Plagues and People in the modern world.

Roy Anderson

Department of Infectious Disease Epidemiology,
School of Public Health,
Imperial College London

1st Year Medical undergraduates Lecture - November 6th 2012

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- Darwin and infectious diseases.
- Human and pathogen evolution.
- Our changing world.
- Pathogen evolution.
- Zoonoses.
- SARS and influenza A (H1N1 and H5N1).
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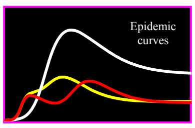
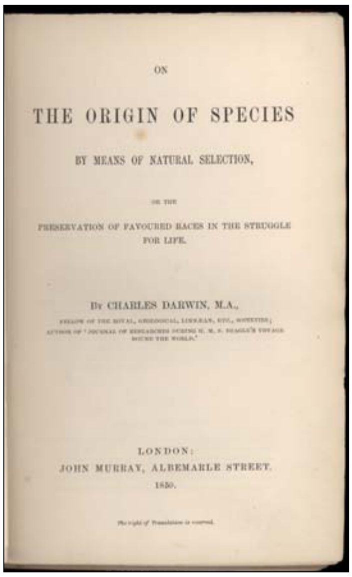


Infectious diseases and evolution


ON

THE ORIGIN OF SPECIES

BY MEANS OF NATURAL SELECTION,

OR THE

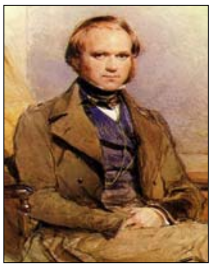
PRESERVATION OF FAVOURED RACES IN THE STRUGGLE FOR LIFE.

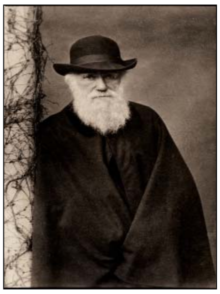
BY CHARLES DARWIN, M.A.,

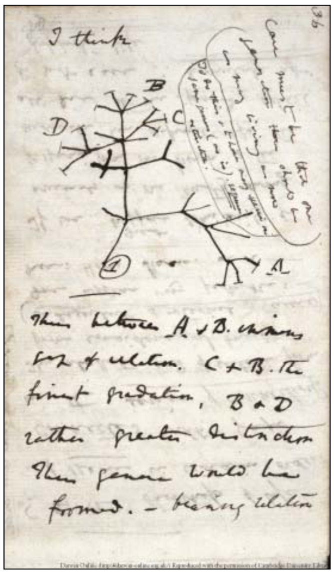
LONDON:

JOHN MURRAY, ALBEMARLE STREET.

1859.







Darwin and infectious diseases

In *On the Origin of Species by Means of Natural Selection, first published in 1859, Darwin eloquently emphasizes the remarkable power of natural selection. To quote from the Origin of Species - -*

'We have seen that man by selection can certainly produce great results, and can adapt organic beings to his own uses, through the accumulation of slight but useful variations, given to him by the hand of Nature. But Natural Selection, as we shall hereafter see, is a power incessantly ready for action, and is as immeasurably superior to man's feeble efforts, as the works of Nature are to those of Art.'

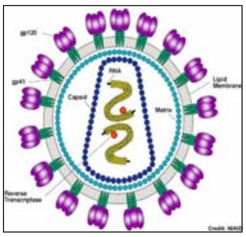
Later, in *The Descent of Man, despite his ignorance of the nature of inheritance, Darwin points out that the variation that is a prerequisite of natural selection originates independently of the selection itself.*

Darwin and Koch

A particular exchange of letters stands out for those interested in the beginnings of our understanding of infectious agents (Palin, 2009 Microbiology Today). In January 1878, Cohn writes to Darwin, discussing Koch's recent discovery of the anthrax bacillus. Darwin's response is as follows:

'I thank you sincerely for your most kind letter and I return your wishes for the New Year with all my heart. Your letter has interested me greatly. Dr Sanderson showed me some admirable photographs on glass by Dr Koch of the Organisms which cause splenic fever (caused by the Anthrax bacillus). But your letter and the valuable work which you have given me make the case much clearer to me. I well remember saying to myself between 20 and 30 years ago, that if ever the origin of any infectious disease could be proved, it would be the greatest triumph to Science; and now I rejoice to have seen the triumph.'

What are infectious agents



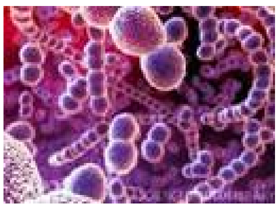
HIV-1 - virus

Ascaris worms

Ascaris eggs

Schistosome worms

Influenza - virus



Streptococcus - bacteria

The Neglected Tropical Diseases - Core Group of 14

- **Protozoan Infections**
  - African trypanosomiasis*
  - Chagas disease*
  - Leishmaniasis*
- **Bacterial Infections**
  - Buruli ulcer*
  - Leprosy
  - Trachoma

- **Helminth Infections**
  - Ascariasis
  - Hookworm Infection
  - Trichuriasis
  - Schistosomiasis*
  - Lymphatic filariasis
  - Onchocerciasis
  - Dracunculiasis
- **Viruses**
  - Dengue*

* Indicates – reservoir hosts known

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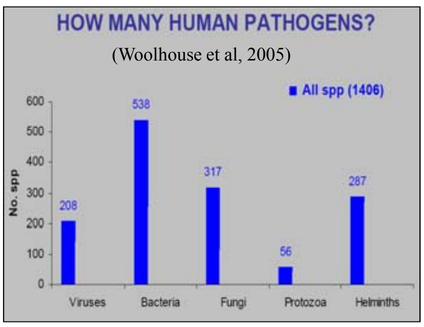
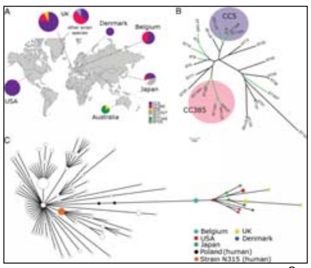
Origins of human infections

1) Inherited from our ancestors.
2) Acquired from wild life.
3) Acquired from livestock.

The fraction which are zoonotic estimated to be between 60-70%



Livestock sometimes acquire infections from humans; such as strains of *Staphylococcus aureus* in chickens (Lowder et al, 2009; *PNAS* 106, 19545-50)



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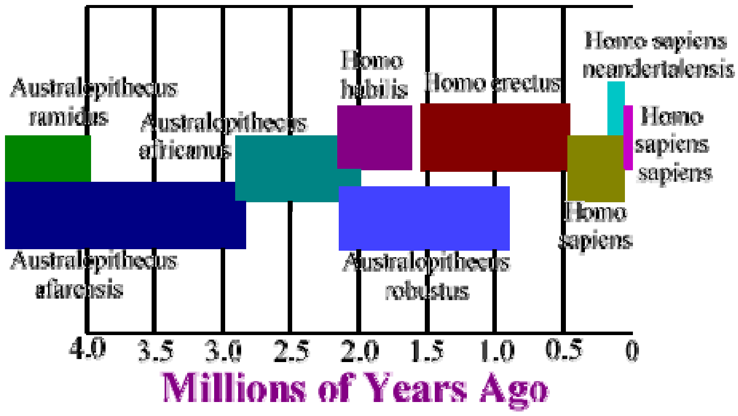
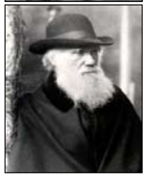
Human evolution



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Changing world


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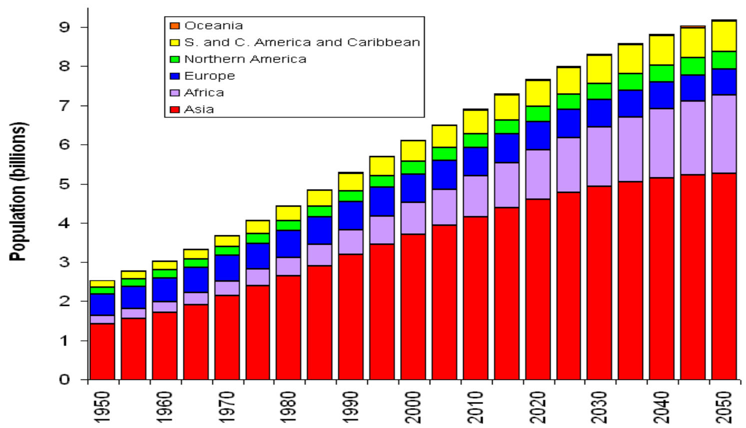
World population growth by continent: past and predicted



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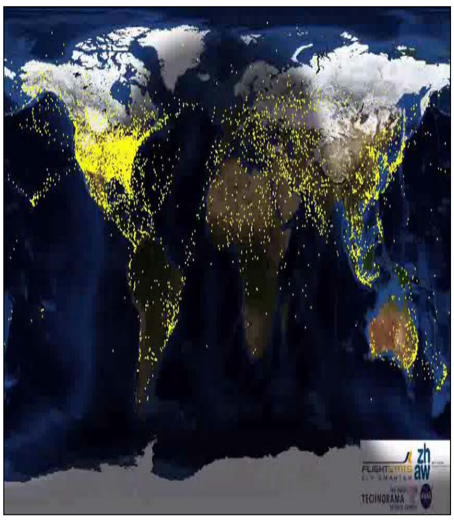
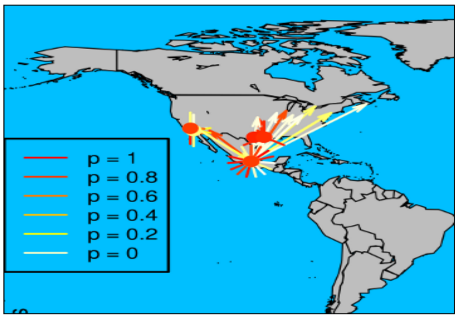
Airline network

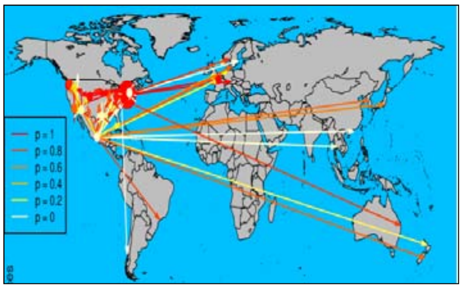
Airline movement patterns 2009, and Hufnagel et al, 2004.

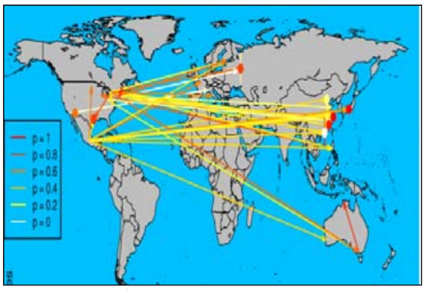


Early spread of H1N1 based on analysis of sequence data

Jombart, Eggo, Dodd & Balloux [2009] Spatiotemporal dynamics in the early stages of the 2009 A/H1N1 influenza pandemic. PLoS Curr Influenza. 2009 ; Heredity 2010, 1-8

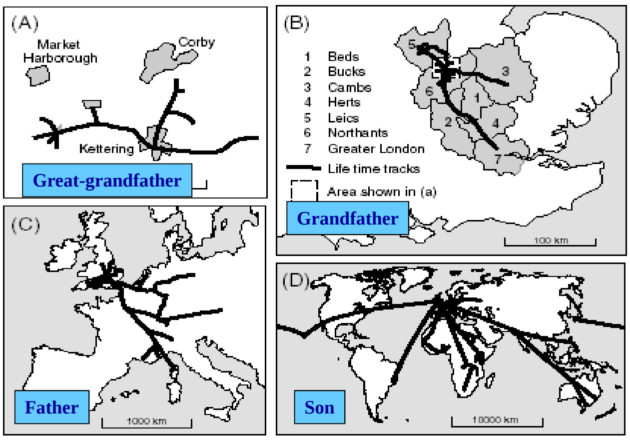






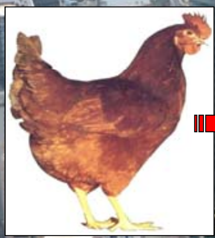
Record of increasing travel over four male generations of the same family.

(A) Great-grandfather. (B) Grandfather. (C) Father. (D) Son. Each map shows in a simplified manner the individual's 'life-time tracks' in a widening spatial context, with the linear scale increasing by a factor of 10 between each generation ***(Bradley, 1994 Geog. Ann. 76:91-104).***



Hong Kong

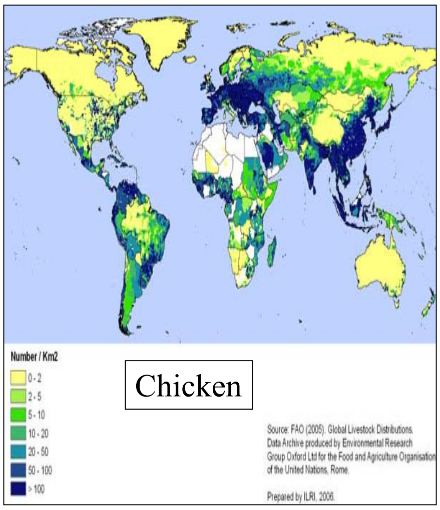
Re-assortment of bird and human influenza viruses

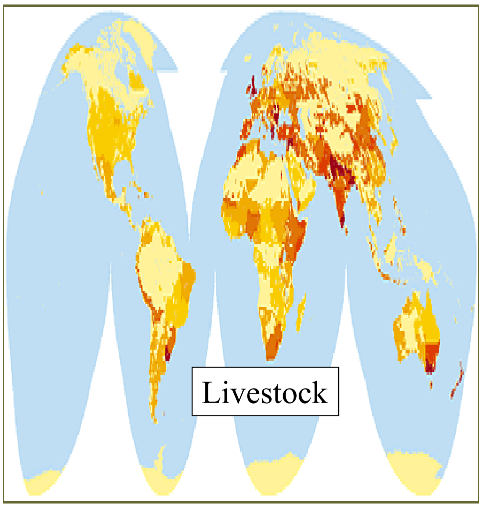


First megacity of 120 million people: Pearl River Delta in China consisting of Hong Kong, Shenhzen & Guangzhou

Megacities	1970	1994	2000	2015
Less Developed Regions				
Africa	0	2	2	3
Asia	2	10	12	19
Latin America	3	3	4	5
More Developed Regions				
Europe	2	2	2	2
Japan	2	2	2	2
North America	2	2	2	2

Chicken and Livestock densities - 2009





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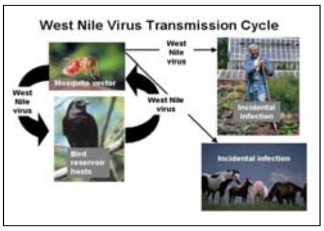
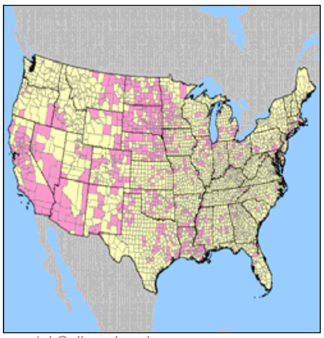
Some recent events

West Nile Virus - USA

- West Nile Virus was first reported in the United States in New York State in the summer of 1999. Since 1999, WNV has caused more than 19,000 cases of human illness including more than 750 deaths in the United States by mid 2009





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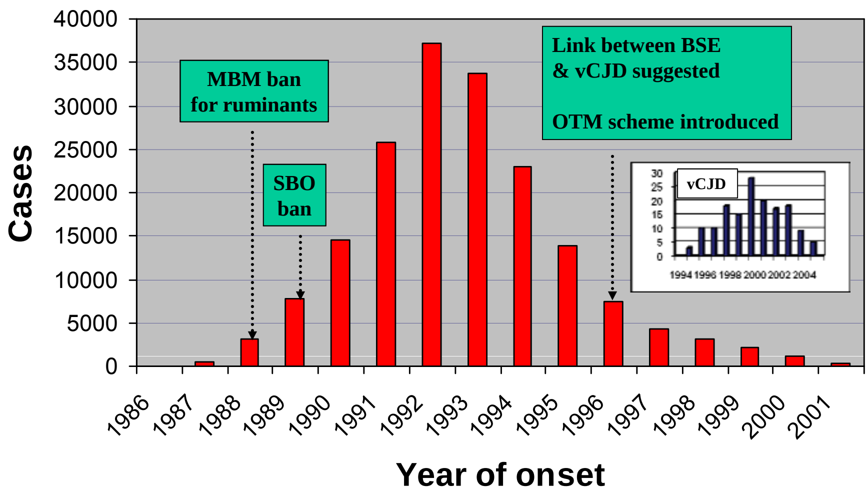
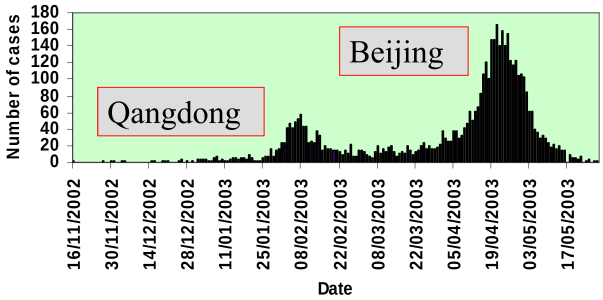
Bovine Spongiform Encephalopathy

BSE was spread from cow to cow via meat and bone meal protein in feed. The aetiological agent has been transmitted to humans (causing vCJD), apparently via consumption of contaminated beef or beef products.

The BSE epidemic in GB



Probable SARS cases – China 2003

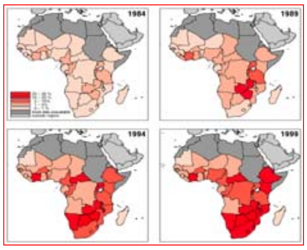


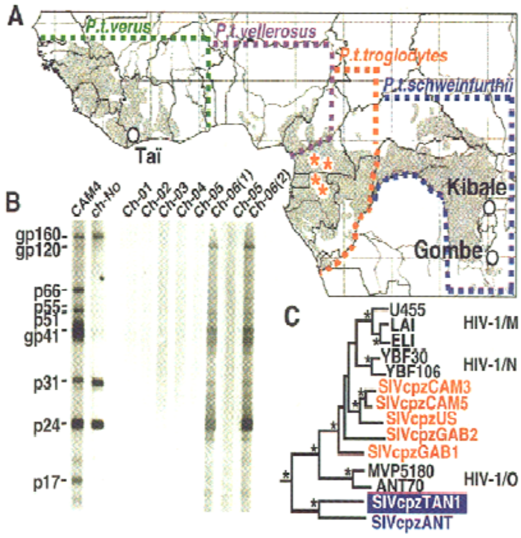
Bats as the origin of SARS

- Genome sequencing shows that the genome organization of all bat SARS-like–CoVs is almost identical to that of the SARS-CoVs isolated from humans or civets. They shared an overall sequence identity of 88% to 92%.
- (Lin-Fa Wang et al 2006, Emerging Infectious Diseases)

HIV – evolution - multiple introductions into humans

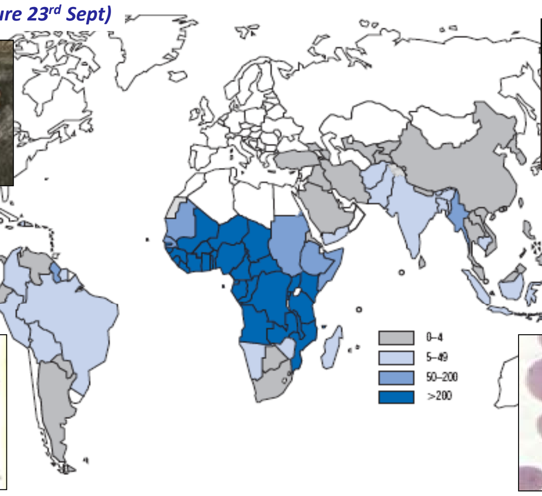
Hahn et al (2002)
(Gabon & Congo)

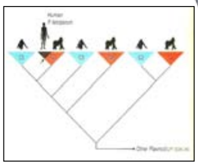


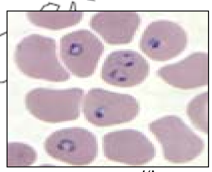


Incidence of malaria per 1000 head of population 2006 (WHO)

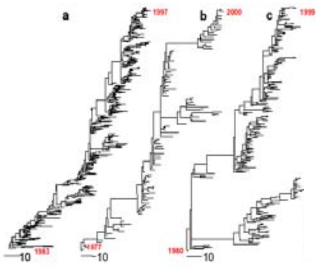
(Lui et al (2010) Nature 23rd Sept)







Evolution



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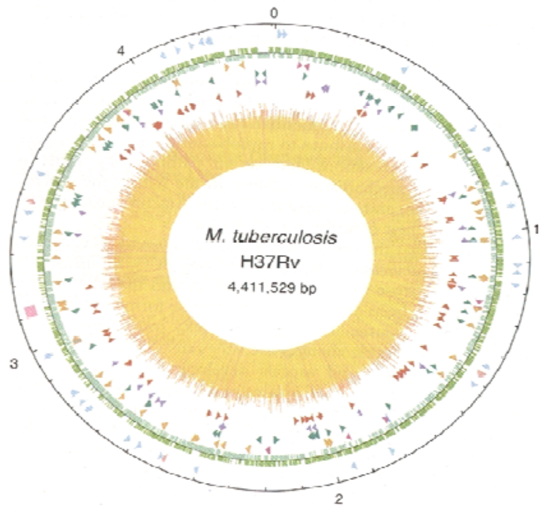
Whole genome sequencing



Circular map of the chromosome of *Mycobacterium tuberculosis* H37Rv (DNASTAR)

4,411,529 base pairs

Cole et al (1998) <u>Nature</u> 393:537-44

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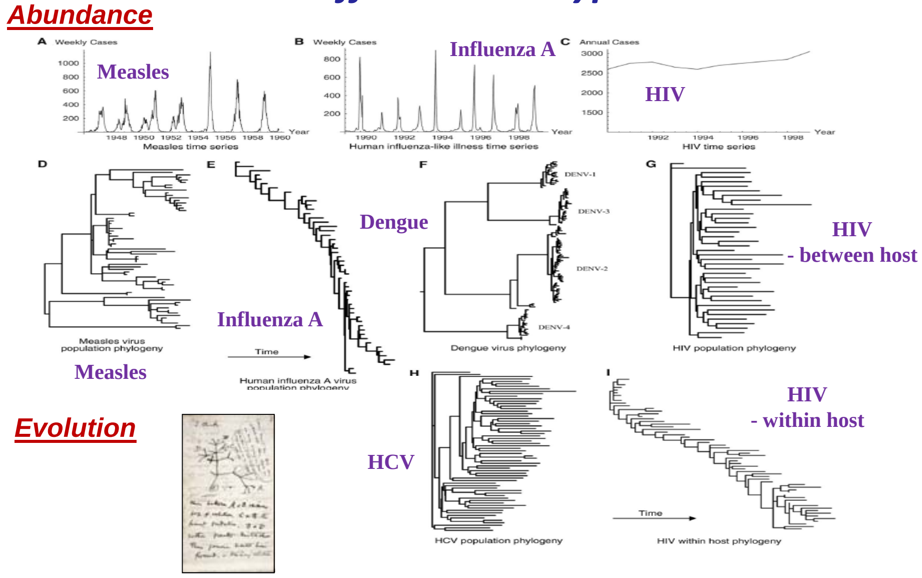
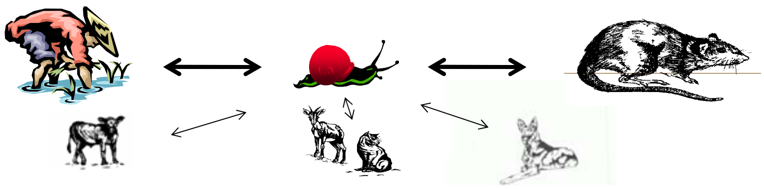
Dynamics and evolution for different viral types.



Epidemiological principles



Schistosoma japonicum

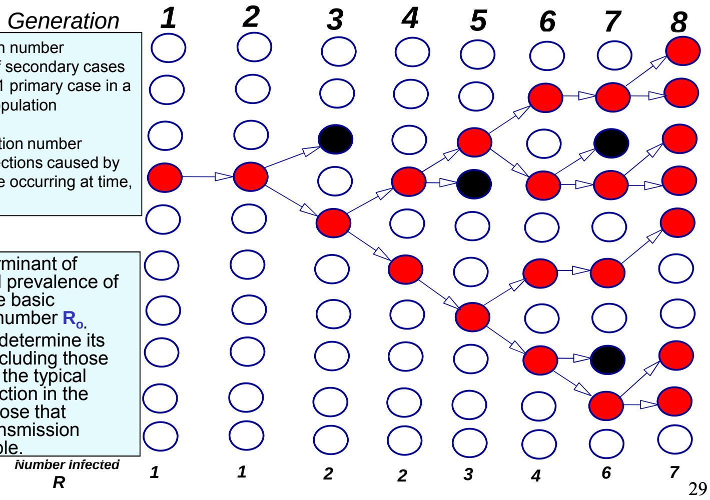
Basic Reproductive number, R_o

Chains of transmission between hosts

R_0 Basic reproduction number
average no. of secondary cases generated by 1 primary case in a susceptible population

R_t Effective reproduction number
number of infections caused by each new case occurring at time, *t*

- The key determinant of incidence and prevalence of infection is the basic reproductive number R_o.
- Many factors determine its magnitude, including those that influence the typical course of infection in the patient and those that determine transmission between people.



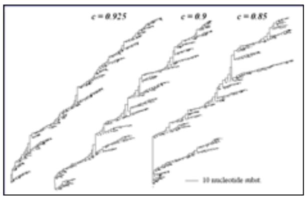
Data needs: detailed population data:

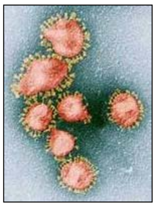
Landscan (Oakridge Natl. Lab.)

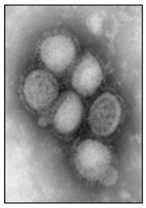
Need both population data (density, age, household) and mixing/travel data.

Population density – based on satellite imagery

SARS and Influenza A



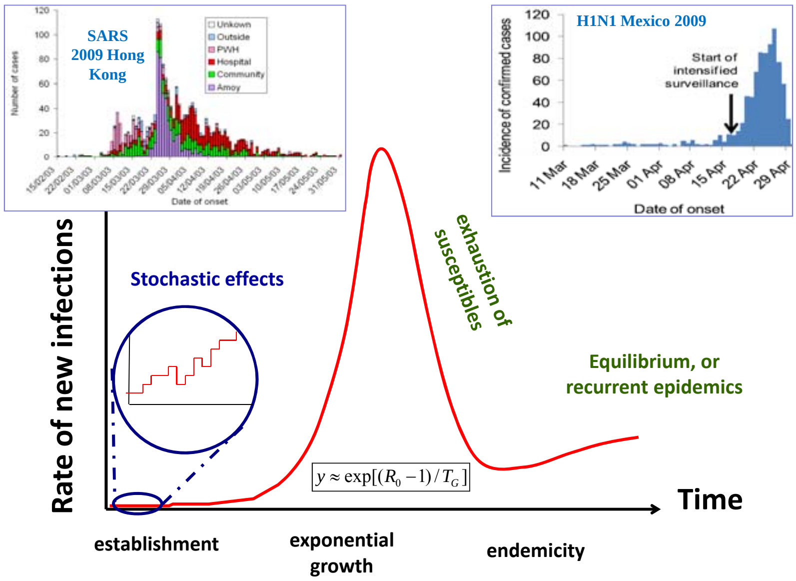




The emergence of a new disease – urgent tasks

- **Indication** – unusual clusters of morbidity/mortality in space and time (e.g. SARS in Quangzhou – China, November 2002).
- Identify aetiological agent.
- Develop diagnostic tests.
- Determine route of transmission.
- Identify clinical algorithms for care – to reduce morbidity and mortality.
- Put in place, or activate, data capture and communication systems.
- Identify and implement key public health measures.
- Keep public informed.

Epidemic timescales



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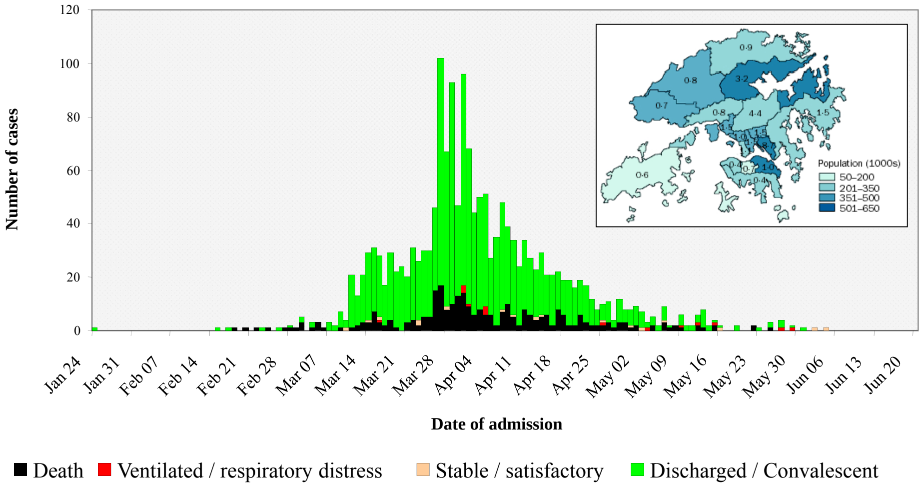
The Hong Kong epidemic

A mix of person-to-person, within hospital and point source spread



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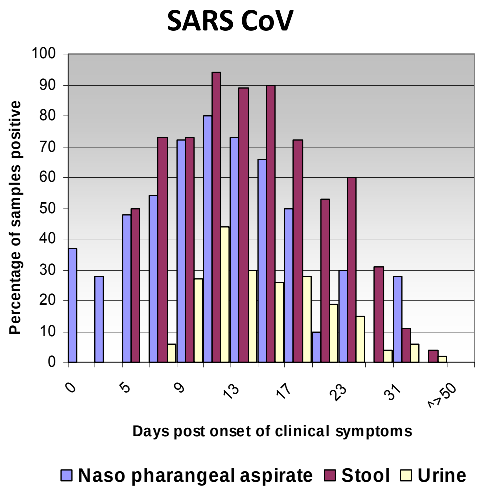
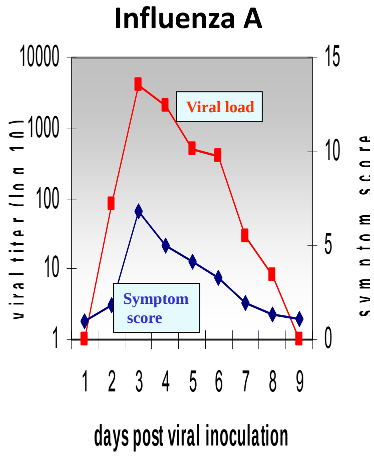
RT-PCR sensitivity

Peiris et al (2003), Hayden et al (1998)





Experimental human influenza A/Texas/36/91 (H1N1) intranasal inoculation 10^5 dose

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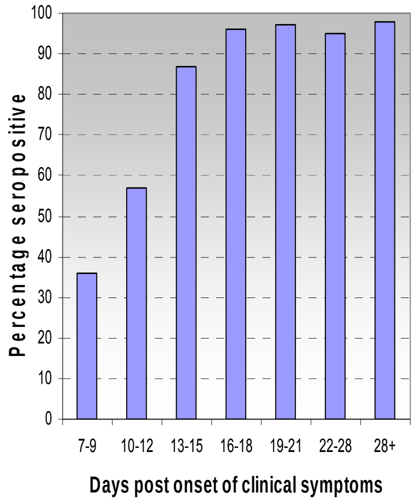
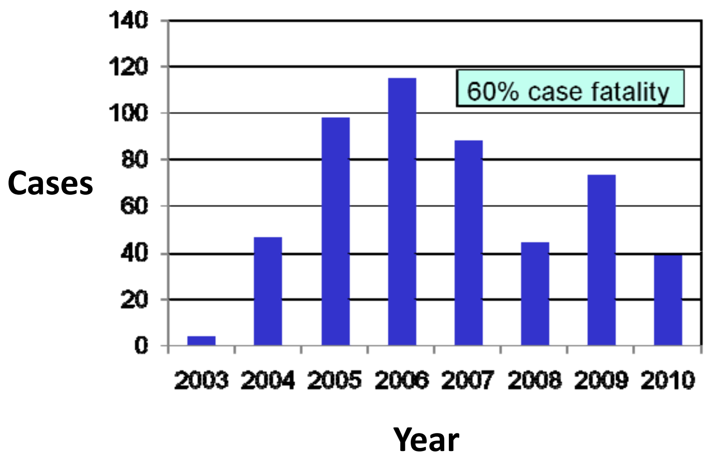
Serology (EIA) – Hong Kong

Lim et al (2003)

Source	No Samples	No Positive	% Positive
Clinics	777	10	1.3
Hospitals	620	49	7.9
Total	1397	59	4.2



Cases of H5N1 in humans reported to WHO by 18th October 2010



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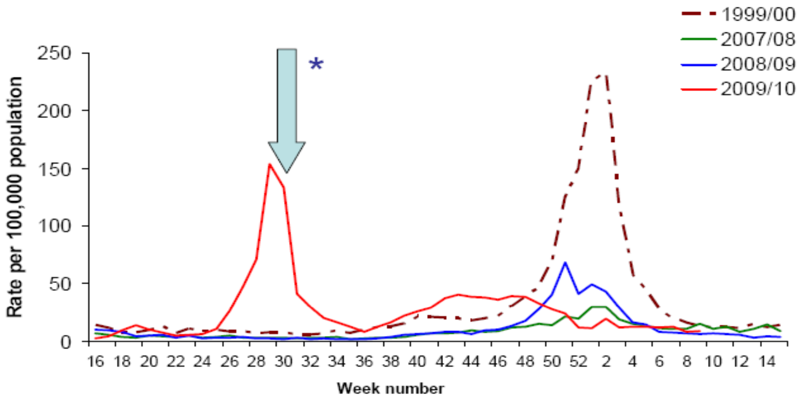
H1N1 in England during the 2009-10 seasons – compared with previous years



Week ending 28 February 2010: **9.0 consultations per 100,000 population**

* Level reduced by availability of NPFS for 2009/2010 period but not earlier periods

Source: RCGP to 28 February 2010

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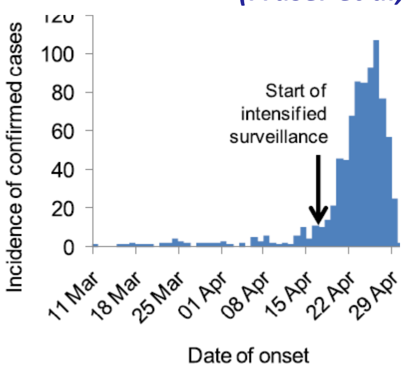
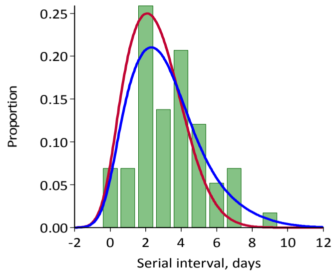
R for Mexico in April-May

(Fraser et al, 2009 Nature)





- *R*=1.5 (95% Cr.I.:1.2-1.9) from confirmed case epi curve.
- *R*=1.4 (95% Cr.I.:1.1-1.9) from spatial back-calculation.
- *R*=1.2 (95% Cr.I.:1.1-1.9) from sequence analysis.

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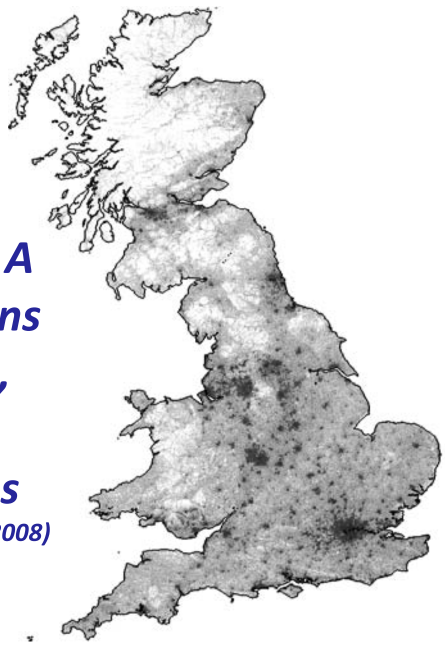
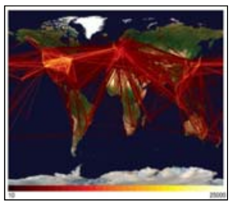
Influenza A simulations - England, Scotland and Wales

(Ferguson et al, 2008)





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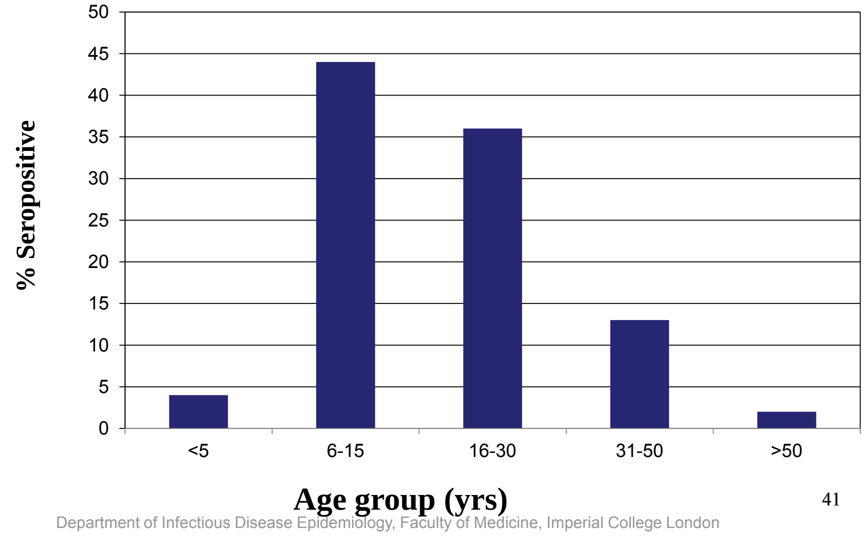
Influenza A: serology - H1N1 household studies

(Cowling et al, 2009)



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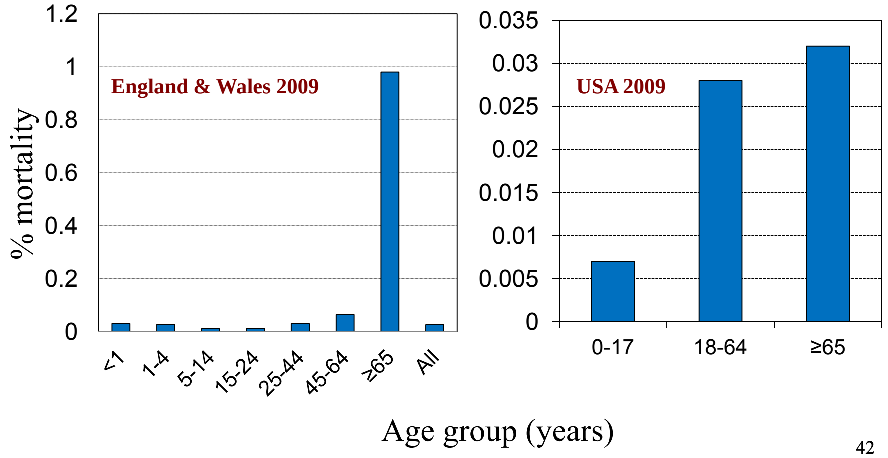
Mortality in the UK by age group H1N1 - 2009



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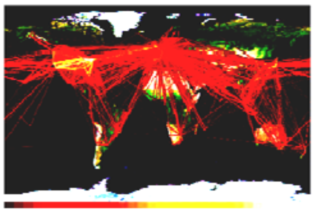
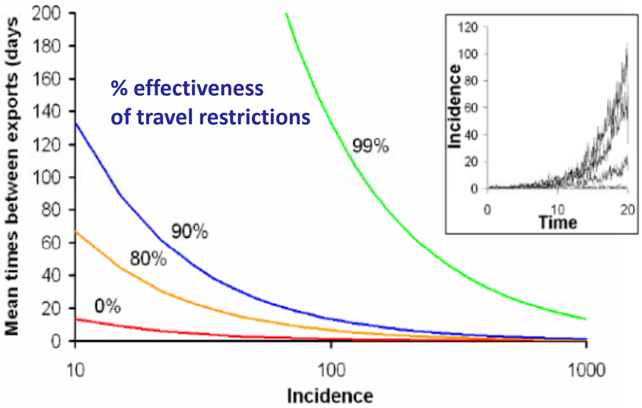
Travel restrictions



Mean time between exports with differing degrees of travel restrictions

(Hollingsworth, Ferguson & Anderson, 2006)



Stochastic effects Incidence as a function of time for four realizations of a stochastic simulation of an influenza epidemic. Incidence is highly variable during the early stages of any epidemic, here ranging between 10 and 120 cases per day by day 20. Incidence increases during the course of an epidemic and the interval between exports will decrease rapidly.

Vaccination

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Blocking transmission by mass vaccination

The magnitude of $\mathbf{p_c}$ - the fraction of the susceptible population that must be immunised to block transmission is given by the following simple expression:,

$$p_c = [1 - 1/R_0]/\varepsilon$$

Vaccine efficacy = ε, ranging from 0-1
For Influenza A …… if R_0=1.6 then p_c=37.5%; if R_0=2.0, then p_c=50%.

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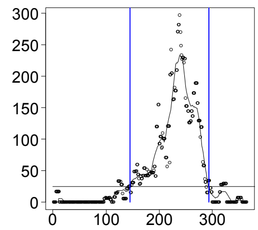
Closure of schools



Closure schools during a pandemic

(Cauchemez et al, 2008, Nature)

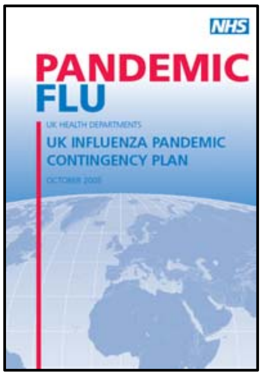
- If people behave during permanent school closure as during holidays:
  - 13-17% relative reduction in the cumulated attack rate overall:

    = 1 in 10 adult cases prevented, 1 in 5 child cases.
  - 38-45% reduction in peak attack rates.

    - same as predicted by simulation model (Ferguson et al., Nature 2006)

Results very sensitive to the extent to which non-school contacts increase when schools are closed – if strength of compensatory behaviours is 1.5 fold larger than during holidays, no reduction.

Clear definition of control policy aims & objectives



Policy objectives?

1) Minimize morbidity and mortality
   – with fixed or variable budget.

2) Buy as much time as possible
   to wait for vaccine development.

3) Minimize duration of the epidemic
   and impact on economy.

4) Minimize peak prevalence below a
   defined level to avoid collapse of
   health care systems.

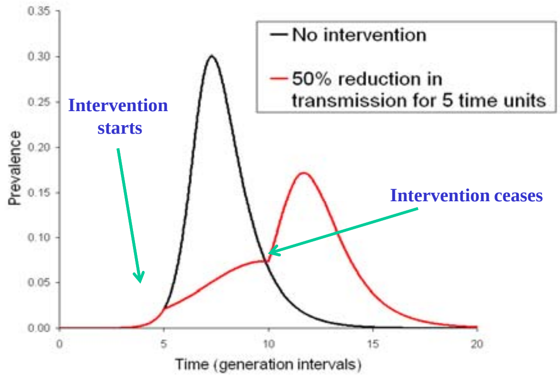
Simple theory

(Hollingsworth, Klinkenberg, Hesterbeck & Anderson, 2010)

- Total epidemic size
- Peak incidence
- Peak prevalence

a = total epidemic size,
T_1 to T_2 = duration of intervention
θ = proportional reduction in transmission
I = cumulative incidence

$$a_{I_{12}} = 1 - \left(\frac{1-I(T_1)}{1-I(T_2)}\right)^{\frac{\theta}{1-\theta}} e^{-R_0 a_{I_{12}}}$$



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Lessons learnt

- Estimation of morbidity and mortality rates early in the epidemic.
- **Serology as soon as possible** – essential for estimation of case fatality (stratified by age and risk factors).
- Identify co-morbidities/risk factors as quickly as possible – first 500 cases.
- On the bases of R_0 and case fatality estimates – define policy objectives.
- Electronic capture of data and display real time.
- **Logistics of antiviral delivery** and policy of use.
- Policy on vaccine delivery to at risk groups - age.
- Vaccine uptake – reasons for refusal.

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End