Infectious diseases –approaches to prediction and the control of pandemics

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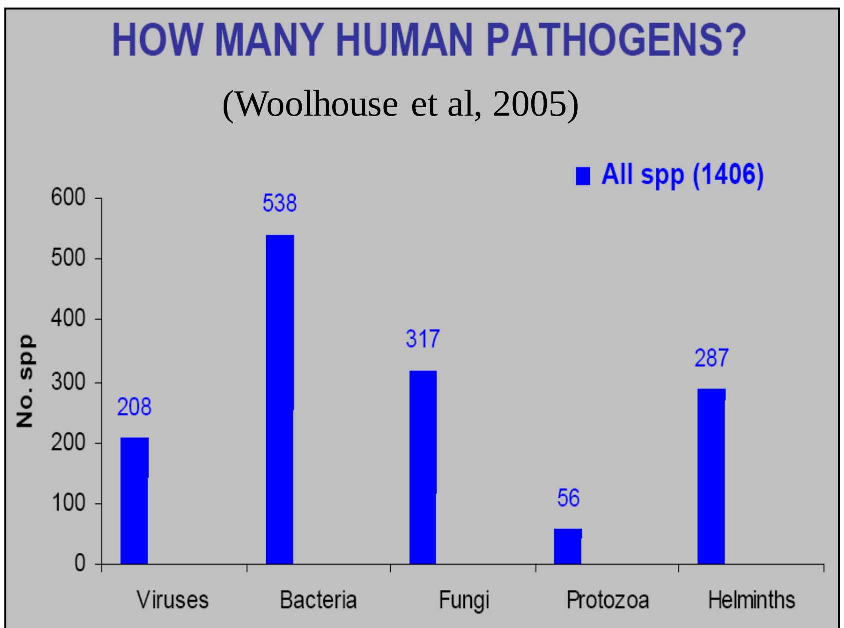
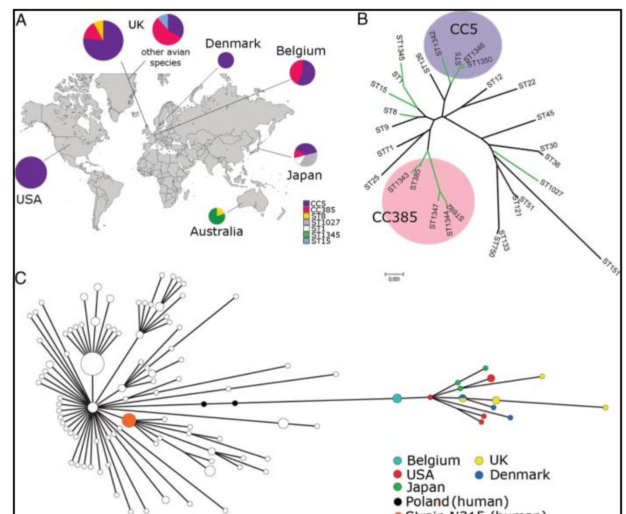
Origins of human infections

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

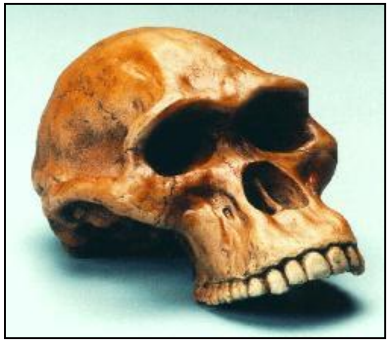
The fraction which are zoonotic estimated to be between 60-70%

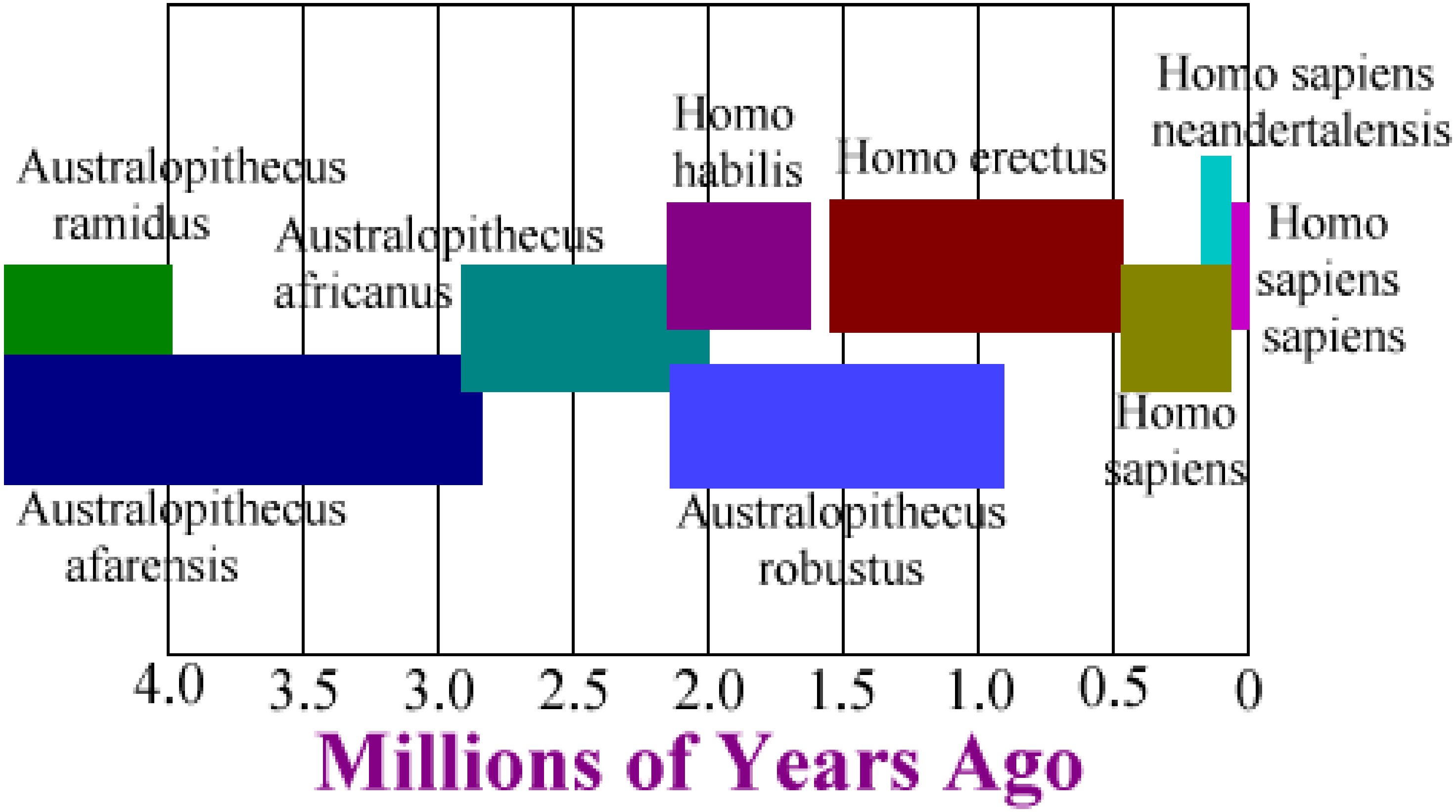


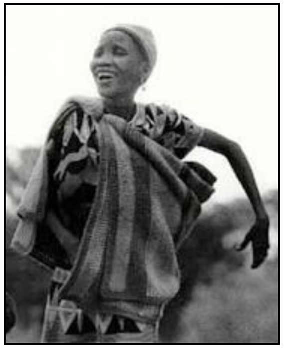
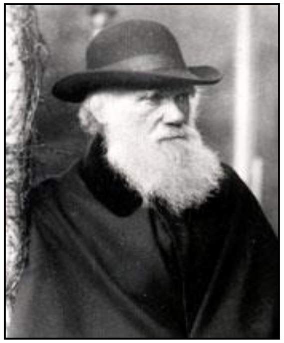
Livestock sometimes acquire infections from humans; such as strains of *Staphylococcus aureus* in chickens (Lowder et al, 2009; *PNAS* 106, 19545-50)



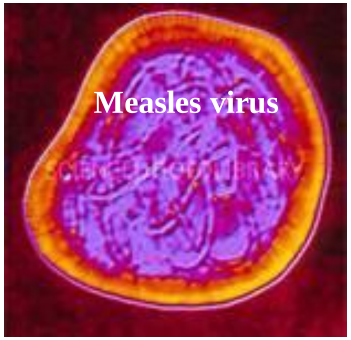
Human evolution






Genetic variation spectrum of human pathogens



Relatively homogeneous ***Great heterogeneity***

Measles virus Mumps virus Rubella virus	Bordetella	Dengue	Pneumococcal RSV Rotavirus HPV Influenza A & B	HIV Malaria

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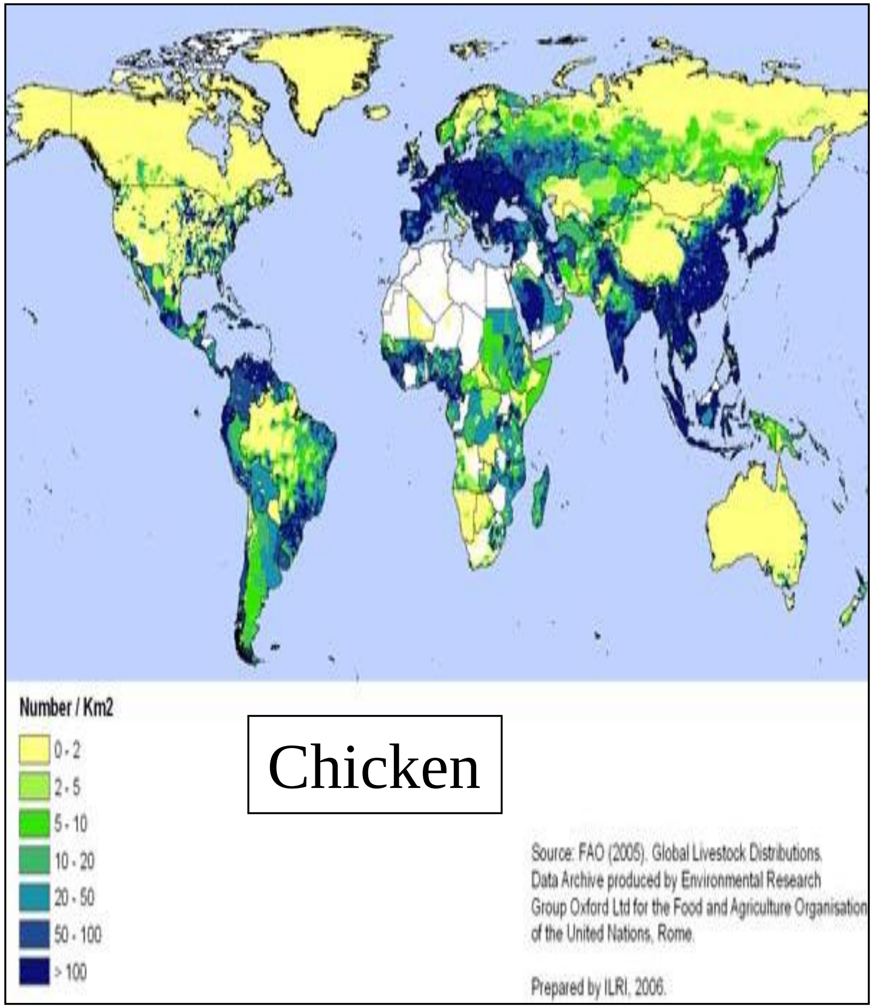
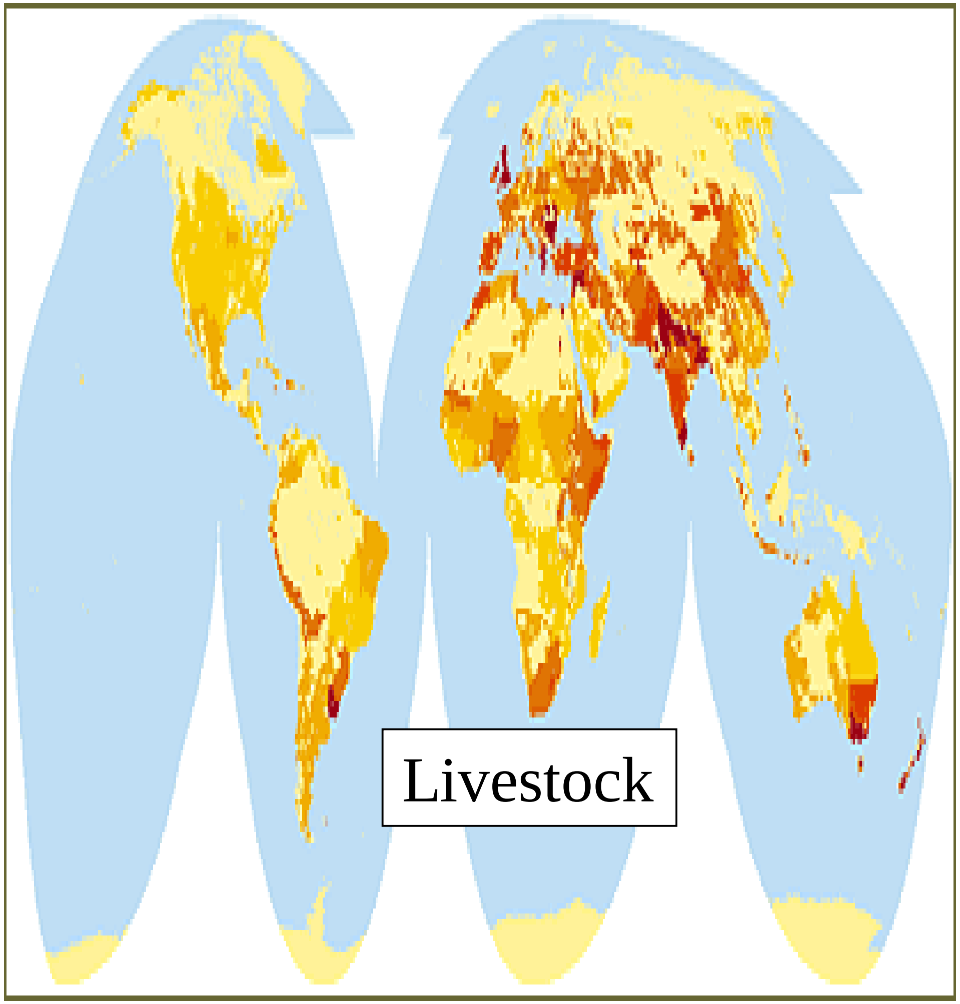
Evolution continues - hybridization between animal and human pathogens

Chicken and Livestock densities on a global sacle



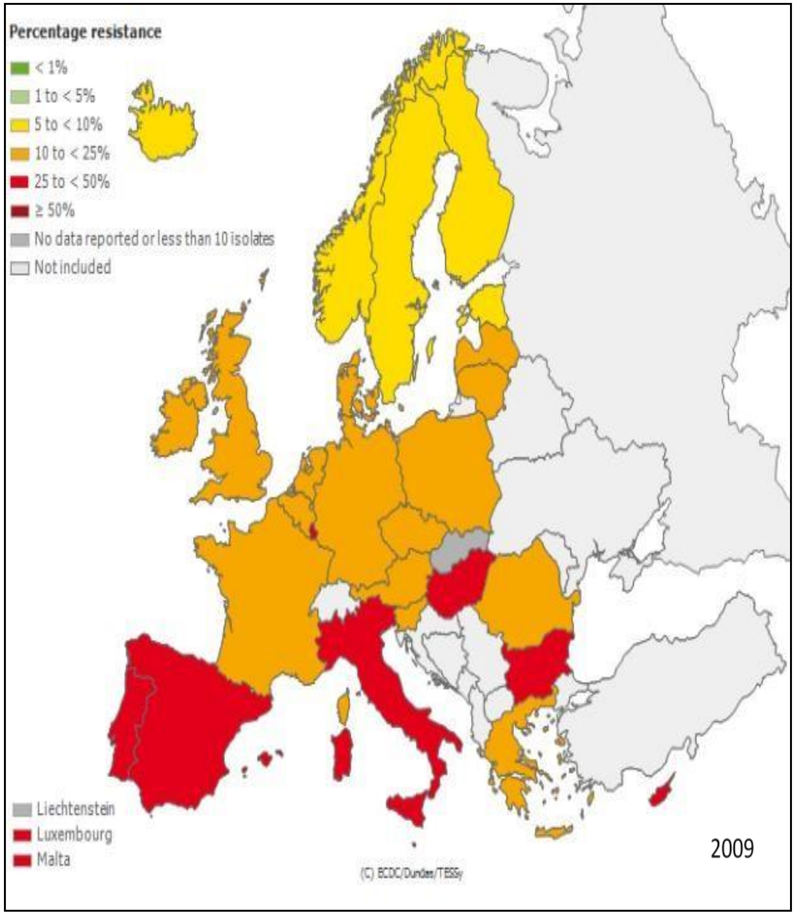


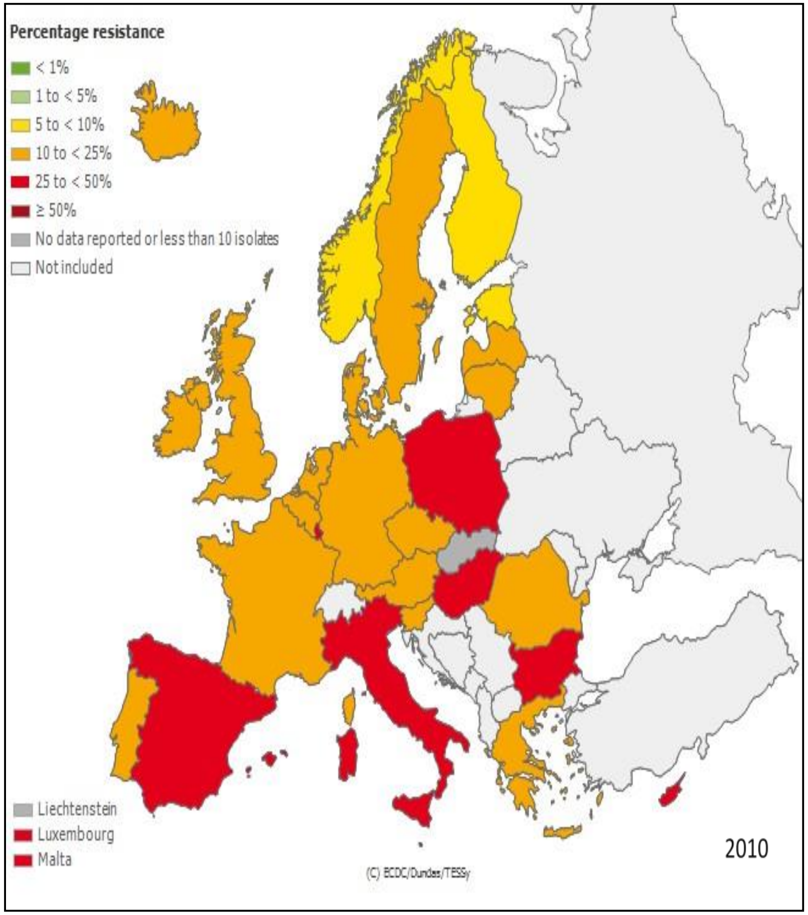
Evolution continues – new infections constantly emerging – the schistosomes.

Bonnie L. Webster, Oumar T. Diaw, Mohmoudane M. Seye, Joanne P. Webster, David Rollinson (2013) Plos NTDs 7: 1-8

- Large-scale multi-loci molecular analysis of species of the ***Schistosoma*** genus with parasite samples collected from children and domestic livestock across Senegal revealed that interactions and hybridization were taking place between all species present in humans and livestock.
- Evidence of hybridization between *S. haematobium/S. curassoni* and *S. haematobium/S. bovis* was commonly found in children from across Senegal, with 88% of the children surveyed in areas of suspected species overlap excreting hybrid miracidia.
- Rodent experiments confirmed that males and females of each species readily pair and produce viable hybrid offspring.

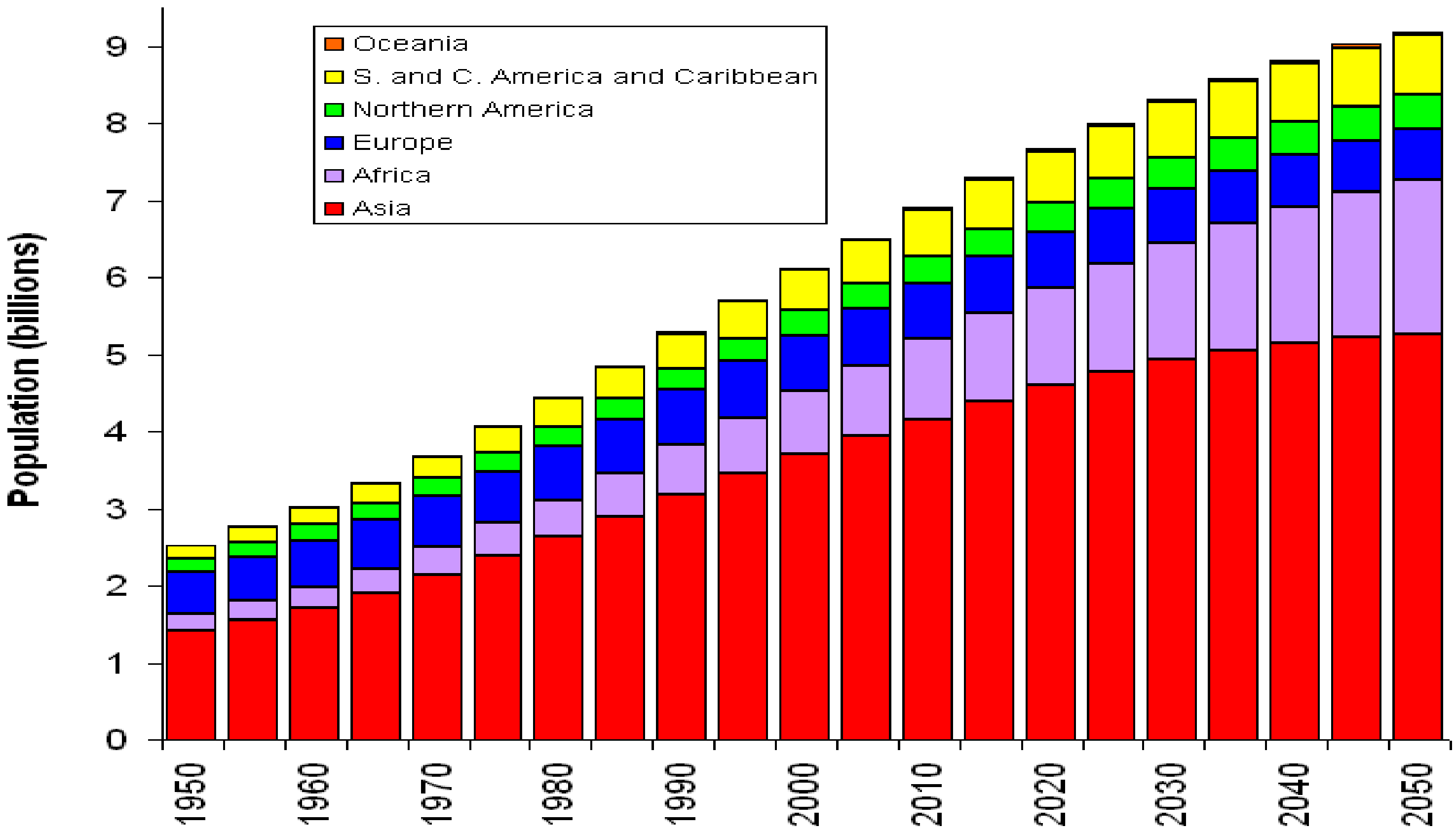
Escherichia coli - % invasive isolates with resistance to fluoroguinolones 2009-10 (EU surveillance)





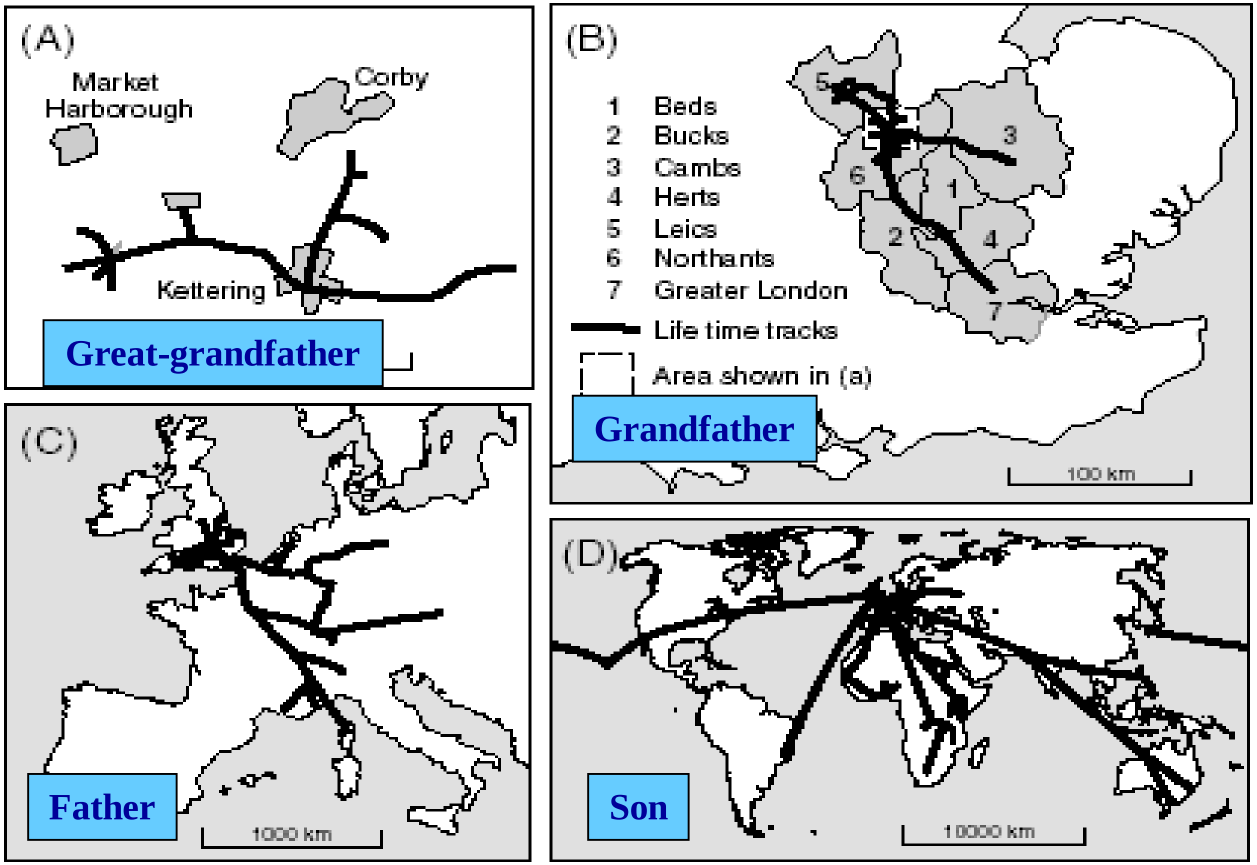
Changing world

World population growth by continent: past and predicted



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

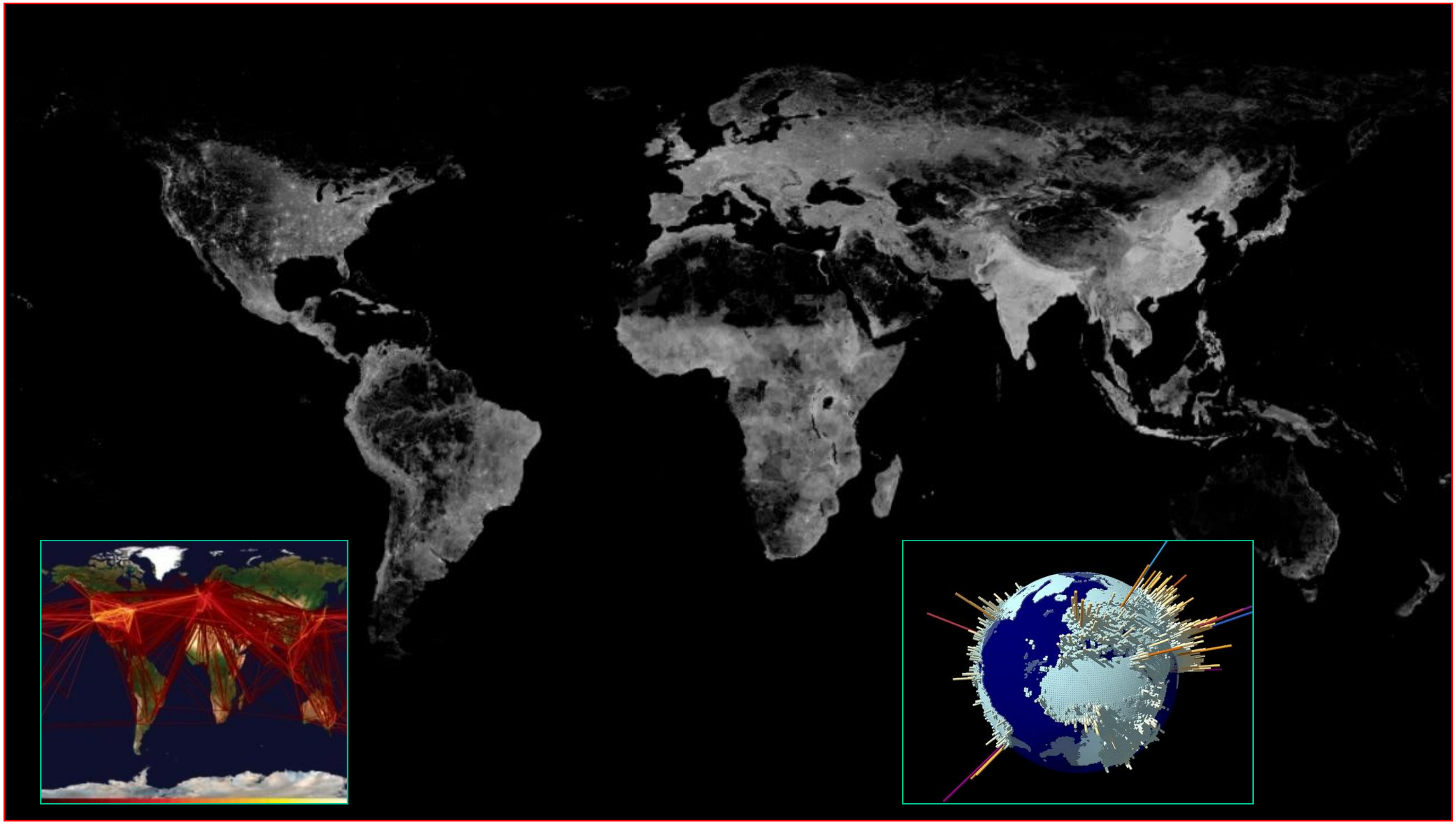
(A) Great-grandfather. (B) Grandfather. (C) Father. (D) Son. Each map shows in a simplified manner the individual's 'life-time tracks' in a widening spatial context, with the linear scale increasing by a factor of 10 between each generation (Bradley, 1994 Geog. Ann. 76:91-104).



Air traffic flow – world picture - 2009

Human population density based on satellite imagery – influenza A spread

(18 months compressed into a few seconds)



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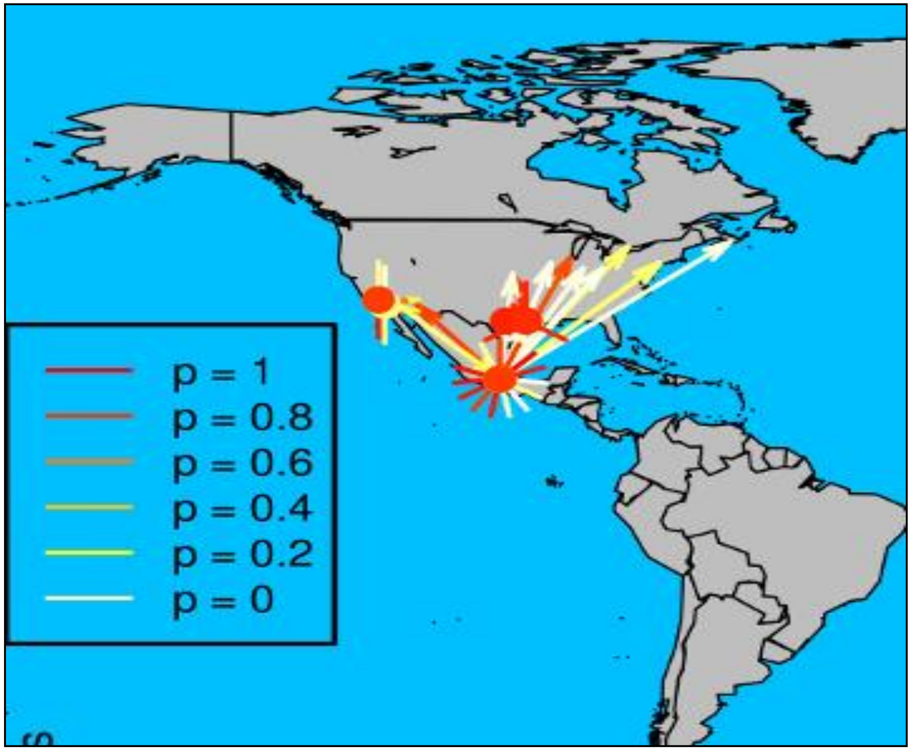
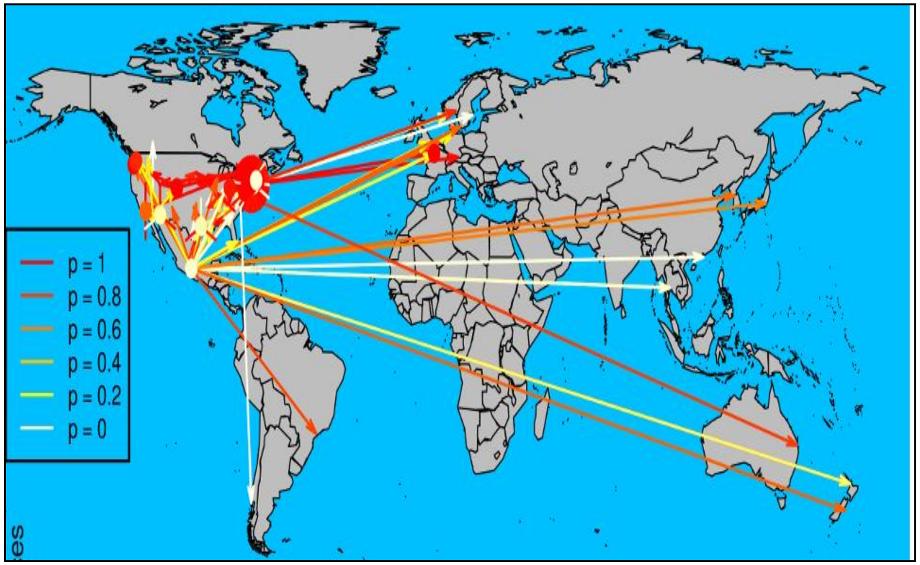
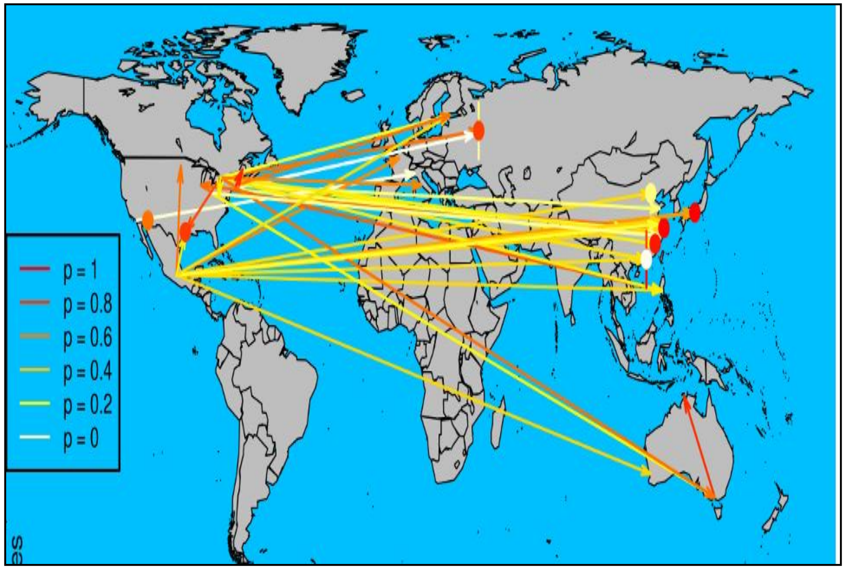


Early spread of H1N1 based on analysis of sequence data

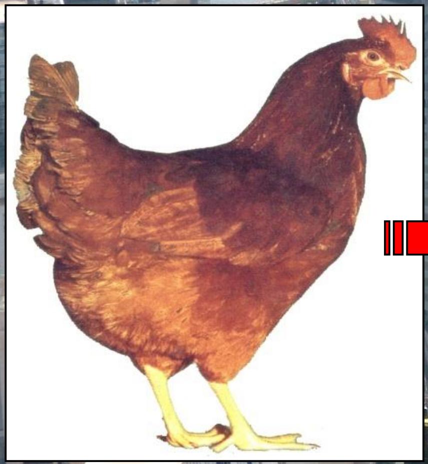
Jombart, Eggo, Dodd & Balloux [2009] Spatiotemporal dynamics in the early stages of the 2009 A/H1N1 influenza pandemic. PLoS Curr Influenza. 2009 ; Heredity 2010, 1-8

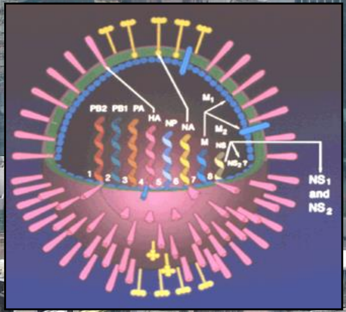




Hong Kong

Re-assortment of bird and human influenza viruses





Less Developed Regions – Megacities (10 million plus)

	1970	1994	2000	2015
Africa	0	2	2	3
Asia	2	10	12	19
Latin America	3	3	4	5

More Developed Regions

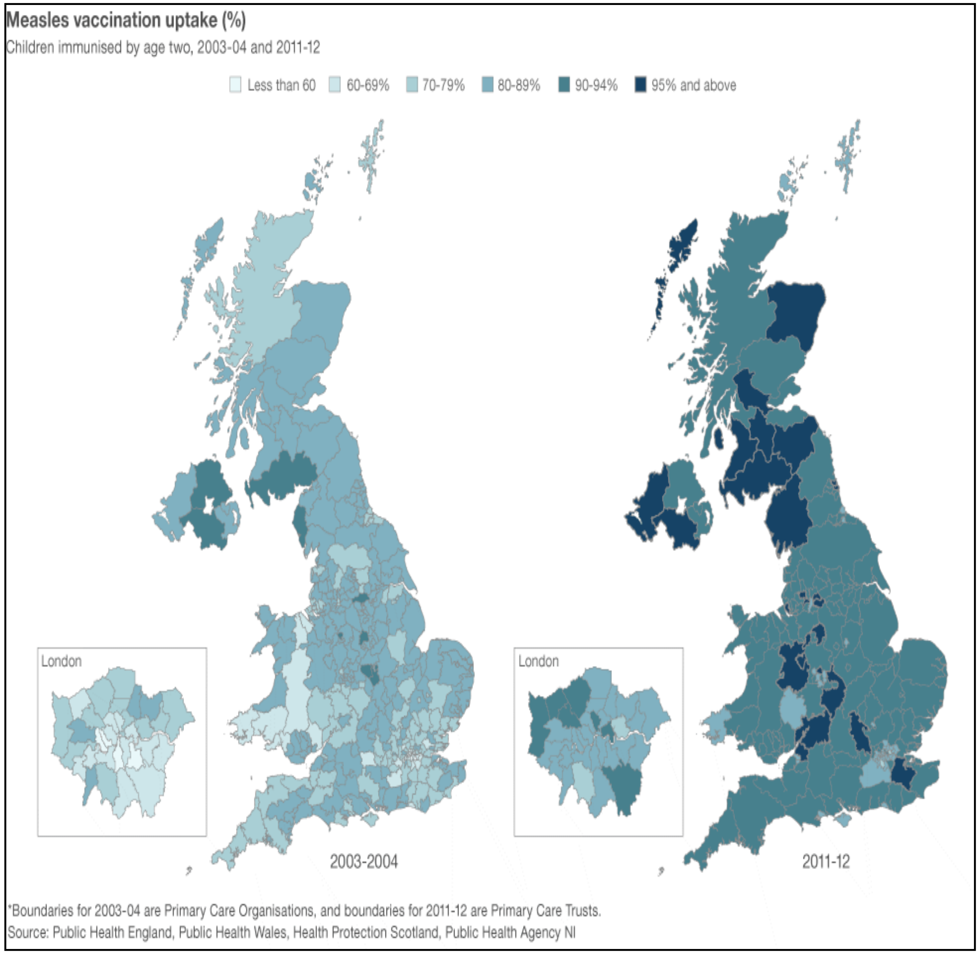
	1970	1994	2000	2015
Europe	2	2	2	2
Japan	2	2	2	2
North America	2	2	2	2

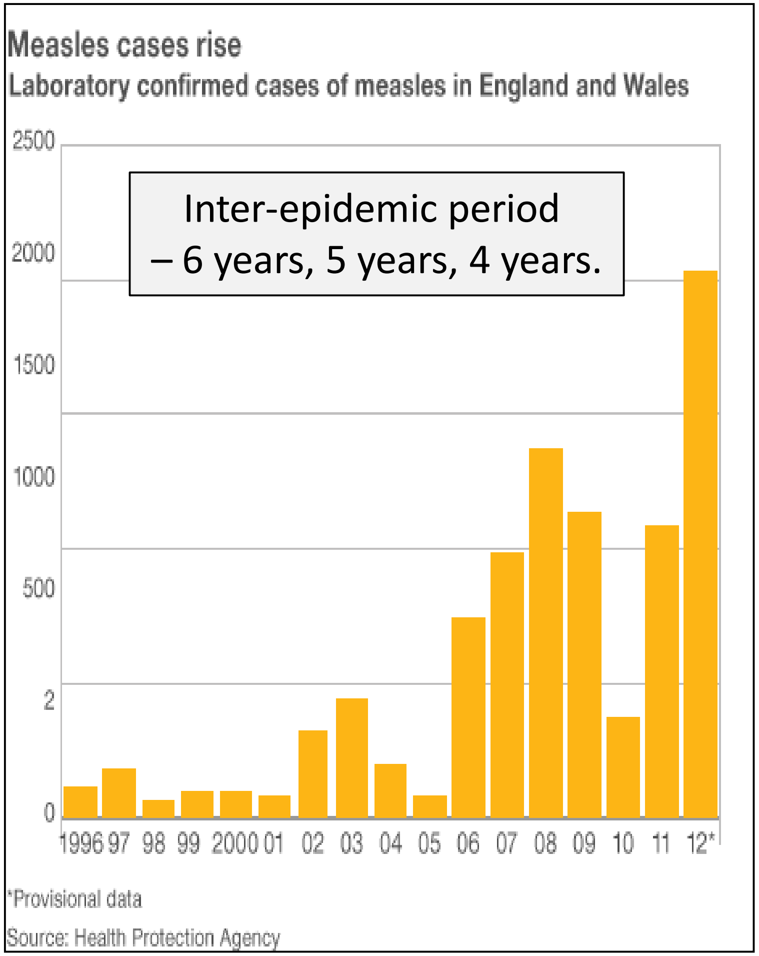
Recent events

Events - 2013-17

Measles epidemic in the UK - 2013

The media furore - started by a controversial paper published in the Lancet in 1998 (Wakefield et al) which raised fears about a link with autism (which has since been comprehensively discredited) - led to significant drop in MMR vaccine uptake.

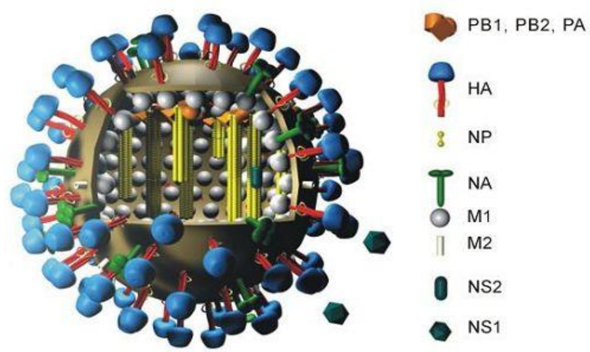


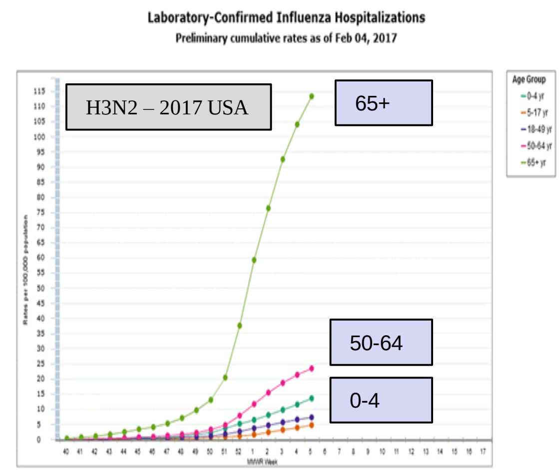


Health and Economic Impact of Seasonal Influenza A vaccination programme in England

Vaccine 30 May 2012 3459-62   Baguelin, Miller and Edmonds

Seasonal influenza vaccination impact was assessed with a transmission model. Vaccination substantially reduces disease burden. The current programme is cost-effective when the vaccine is well matched to strain circulating.





Conclusion

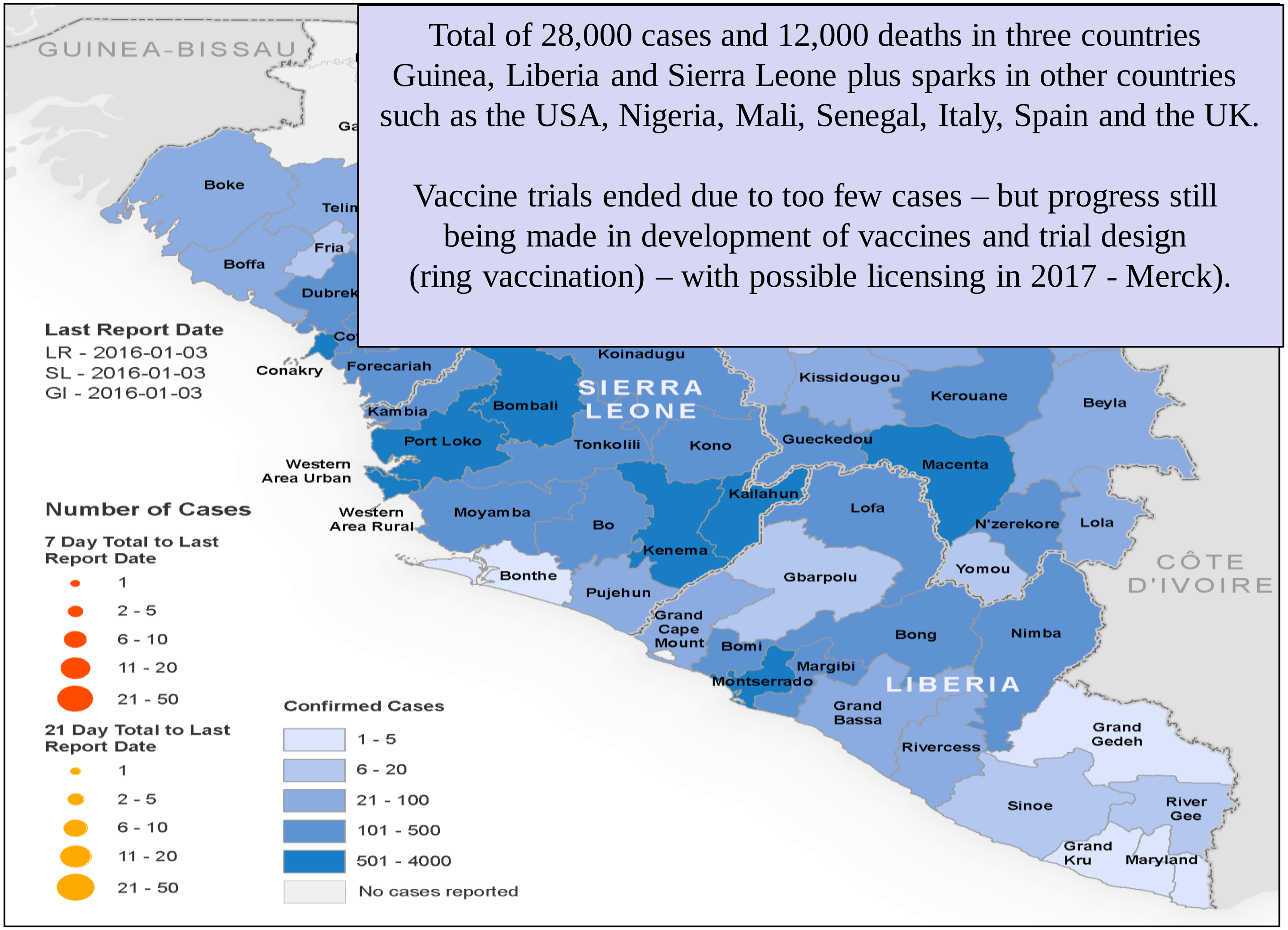
The 2012 seasonal influenza vaccination programme appears to substantially reduce disease burden and provides good value for money.

2014-15 flu vaccine was much less efficacious due to poor matching.

Ebola – 2013-15 outbreak - epidemiology

- Spread by direct contact with blood, bodily fluids or semen from infectious patient – or contaminated surfaces – no evidence of air borne transmission as yet – but this is a more transmissable strain than usual.
- Fever typically denotes infectiousness.
- Incubation period – 2-21 days (mean 8-10 days 2014; 12.7 days 2011 outbreak).
- Generation time – 10-12 days.
- Doubling time 4-5 days.
- R_0 is roughly 2-3.5 – each primary case generating 2 to 3 secondary cases over the first 35 weeks of the epidemic.
- Super-spreaders important
- Survival rate 47-50%
- Isolation of contacts – for 21 days post contact – use condoms for sexual partners.

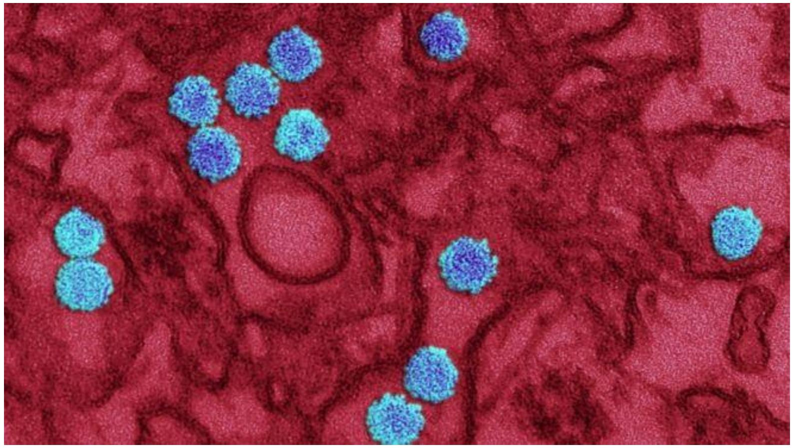
The 2015-16 Ebola outbreak in West Africa



Total of 28,000 cases and 12,000 deaths in three countries Guinea, Liberia and Sierra Leone plus sparks in other countries such as the USA, Nigeria, Mali, Senegal, Italy, Spain and the UK.

Vaccine trials ended due to too few cases – but progress still being made in development of vaccines and trial design (ring vaccination) – with possible licensing in 2017 - Merck).

Emergence of Zika virus infection epidemic in S America - association with microcephaly in infants born to infected mothers confirmed in Feb 2016



Zika virus – distribution map – past and present 2016

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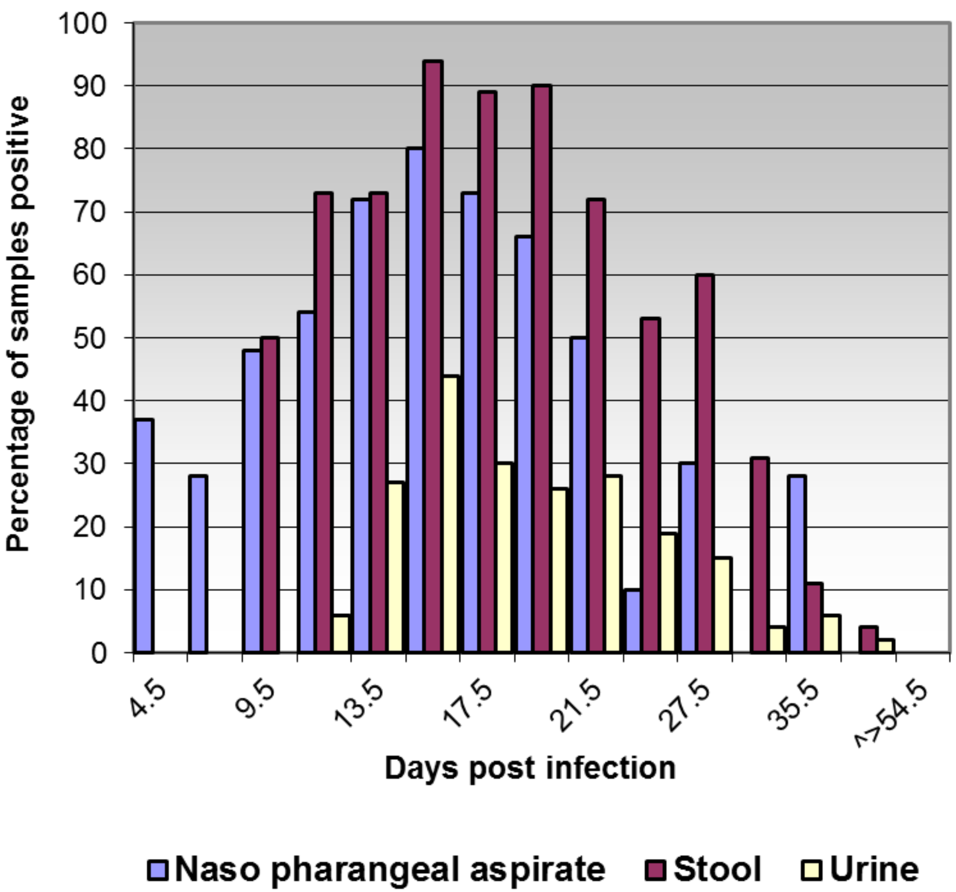
Bats as the origin of SARS

- 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%.

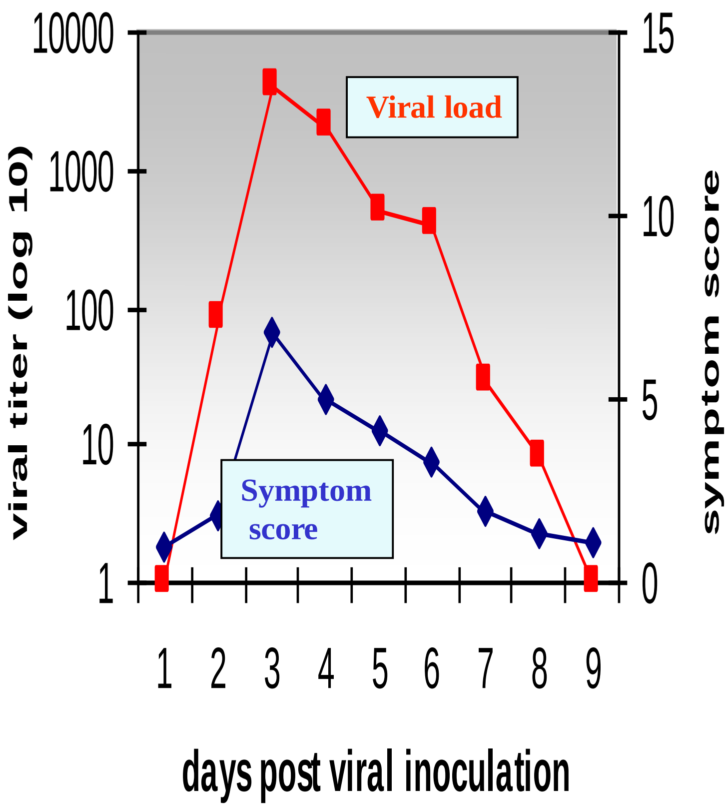
- (Lin-Fa Wang et al 2006, Emerging Infectious Diseases)

SARS and Influenza A - qPCR - patterns of viremia in patients [Peiris et al (2003), Hayden et al (1998)]

SARS CoV



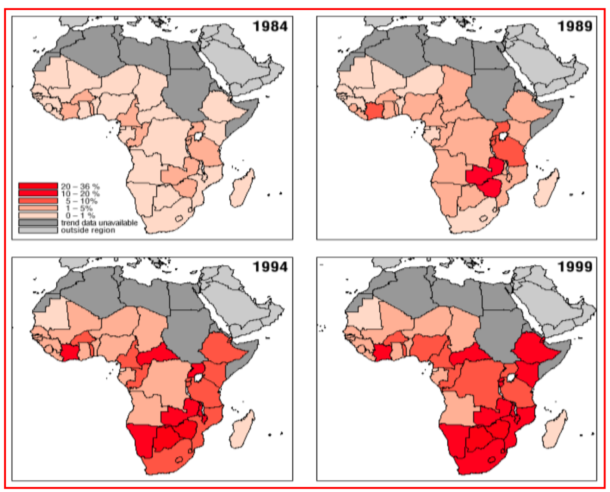
Influenza A

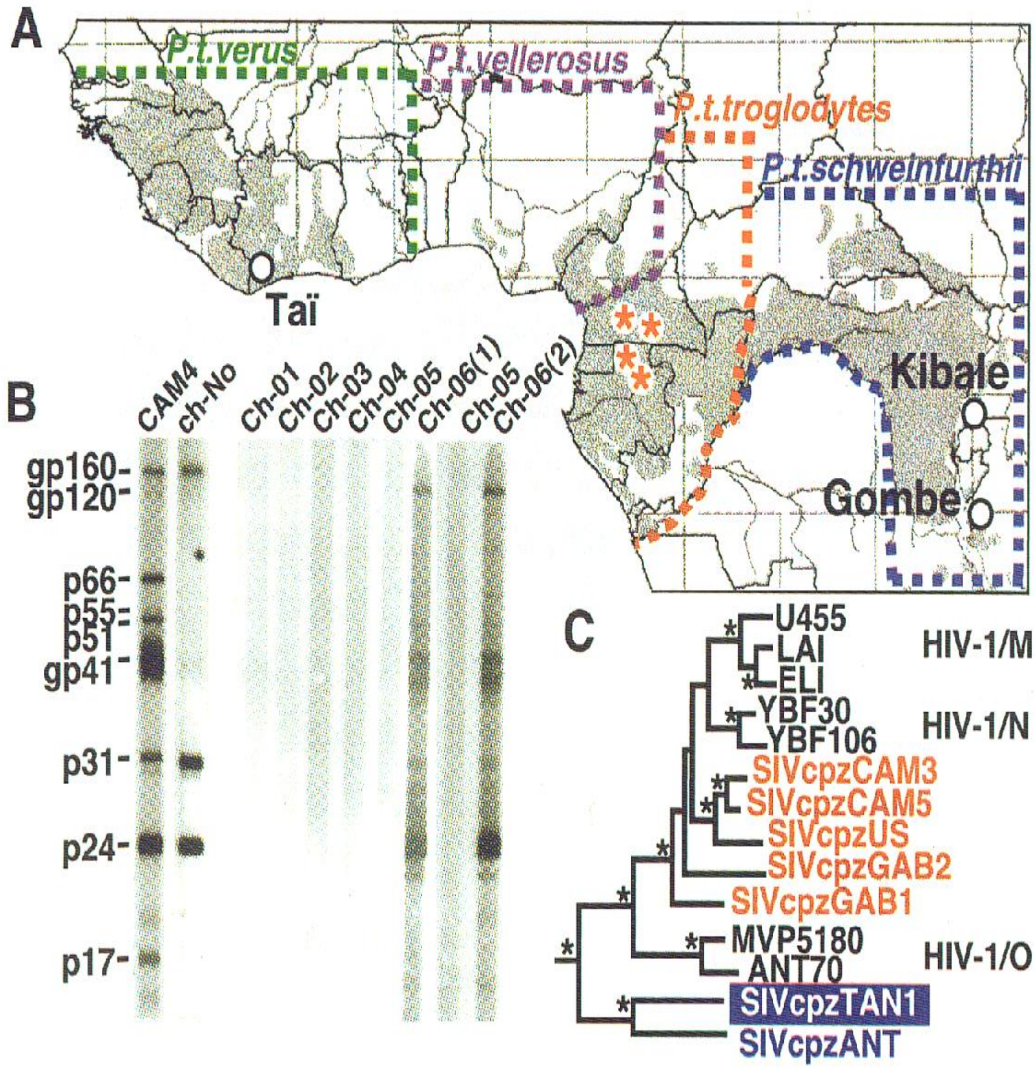


Experimental human influenza A/Texas/36/91 (H1N1) intranasal inoculation 10^5 dose

HIV – evolution - multiple introductions into humans

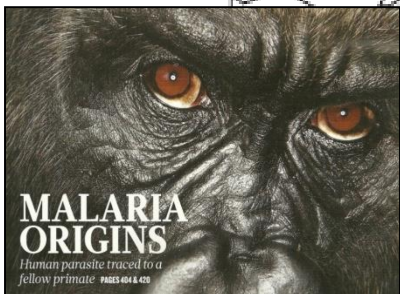
Hahn et al (2002)
(Gabon & Congo)



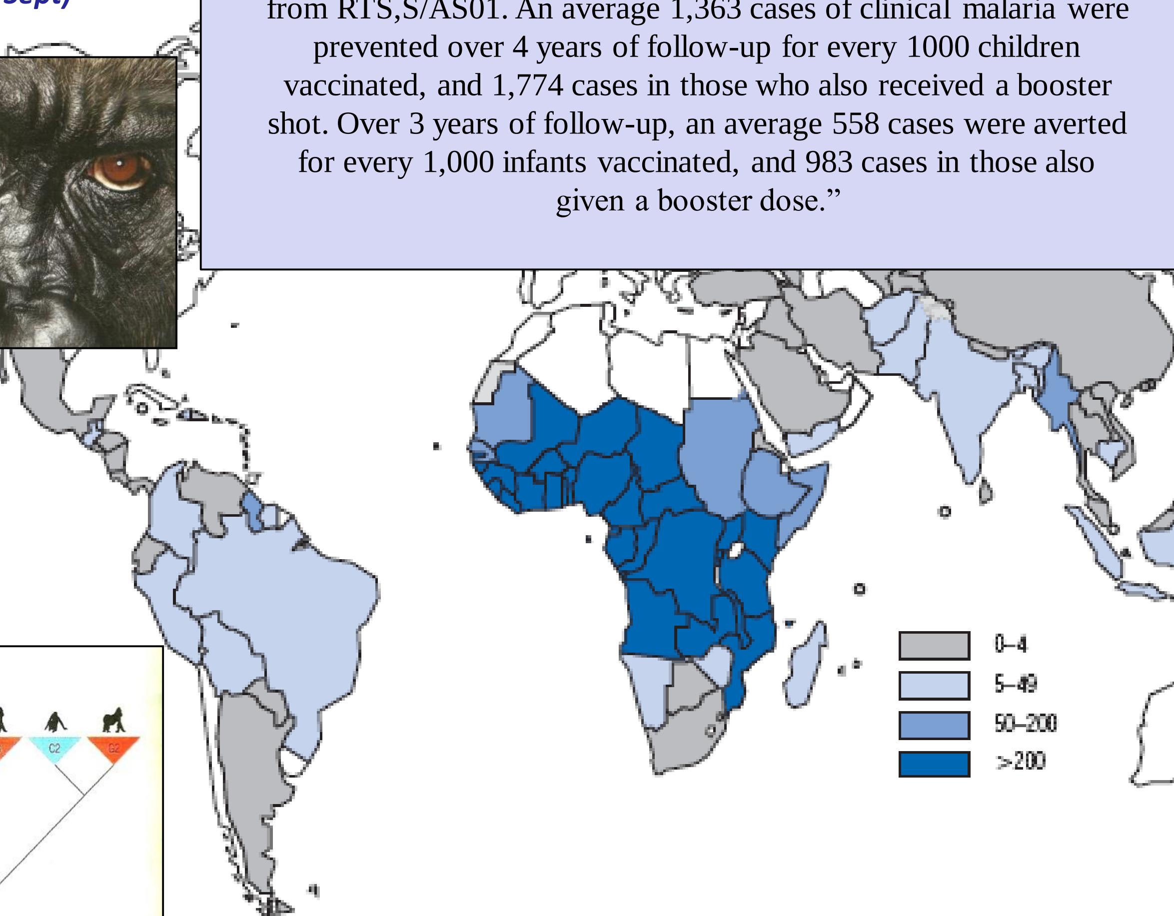


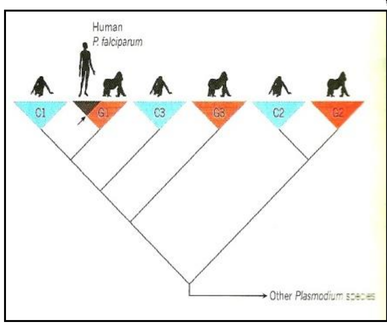
Incidence of malaria per 1000 head of population 2006 (WHO)

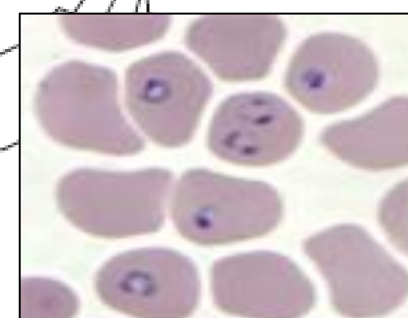
(Lui et al (2010) Nature 23rd Sept)



April 2015 - Lancet Malaria vaccine RTS,S Clinical Trials Partnership
Despite the falling efficacy over time, there is still a clear benefit from RTS,S/AS01. An average 1,363 cases of clinical malaria were prevented over 4 years of follow-up for every 1000 children vaccinated, and 1,774 cases in those who also received a booster shot. Over 3 years of follow-up, an average 558 cases were averted for every 1,000 infants vaccinated, and 983 cases in those also given a booster dose.”





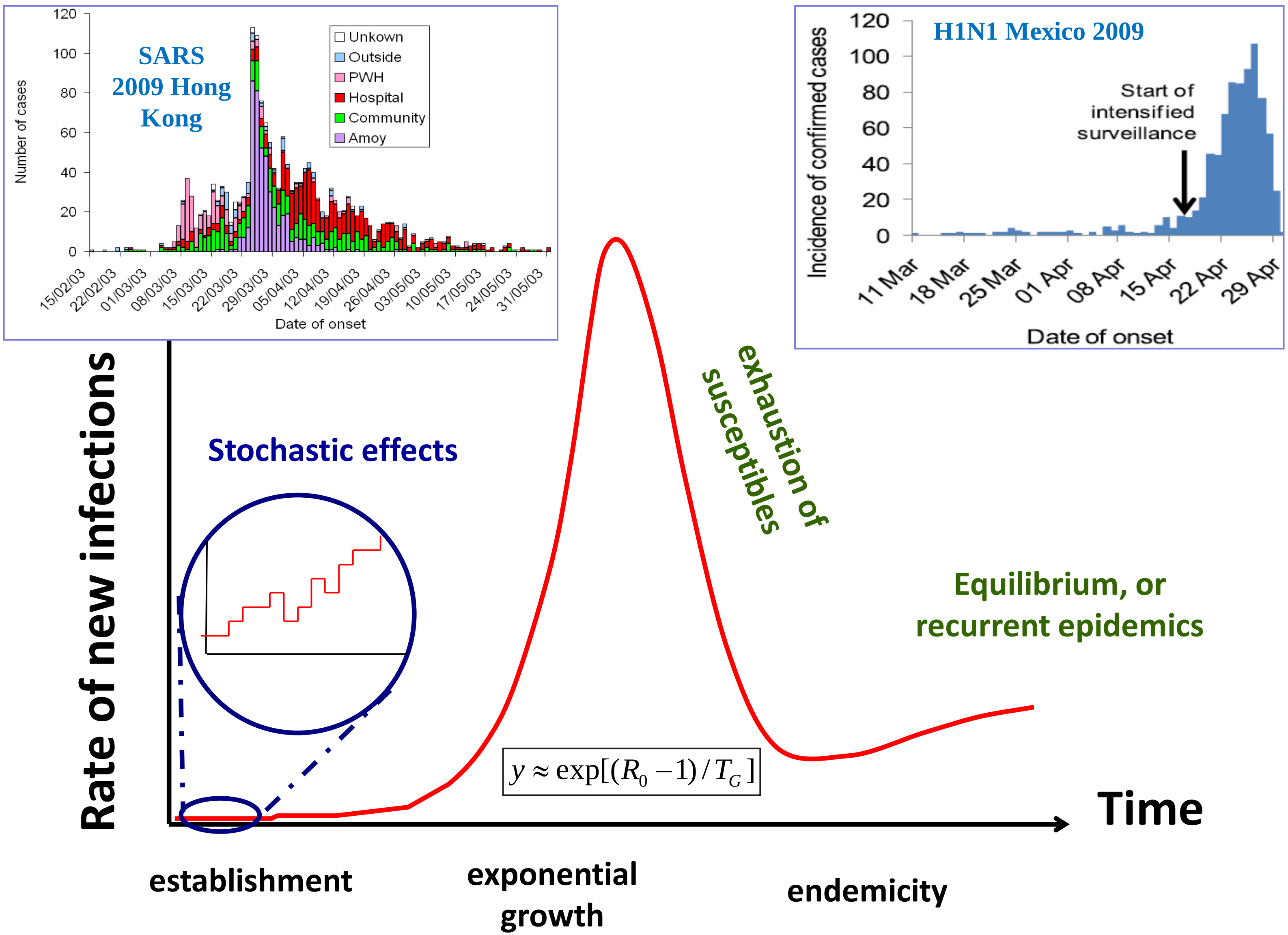


Control of pandemics

The emergence of a new disease – urgent tasks

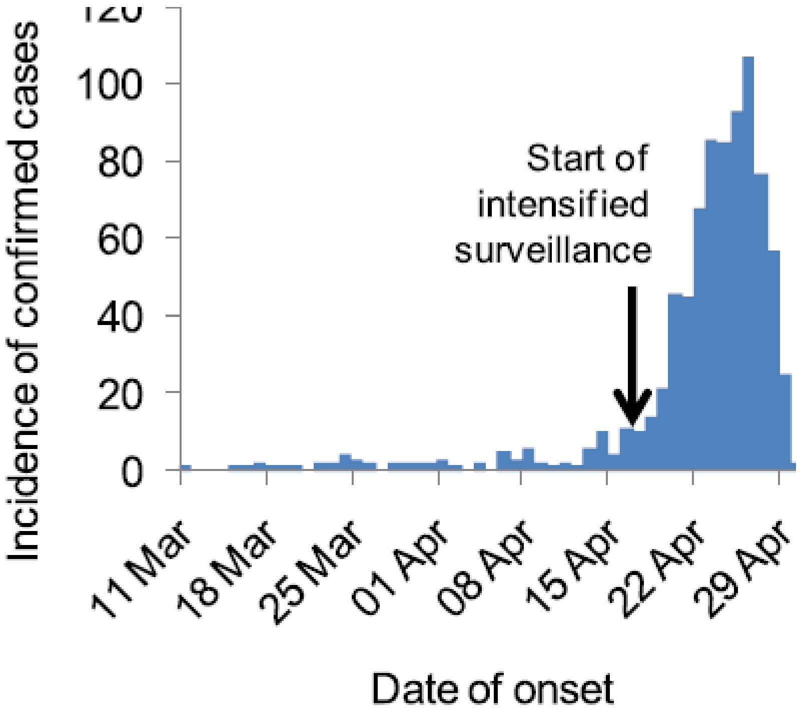
- **Indication** – unusual clusters of morbidity/mortality in space and time (e.g. SARS in Quangzhou – China, November 2002).
- Identify aetiological agent.
- Develop diagnostic tests.
- Determine route of transmission.
- Identify clinical algorithms for care – to reduce morbidity and mortality.
- Put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

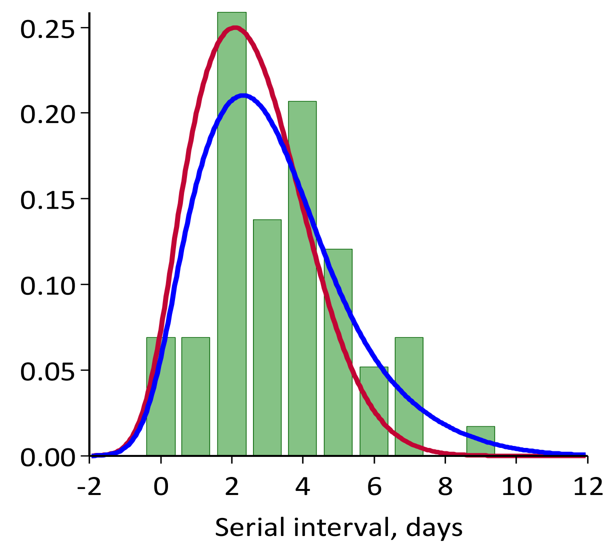
Epidemic timescales



R for Mexico in April-May

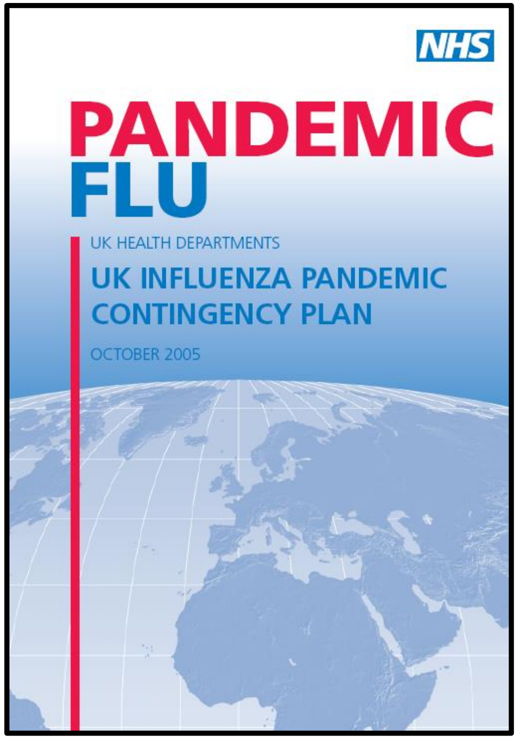
(Fraser et al, 2009 Nature)





- *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.

Clear definition of control policy aims & objectives



Policy objectives?

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

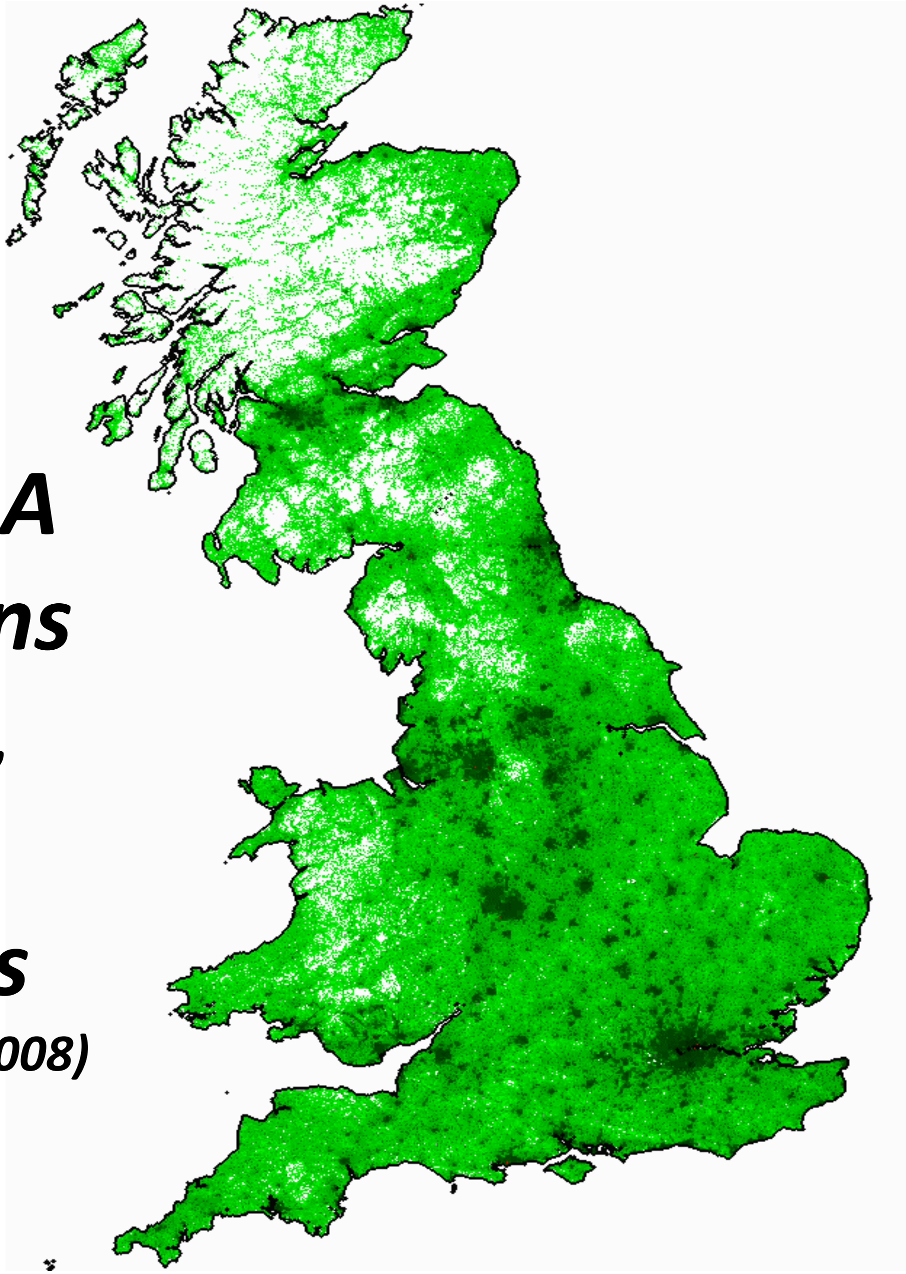
2) Buy as much time as possible to wait for vaccine development.

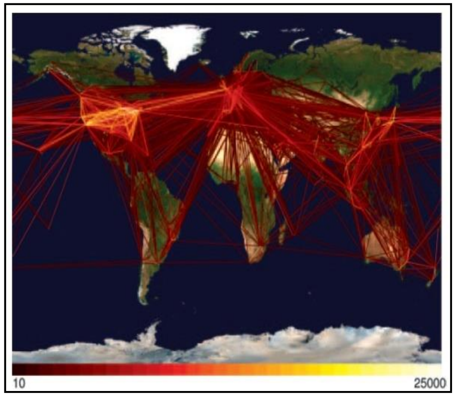
3) Minimize duration of the epidemic and impact on economy.

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

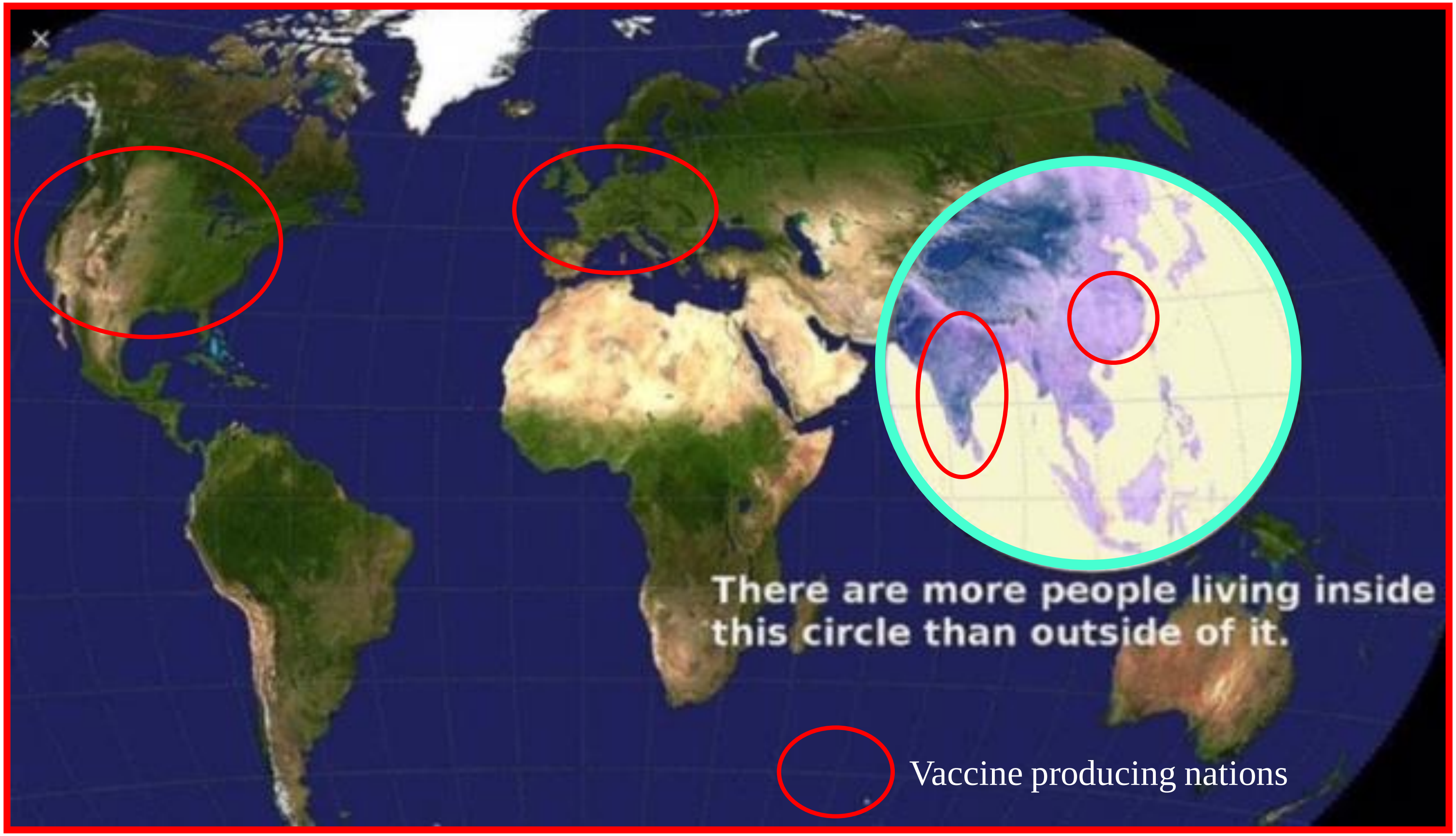
Influenza A simulations - England, Scotland and Wales

(Ferguson et al, 2008)



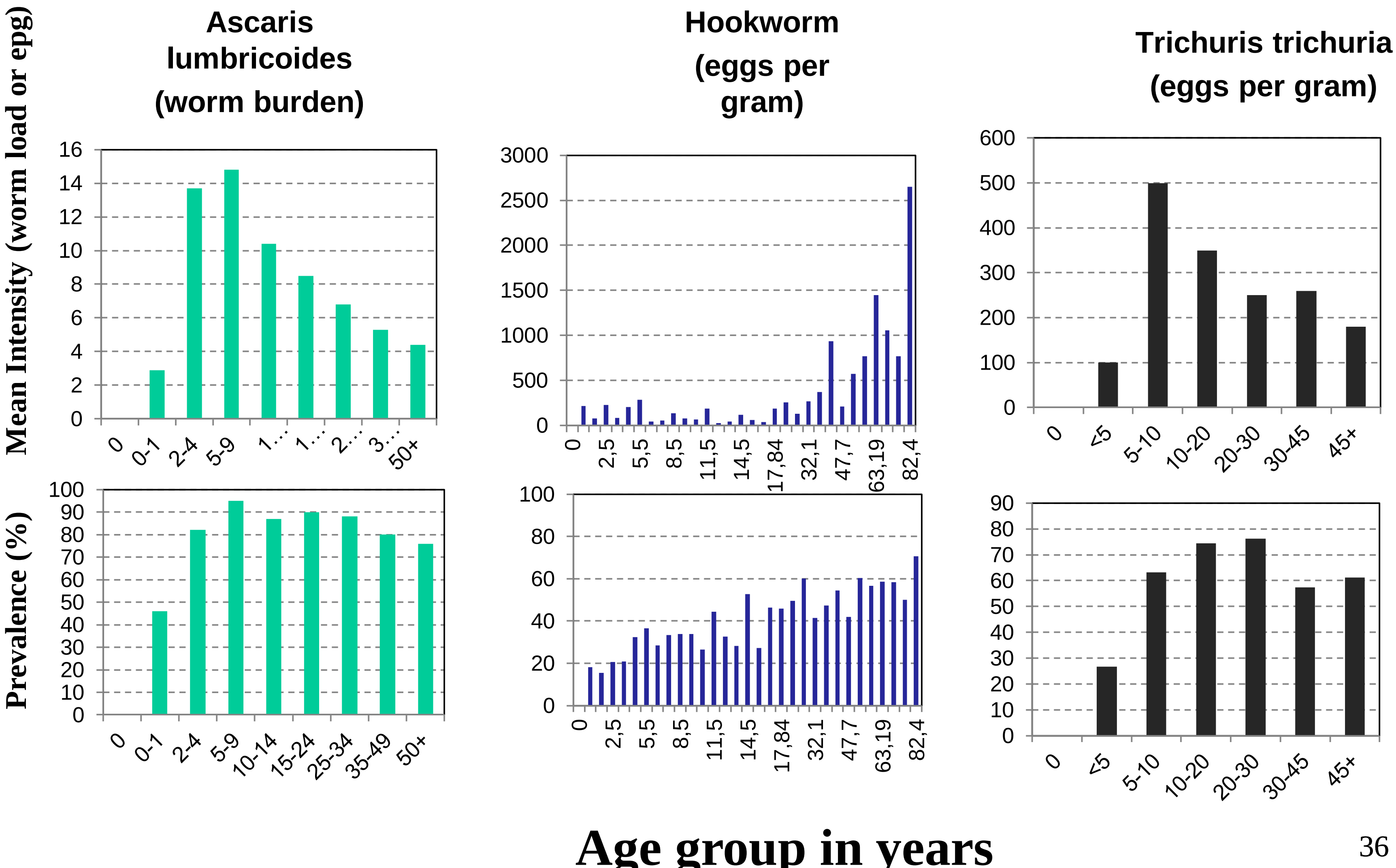


Vaccine producing nations and world population distribution



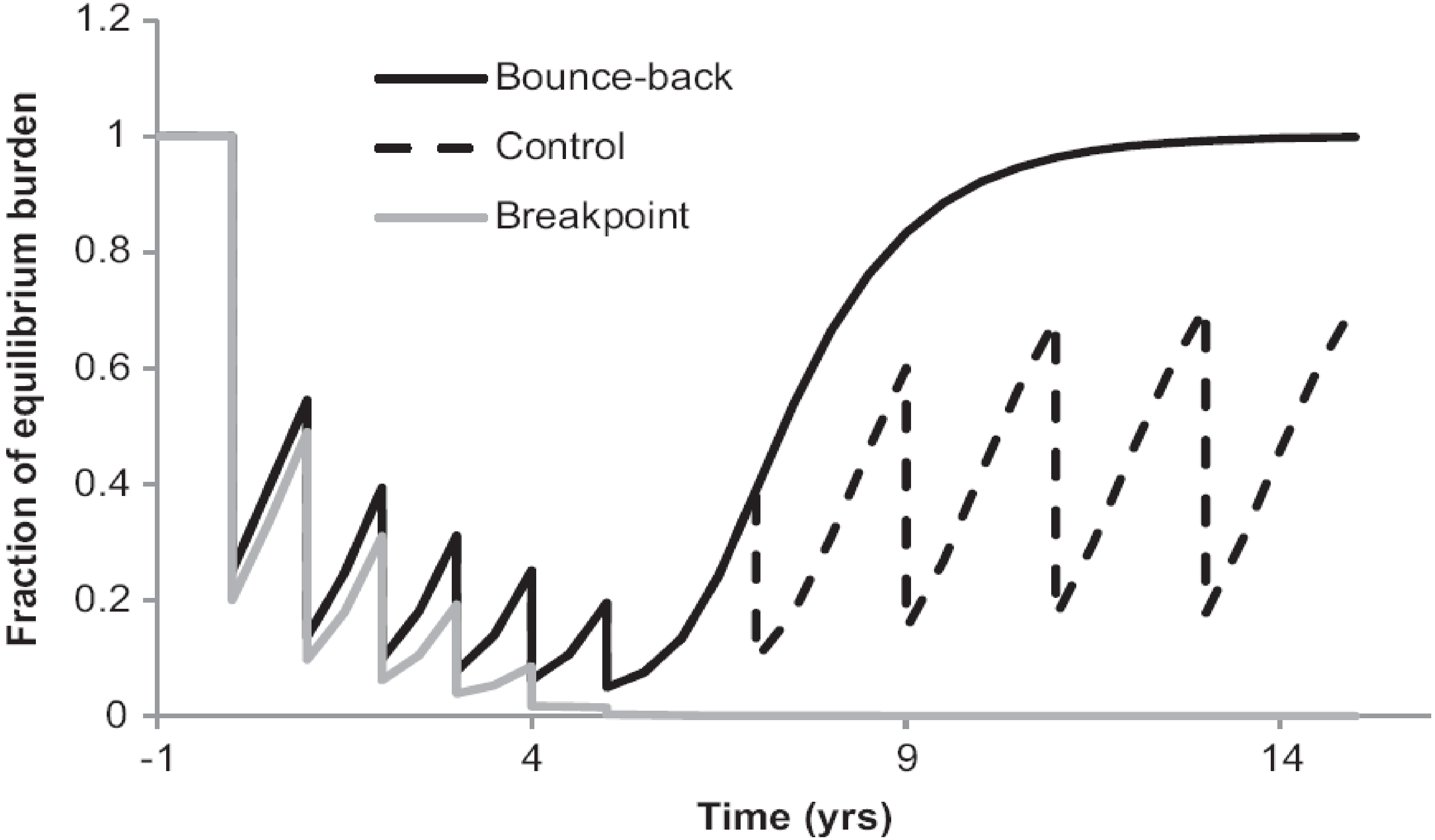
The Neglected Tropical Diseases; <u>Ascaris lumbricoides</u> in the Pulicat villages in Tamil Nadu in India

Age-intensity profiles for mean intensity and prevalence (%) for the three major soil transmitted helminths.



Effect of treatment on the dynamics of infection intensity

In all scenarios yearly treatment is introduced for six yearly rounds. In the bounce-back scenario (black solid line), the treatment program is halted. If treatment is continued at two-yearly intervals (black dashed line) then intensity bounces back, but to lower levels. If the treatment coverage is slightly higher, and is high enough to cross the breakpoint within the 6 years of yearly treatment (gray line). Simulations for k =0.15, R_0 = 4.5, L= 1 year, treatment coverage 75% (black lines) and 80% (gray line).



Conclusions

- New pathogen will emerge more frequently in the coming decades – better detection and continued evolution as our population expands, travels more and encroaches on natural wild life habitats.
- Modern medicine – can help solve problems ‘ eventually’ but regulatory structure in emergencies needs changing.
- Developing a vaccine is not the barrier to control – it is creating the financial and logistical models for manufacture and distribution – for a possible ‘one off’ event.
- Influenza A presents the greatest threat at present of the known pathogens.

The End