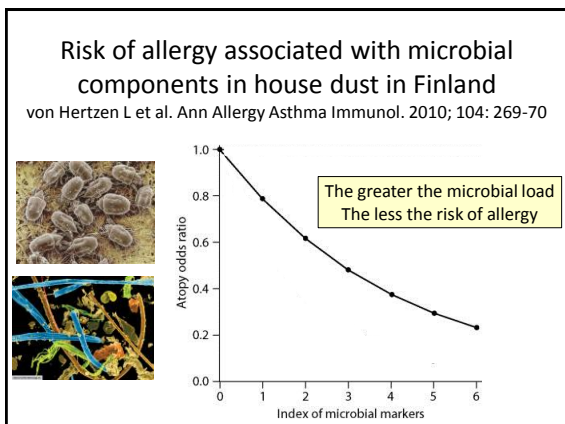
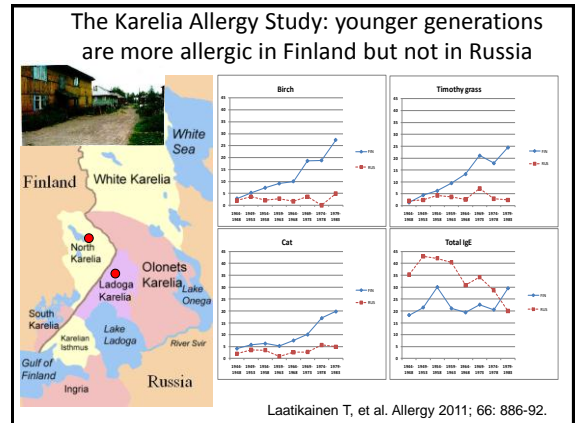
Miegunyah Lecture 2012  
 Stephen T Holgate,  
 III Division,  
 School of Medicine,  
 University of Southampton  
 sth@soton.ac.uk



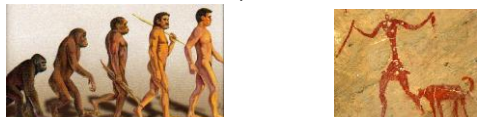
- But what are those environmental factors?
- Contrary to expectations draconian allergen reduction strategies failed to impact on either the origins of asthma in high risk children or established asthma!
- By reducing dust mite exposure, are we reducing other critical elements of exposure in the environment?



**10 year prevalence survey of Wagga Wagga and Belmont: Peat JK et al. BMJ 1994; 308:1591**  
 "We suggest that exposure to higher allergen levels has increased airway abnormalities in atopic children or that mechanisms that protected airways of earlier generations of children have been altered by new environmental factors".



### Evolution of microbial exposures and disease



**Microbes in environment**  
**Paleolithic (from 2.6 million - 10,000 years ago):** Hunter gatherer small groups by lakes and rivers; scavenging

**1ST EPIDEMIOLOGICAL TRANSITION**  
**Neolithic (10,000 - 3,000 yrs BC):** Larger social groups, animal husbandry, prolonged animal contact, domesticated cats & dogs + rodent pests. Increased orofaecal transmission.  
**Bronze age (2-3,000 yrs BC):** Larger communities – Influenza, mumps, smallpox, measles, plagues (including endemic infections).  
**Iron age to pre-industrial age (about 1500 BC to 1800)**  
 97% still living in rural environment e.g. farms, animal & mud contact, untreated water. Plagues and epidemics but little change in everyday exposure since Paleolithic period.






**2nd EPIDEMIOLOGICAL TRANSITION**  
**Modern age (from early 19th century)** Urban spread with concrete and tarmac so less mud. Clean chlorinated water, washed food. Soap & detergents. Diminished orofaecal transmission. Less animal contact. Antibiotics. De-worming. Loss of exposure to environmental saprophytes. Disappearance of worms. Less orofaecal spread of *H.pylori*, HAV, Salmonella. Less Toxoplasma. Restricted exposure to gut microbiota of other individuals. Intermittent disturbance of gut microbiota by antibiotics.

**Change only in 10 years (1990-2000)**  
 Landsat, satellite photos: Chengdu, Capital of Sichuan Province, China, 11 million inhabitants

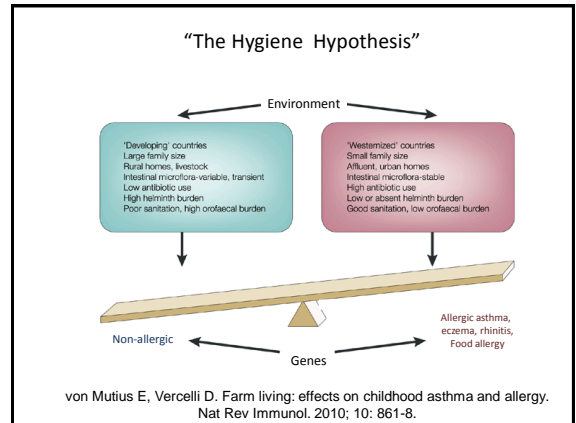


Xi Jinping: the 'big personality' taking charge in China

**Lifestyle factors associated with increased allergy and asthma**

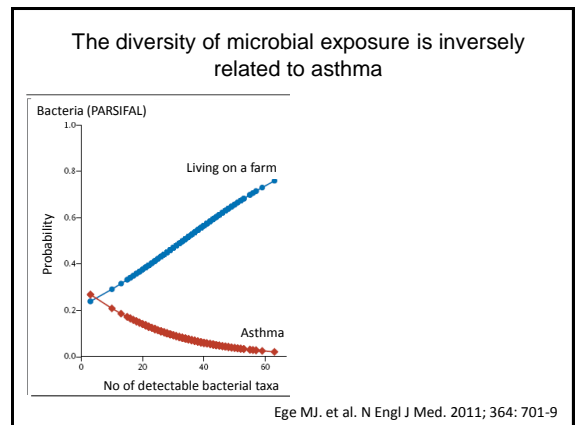
- > Urban vs rural living (West vs East) ↑
- > Being brought up on a livestock farm ↓
- > Antibiotics in pregnancy and early life ↓
- > Birth order and large family size ↓
- > Caesarean section ↑
- > Anthroposophist lifestyle ↓
- > Communal day care ↓
- > Oily fish intake ↓
- > Paracetamol in pregnancy and infancy ↑
- > Maternal tobacco smoking ↑
- > ? Air pollution and environmental chemical exposure ↑
- > Parasite infection ↑




**Bavarian women milking cows and their offspring exposed to a unique inhaled and food environment**








### Inhibitory influence of living on a livestock farm over the development of allergy

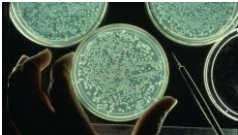


1. Prenatal and early-life exposures alter expression of innate immunity genes: the PASTURE cohort study. Loss G. et al. *J Allergy Clin Immunol.* 2012; 130: 523-30.
2. Exposure to microbial agents in house dust and wheezing, atopic dermatitis and atopic sensitization in early childhood: a birth cohort study in rural areas. Karvonen AM. et al. *Clin Exp Allergy.* 2012; 42: 1246-56.
3. Farming environments and childhood atopy, wheeze, lung function, and exhaled nitric oxide. Fuchs O. et al. *J Allergy Clin Immunol.* 2012; 130: 382-8.
4. Protection from childhood asthma and allergy in Alpine farm environments-the GABRIEL Advanced Studies. Illi S. et al. *J Allergy Clin Immunol.* 2012; 130: 382-8.
5. Amish children living in northern Indiana have a very low prevalence of allergic sensitization. Holbreich M. et al. *J Allergy Clin Immunol.* 2012; 129: 1671-3.

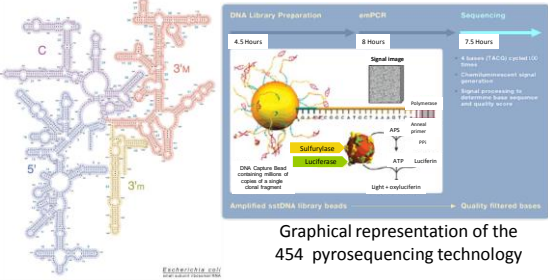
### Louis Pasteur: the discovery of antibiotics



After serving briefly as professor of physics at Dijon Lycée in 1848, he became professor of chemistry at the University of Strasbourg, where he met and courted Marie Laurent, daughter of the university's rector, in 1849. They were married on May 29, 1849, and together had five children, only two of whom survived to adulthood; the other three died of typhoid. These personal tragedies inspired Pasteur to try to find cures for diseases such as typhoid.



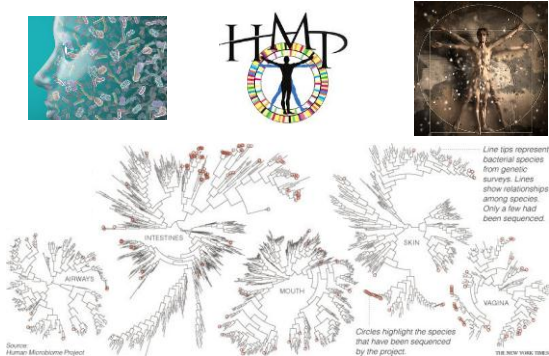
### The 16S Ribonucleic acid (rRNA) gene is used for phylogenetic studies as it is highly conserved between different species of bacteria



**Graphical representation of the 454 pyrosequencing technology**

Woes CR, Fox GE. *PNAS* 1977; 74: 5088-90.

### The Human Microbiome Project: gathering and sequence DNA from the thousands of microbe species living in or on the human body



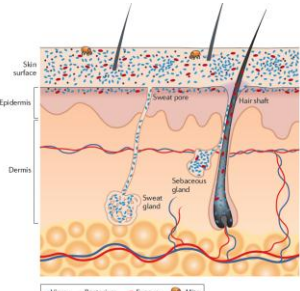
Line tips represent bacterial species from genetic surveys. Lines show relationships among species. Only a few had been sequenced.

Circles highlight the species that have been sequenced by the project.

Source: Human Microbiome Project

### Schematic cross section of human skin: Microorganisms (bacteria, viruses, fungi) and mites cover the skin and live deep in the hair and glands

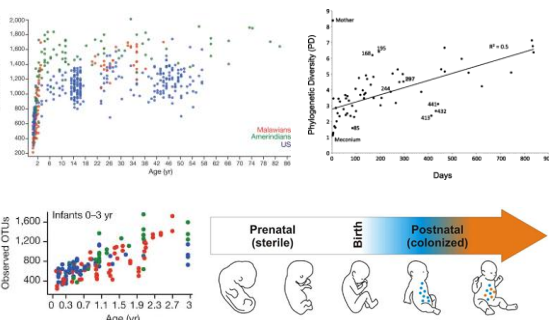
Grice EA, Segre JA. *Nature* 2011



Legend: Virus, Bacterium, Fungus, Mite

### Human gut microbiome viewed across age and geography.

Yatsunenko T et al. *Nature.* 2012; 486: 222-7



Phylogenetic Diversity (PD)

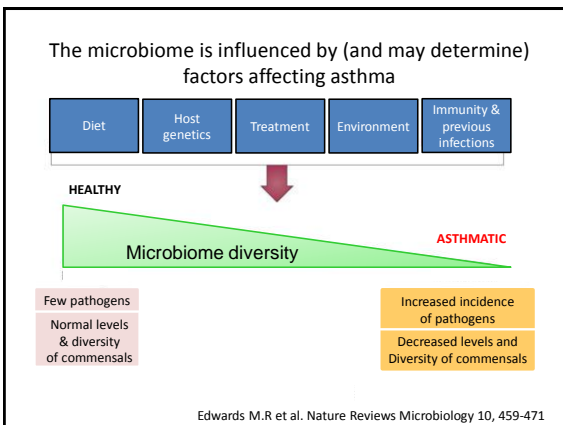
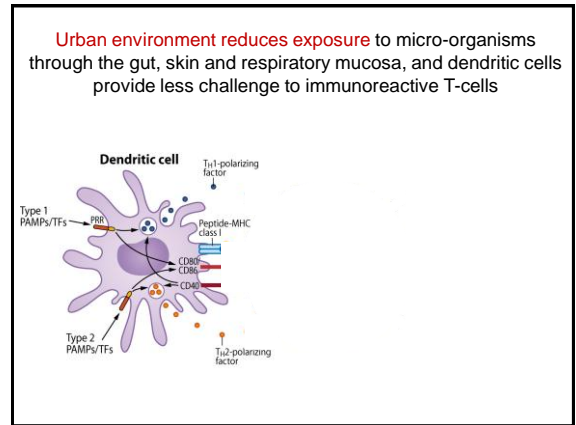
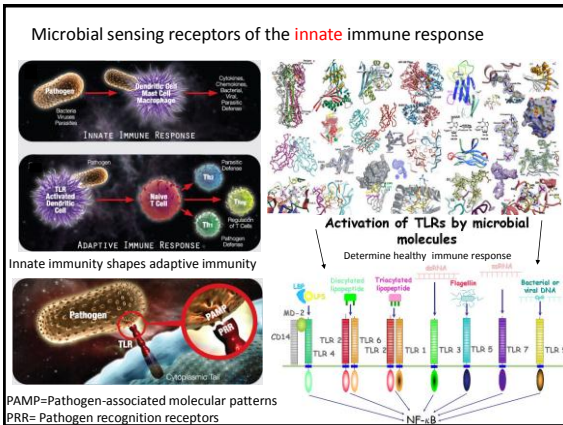
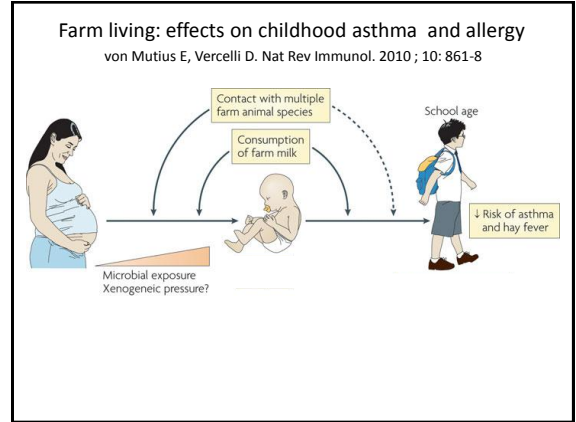
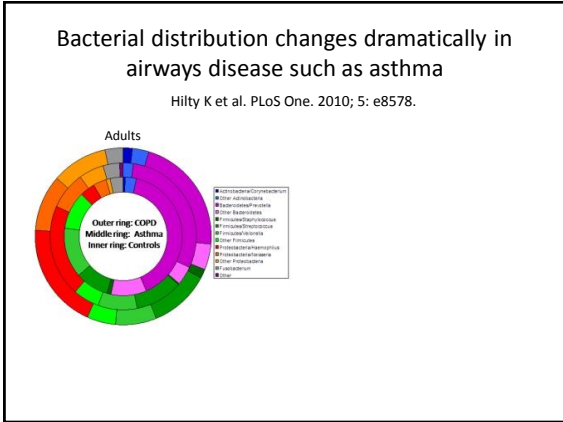
Days

Observed OTUs

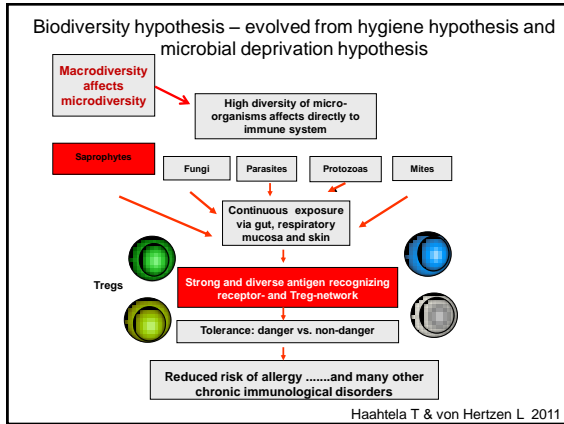
Age (yr)

Infants 0-3 yr

Prenatal (sterile) Birth Postnatal (colonized)



- ### Conclusions
1. Asthma and allergy are increasing worldwide as a consequence of urbanisation.
  2. Environmental factors associated with lifestyle are the most likely drivers of such trends.
  3. Alterations in the extent of stimulation of our innate immune response is the most likely mechanism for the increase in asthma (and other chronic inflammatory disorders).
  4. Reduced diversity and intensity of microbial exposure, especially bacterial products, seems to be the prime culprit.
  5. Increasing the level of protective immunity of the lung by altering the microbiome and/or raising the capacity to neutralise viral infection is more likely to be the most productive way of achieving protection against acute and chronic lung disease.



Species dying as fast as ever as 2010 conservation target passes

The Times April 30<sup>th</sup> 2010

• And, perhaps not surprisingly, the HMP discovered that microbial distributions in the human body are not so different from those in ocean ecosystems.

• There's good reason to believe that destruction of species and the simplification of ecosystems that seem to be overtaking us, in addition to being an environmental, food, and social justice issue, is also a health issue.

• Animal populations have fallen by 31 per cent since 1970, living corals by 38 per cent and mangroves and sea grasses by 19 per cent. The annual rates of loss have shown no improvement since 2002, according to the study of more than 40 international monitoring systems.

• The main causes of species loss were all linked to human activities, including habitat destruction, hunting, the introduction of alien predators, the spreading of disease and climate change

➤ Microbes defy a simple notion of individuality.

➤ They are essential to our biology and they travel with us from birth to death.

➤ Yet, they also flow between us, and can be found in water, food and soil.

➤ The more we understand about the human microbiome the more we realise that everything is connected: **humans**

Michelangelo (6 March 1475 – 18 February 1564)

**The creation of Adam**

Sistine Chapel, Vatican City, Rome

