

Modelling the Evolution of the Influenza Virus

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- Basic Phenomenology of Influenza
- Modeling Viral Evolution
- Modeling Epidemic Spreading
- A simple model for Influenza Dynamics
(F. Tria, M. Lassig, L. Peliti, SF)



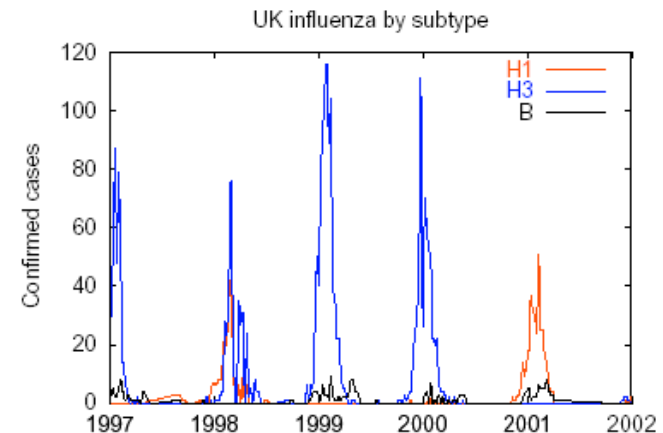
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Influenza:

A: large variety of animals (including human and aquatic birds)

B: human (isolation in seal) moderate epidemics.

C: human (isolation in swine and dog) not an important source of morbidity.





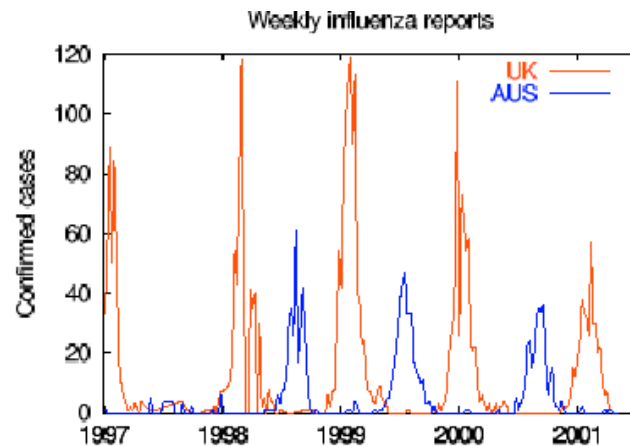
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Influenza A in human

Respiratory infection with headach, fever cough

Important cause of morbidity and mortality (in elderly people)

Seasonal Epidemics in temperate regions



Present throughout the year in tropical areas



Severe Pandemics (humans):

20th Century: 1918 (Spanish), 1957 (Asiatic), 1968, 1977.

Spanish flu ~ 20 M people

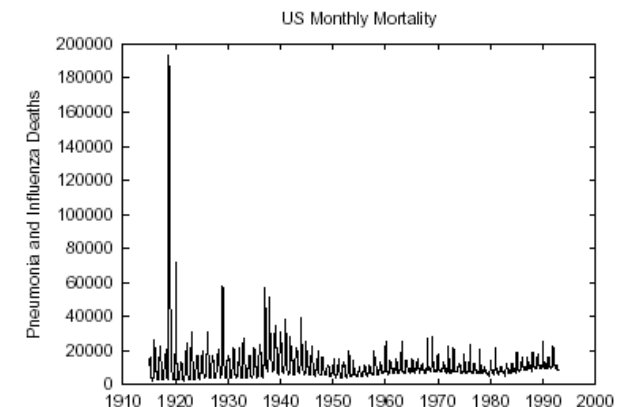
Asiatic ~ 1-4 M

1968 ~ 1-4 M

But, hystorically documented pandemics in

1580 (Influenza planetaria), 1729, 1781, 1890....

Avian epizoosis since 1997 (2003).



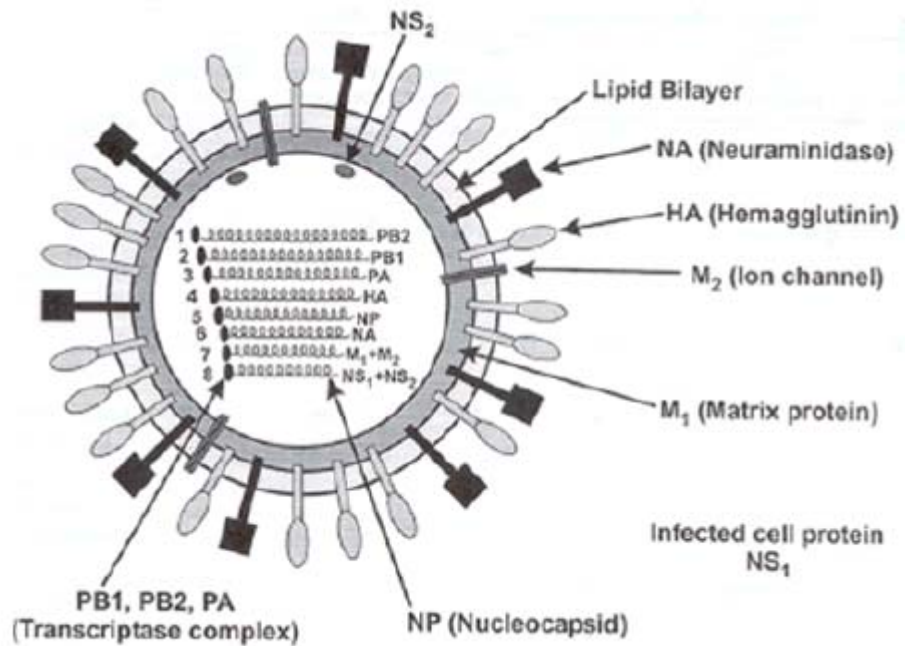
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Basic Phenomenology of Influenza



RNA Virus

8 RNA segments, 11 genetic products





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Influenza A subtypes

Classified in base of the differences in the receptor binding membrane proteins **Important Antigenic Sites**

Hemagglutinin (HA) Neuramidinase (NA)

HA: binds to the cell receptors (entrance of virus in host cell)
16 subtypes H1,...,H16

NA: free virus particle from host cell
9 subtype N1,...,N9

functional part highly conserved,
antigenic sites high mutation rate



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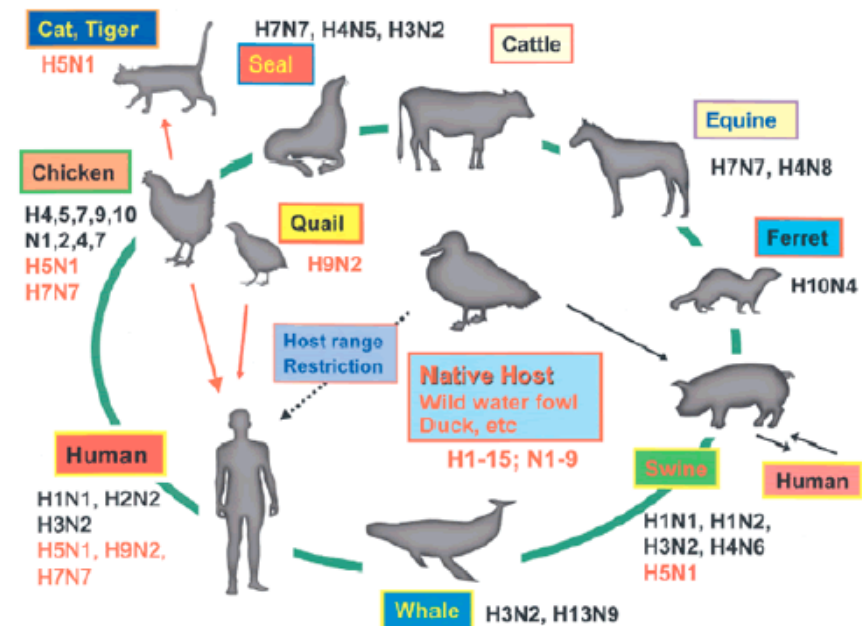
Wild aquatic birds provide the reservoir for genetic diversity of the virus.

All H_n and N_m
 $n=1, \dots, 16$
 $m=1, \dots, 9$
have been found in
wild aquatic birds.

Host range restriction.

Passage to different species.

Summary of the ecology of influenza virus





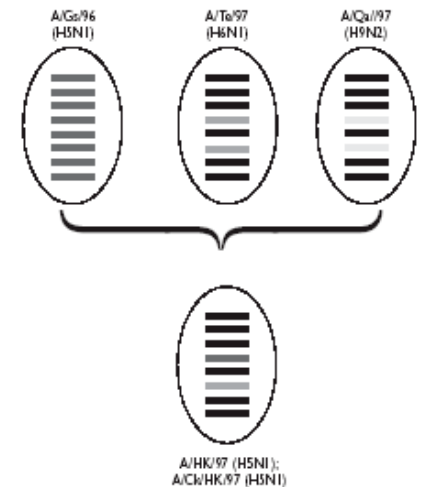
Wild aquatic birds: mostly asymptomatic
genetic diversity reservoir

Domestic poultry: Low Pathogenic Avian Influenza (LPAI)
Highly Pathogenic A. I. (HPAI)

Variety of mammals: Swine, Horse, Whale, seal, dog....

There are interspecies barriers, but virus can adapt to different species.

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Modificado de la referencia 41

FIG. 4. REASOCIACIÓN GENOTÍPICA DE LOS VIRUS H5N1 DEL VIRUS DE HONG KONG EN 1997 CON OTROS VIRUS (H6N1 Y H9N2): LAS ABREVIATURAS UTILIZADAS CORRESPONDEN A: A/GOOSE/GUANDONG/1/96 (H5N1) [A/Gs/96 (H5N1)]; A/TEAL/HONG KONG/G1/97 (H6N1) [A/Te/97 (H6N1)]; A/QUAIL/HONG KONG/97 (H9N2) [A/Qa/97 (H9N2)]; A/HONG KONG/156/97 (H5N1) [A/HK/97 (H5N1)]; A/CHICKEN/HONG KONG/Y280/97 (H5N1) [A/Ck/HK/97 (H5N1)]. LOS SEGMENTOS SE PRESENTAN DE ARRIBA ABAJO COMO: PB2, PB1, PA, HA, NP, NA, M Y NS

Evolution of the human influenza virus (I):

Antigenic Shift

Reassortment of human and avian virus segments

Different Virus infecting the same cell put in common their segments to form a new variant

Large rare events Associated to pandemics

1918 H1N1 : 1957 H2N2 : 1968 H3N2 : 1977 H1N1+H3N2

Present Avian epizootic H5N1.



Evolution of the human influenza virus (II):

Genetic Drift

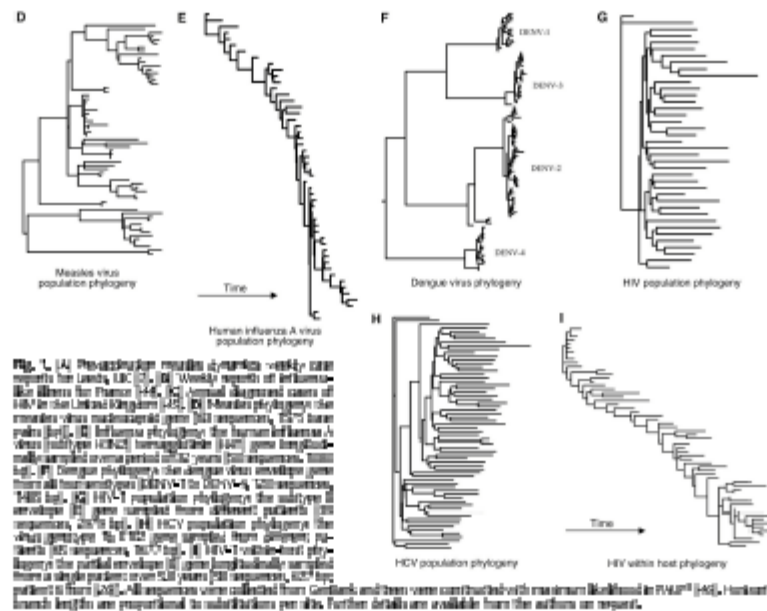
Point mutation in the Virus Genome (Substitutions, Deletions, Insertion)

HA and NA : main antigenic sites (target of the immune system)
High rate of non-synonymous substitutions. Escape from the Immune Systems

High level of morbidity maintained by the fast evolution of the virus.
Vaccine has to be changed every year.

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Evolutionary trees



Large spectrum immunity: Measles ramified trees → Neutral evolution

short range immunity: Influenza A (18 Codons of HA1) comb like tree →

Immune system selective pressure



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The tree exhibits a well-defined backbone: branches have a median lifetime of 1.45 years

At any given time, the strain nearest to the backbone can be identified as that which has accumulated the largest number of nonsilent mutations in 18 special codons of the HA gene (*Fitch et al., 1997*)

Repulsion effect due to interaction with the immunity of previous pandemic strains?

Notice the similarity between the influenza A tree and the in-patient HIV tree



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Modeling Viral Evolution

Darwinian Paradigm

Reproduction: Offsprings are similar to the parents

Mutation: Offspring are not identical to the parents

Selection: Inheritable changes can affect the reproductive success



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Fitness: Measure of the reproductive potential of a genotype

Absolute fitness: W_g of a genotype g : expected number of offspring of an individual with that genotype. (actual number is stochastic)

Relative fitness: Absolute fitness rescaled by a factor (e.g. $N \langle W \rangle$)

Separate the effect of growth of population from evolutionary dynamics (change in gene frequencies in the population)



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Population of M individuals with different genotypes S
 W_S fitness of genotype S ($S=1, \dots, N_g$).

Genotype distribution at next generation

- 1) Haploid population asexual reproduction
- 2) Large population of fixed size M
- 3) **No mutations**